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HOMOGENOUS TRANSITION METAL CATALYSIS IN ENOLATE ARYLATION

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A thesis submitted to the Faculty of Science
University of the Witwatersrand
Johannesburg
In fulfillment of the requirements for the
Degree of Doctor of Philosophy

September 2005

DECLARATION

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Dr C J Parkinson and Professor C B de Koning. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

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12th day of September 2005

ABSTRACT

The application of homogenous transition metal catalysis to the arylation of enolates to develop new synthetic procedures which are more environmentally benign, atom-efficient and economically viable than current methods was the motivation behind the current work. The specific choice of molecules with an aromatic group in the α-position of a ketone, carboxylic acid, amide or other electron-withdrawing group arose from the fact that many natural products, pharmaceutical actives and synthetic intermediates contain such a substructure while the syntheses of these substructures are often cumbersome.

The application of homogenous catalysis to various types of enolates was explored and in the process several developments were achieved and discoveries made. These included the use of inorganic bases under phase transfer conditions for the Heck reaction of acrylic acid as well as the synthesis and application of phosphine and phosphite ligands in the Heck reaction of acrylic acid esters. The successful use of low palladium loadings (as low as 0.01mol%) in the arylation of diethyl malonate using aryl chlorides and the application to the synthesis of ketoprofen and phenobarbital was demonstrated. The novel application of palladium catalysis to the arylation of methanesulfonamides and the first example of a bromoindole derivative as the aryl halide partner in an enolate arylation reaction was demonstrated. Ligand-free palladium catalysed phenylation of pinacolone followed by Baeyer Villiger oxidation led to a proposed novel synthetic route to *tert*-butyl esters of 2-arylacetic acids. The palladium and copper catalysed arylation of acetoacetate esters, with *in situ* decarbonylation, provided a different route to 2-arylacetic acid esters which are useful in the preparation of non-steroidal anti-inflammatory compounds.

ACKNOWLEDGEMENTS

I wish to express my gratitude to the following people who assisted me during the experimental work and the writing of this thesis:

My promoters Dr. Chris Parkinson (CSIR) and Prof. Charles de Koning for their guidance, motivation and useful discussions.

To my close working colleagues, especially Chris, Mandy, Greg, Sandy, Subash and Chris van der Westhuyzen for their assistance, encouragement, fruitful discussions and friendship!

My thanks also go to those who assisted me in analytical and administrative tasks:
Tommie van der Merwe for high resolution mass spectrometry
Clement Stander and Godfrey Kupi for GC-MS analysis
Sue Rhodes and Madelyn Bekker for assistance during NMR analysis
Sandy Farnworth for taking care of administration of the projects spanning this thesis.
Ann Sparrow for compiling journal articles and
Christa Marais for literature and patent searches.

CSIR for providing the opportunity and funding for further study while in their employ and in this regard I wish to express my thanks to Fanie Marais and Chris Parkinson for their encouragement and securing funding for the projects spanning this thesis.

A special word of thanks to family and friends for their encouragement during tough times and especially to my loving wife, Belinda, and children, Jacques and Chanté, for their love and understanding despite long hours spent on the writing of this thesis – thank you for being there for me!

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LIST OF ABBREVIATIONS

BHA	Butylated hydroxyanisole
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
GC	Gas (liquid) chromatography
DABCO	1,4-Diazabicyclo[2,2,2]octane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EHA	2-Ethylhexanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
KOtBu	Potassium *tert*-butoxide
LiOtBu	Lithium *tert*-butoxide
*m*CPBA	*m*-Chloroperbenzoic acid / 3-chloroperbenzoic acid
NaOtBu	Sodium *tert*-butoxide
NMP	1-Methyl-2-pyrrolidinone / *N*-methylpyrrolidinone
NSAID	Non-steroidal anti-inflammatory drug
OMC	Octyl 4-methoxycinnamate / 2-ethylhexyl *p*-methoxycinnamate
PCy_3	Tricyclohexylphosphine
$PtBu_3$	Tri-*tert*-butylphosphine
$Pd(dba)_2$	Bis(dibenzylidineacetone)palladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
PPh_3	Triphenylphosphine
PTC	Phase transfer catalyst
THF	Tetrahydrofuran
TON	Turnover number

CHAPTER 1

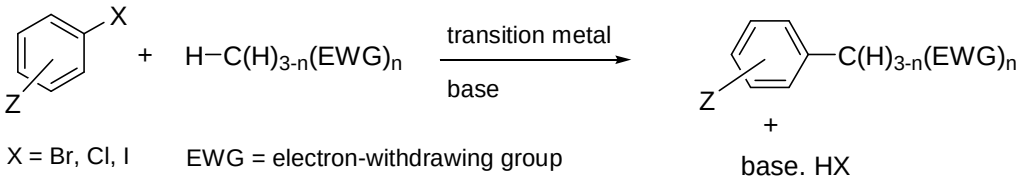
INTRODUCTION

The requirement for the development of technology to assemble molecules which contain an aromatic ring in the α-position of a ketone, ester, amide or other electron-withdrawing group, arises from the fact that many natural products, pharmaceutical actives and synthetic intermediates contain such a substructure. In general, no cost efficient and environmentally friendly synthetic method exists to assemble these substructures[1].

It is believed that the most atom efficient route to α-aryl carbonyl compounds is by direct formation of the bond between the aryl unit and the α-carbon. The reaction between an enolate nucleophile and an aryl halide could create such a bond and is referred to as an arylation reaction.

1.1 The Arylation Reaction

In the general sense, an arylation reaction is seen as the attachment of any aromatic group to a range of atoms but for the scope of this study, the arylation reaction is defined as the formation of a bond between an aromatic moiety and carbon atom attached to one or more electron-withdrawing groups in the presence of a catalytic amount of a transition metal or complex thereof (Scheme 1). It can also be seen as the replacement of an acidic hydrogen atom on an enolisable carbon.

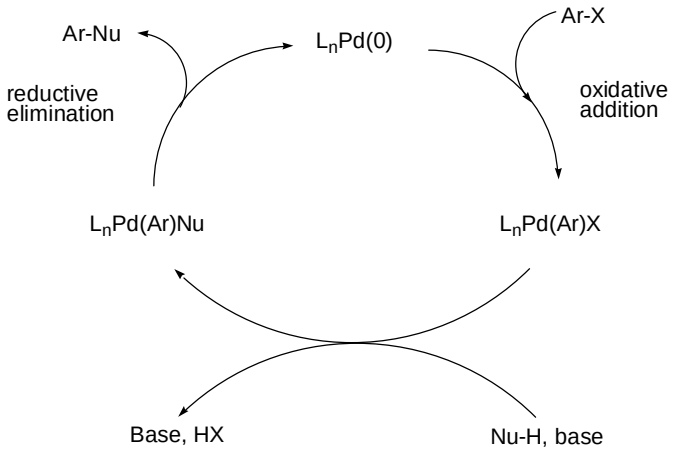


Scheme 1. The arylation reaction

The carbon-carbon bond forming reactions are further limited to the formation of bonds between enolates (hard, pKa>19 or soft, pKa<15) and aromatic systems in the form of aromatic halides. Aryl bromides and chlorides, in particular, were considered

although aryl iodides have not been specifically excluded. In addition to enolates, the coupling of olefinic substrates (the Heck reaction) to aryl halides was also looked at.

Other types of arylation reactions will not be entirely excluded from discussions as several parallels can be drawn between enolate / olefin arylation and, especially, aromatic amination. Aromatic amination has attracted significant attention over the past 10 years and a large amount of data and mechanistic evidence is available[2-4]. Alkyl aryl ether[5,6] formation and the Suzuki[7], Stille[8,9] and Negishi[10] coupling reactions are other closely related reactions and developments in these areas have also provided valuable insights into the workings of enolate arylation. All these reactions are very similar and share at least some aspects of the catalytic cycle (see Scheme 2). The first step in the catalytic cycle involves insertion of Pd (0) into the aryl halide bond (oxidative addition) and is believed to be universal for these reactions. This is followed by the association of the nucleophile, the form and type of which, determines the type of reaction. Product formation takes place when the palladium complex, containing both the aryl and nucleophile components, collapses and the Pd(0) complex is released (reductive elimination). This is evidenced by the similarity in catalyst precursors and ligands as well as the reaction conditions employed.



Scheme 2. General mechanism of palladium catalysed arylation

The formation of carbon-carbon bonds involving an aromatic compound is traditionally performed by electrophilic aromatic substitution. The Friedel-Crafts acylation reaction between an electron-rich aromatic compound and an acyl halide or

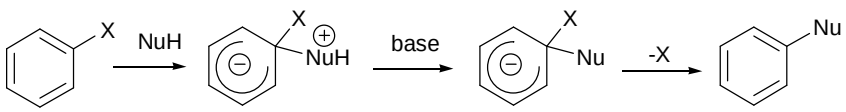
anhydride activated by a Lewis acid is a well-known example[11]. This does, however, not allow for the introduction of an aromatic substituent in the α-position of a carbonyl compound. In the past numerous methods have been devised to accomplish aromatic nucleophilic substitution but have generally been limited with respect to the scope of substrates and the requirement of harsh conditions which do not tolerate other sensitive functionalities on the substrates[12]. Consequently, the formation of carbon-carbon bonds involving an aromatic substituent reacting with a nucleophilic partner has remained a challenging synthetic task.

1.2 Nucleophilic Aromatic Substitution

Traditionally, nucleophilic substitution reactions at an aromatic nucleus were classified into four categories and will be discussed briefly to provide an overview:

- Reactions of substrates activated by electron withdrawing groups in the *ortho* or *para* position (S_NAr) or as in the case of metal-π-arene complexes (for example $(CO)_3Cr$-η^6-Ar-X).
- Reactions catalysed by very strong bases and proceeding through a benzyne mechanism
- Reactions initiated by electron donors ($S_{RN}1$)
- Substrates where the nitrogen of a diazonium salt is displaced (S_N1).

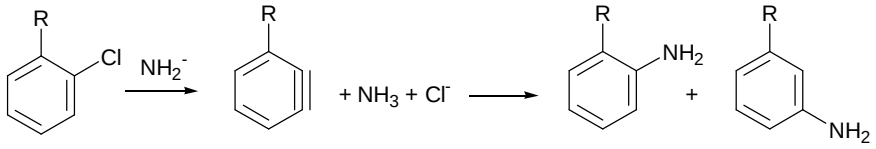
The S_NAr mechanism consists of 2 steps, in the first step a bond is formed between the attacking nucleophile and the substrate forming an arenium ion (otherwise known as a Meisenheimer salt) which then collapses to the product by bond breaking between the aromatic substrate and the leaving group (Scheme 3).



Scheme 3. Nucleophilic substitution by the S_NAr mechanism

The first step is almost always the rate-determining step and therefore the rate of reaction is significantly accelerated by the presence of electron-withdrawing groups especially those in the *ortho* and *para* positions which can remove electron density from the aromatic ring and particularly groups capable of further stabilizing the negative charge as extra contributors to the resonance hybrid. Since the leaving group can also affect the electron-density at the site of attack, strongly electronegative leaving groups will accelerate the attack of the nucleophile and hence the overall rate of reaction. For this reason the reactivity order of the halogens are reversed with F>>Cl>Br>I. Nucleophilic substitutions on aromatic substrates containing groups like nitro, quaternary amine, trifluoromethyl, carbonyl groups etc. are most likely to be the S_NAr mechanism.

When substitution is to be carried out on an aromatic system where no or few activating groups are present other conditions are required. A specific class of reaction can be utilized where a leaving group is present. These reactions require the use of strong bases, the most common of these being KNH_2 or $NaNH_2$ in liquid ammonia. The base abstracts the most acidic proton (*ortho* to the halogen substituent) followed by elimination of the vicinal leaving group, giving the highly reactive benzyne intermediate. The attack of the nucleophile has 2 options, either at the same position as the leaving group or in the position next to it (Scheme 4). The position of substitution is determined by other substituents on the ring. When bromide or iodide is displaced, proton removal is the rate limiting step and therefore bromide reacts faster than iodide.

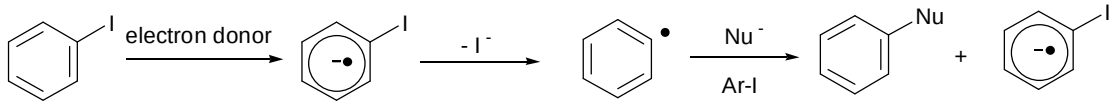


Scheme 4. Aromatic nucleophilic substitution by the benzyne mechanism

When the more electronegative fluoride or chloride is the leaving group, bond cleavage is a more important factor and hence chloride reacts faster than fluoride. The preparation of *m*-chloroanisole from 1,2-dichlorobenzene and 1,3-dichlorobenzene and

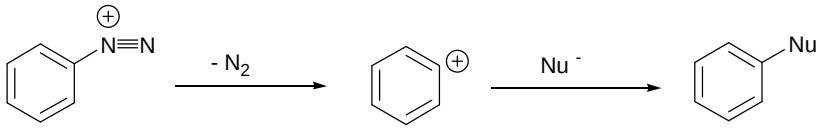
p-chloroaniline from 1,4-dichlorobenzene are well-known examples of where this mechanism operates as well as the ethylation of benzene with iodoethane[13].

Another class of nucleophilic substitution reactions is initiated by an electron donor which leads to the formation of an aromatic radical. The aromatic radical combines with the nucleophile to give the radical anion of the product. The product is released by transfer of the electron to the next substrate molecule to repeat the cycle (Scheme 5). These reactions are promoted by solvated radicals like dissolved sodium or potassium atoms and retarded by radical scavengers. These reactions can be initiated photochemically, electrochemically or even thermally[14]. Most examples involve aryl iodides and the use of liquid ammonia.



Scheme 5. Nucleophilic aromatic substitution by the $S_{RN}1$ mechanism

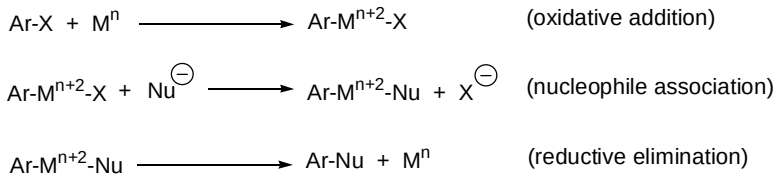
The last class of aromatic substitution reaction to be discussed herein approximates to an S_N1 process. Although a true unimolecular substitution mechanism for aryl halides and sulfonates is rare, the substitution of diazonium salts does go through a S_N1 process. The rate of reaction is first order in the diazonium salt and is not dependant on the concentration of the incoming nucleophile. The best known example of this substitution reaction is the Sandmeyer reaction where a diazonium salt is replaced by chloride, bromide or cyanide in the form of a copper salt (Scheme 6). The Meerwein arylation of activated alkenes [15] and the Gomberg-Bachman-Hey biaryl formation[16] and its intramolecular version, Pschorr cyclization[17] all employ aryldiazonium salts although they involve radical processes.



Scheme 6. Nucleophilic aromatic substitution by the S_N1 mechanism

1.3 Newer Methods of Aromatic Substitution

A different type of aromatic substitution reaction has been developed in the past few decades which does not fall into the above classification (given previously) as the electrophilic partner, the aromatic ring carrying a halogen, becomes part of an organometallic complex and has undergone an *umpolung* and could be regarded as carrying a negative charge. This process is called oxidative addition, and the metal goes from M^n to M^{n+2} carrying both the aryl and halide as anionic ligands. The labile halide ligand is exchanged with the carbon nucleophile (either C or O bound in the case of an enolate) and can be called enolate association. The product forming step is called reductive elimination which is in principle the reversal of oxidative addition in which an electron pair is returned to the metal (M^{n+2} to M^n). This coupling of ligands can be considered to proceed through a concerted mechanism.



Scheme 7. Nucleophilic substitution assisted by a transition metal

The options for such reactions are threefold:

1. The nucleophile is an organometallic reagent (Mg, Zn, Al, Sn, B or Cu reagents). An aryl halide is used as electrophile and a transition metal catalyst is used.
2. The nucleophile is generated with a base and is stabilized by an electron withdrawing group. This can be done *in situ* or a preformed alkali metal salt could be used. The electrophilic partner is an organometallic reagent (not aryl halide), for example a bismuth(V), lead (IV) or iodine(III) reagent.
3. The nucleophile is generated with a base and is stabilized by an electron withdrawing group (*in situ* or preformed alkali metal salt) or an alkene or alkyne and the electrophilic partner is an aryl halide and a transition metal

catalyst is used. This is the most direct route as it circumvents the use of stoichiometric main group reagents.

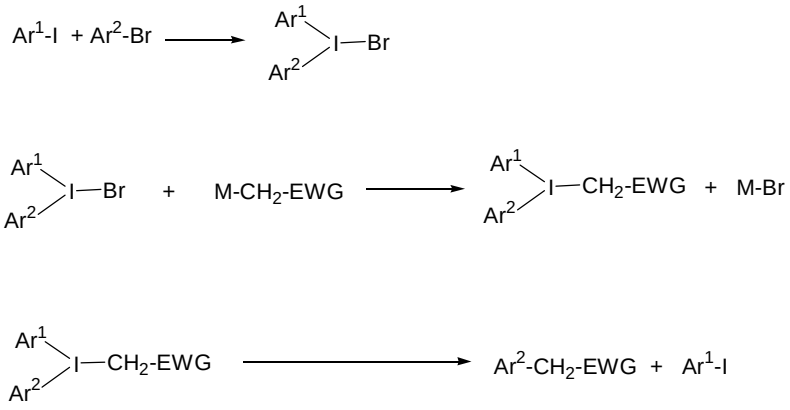
Many examples exist where the nucleophile during the arylation reaction is an organometallic reagent which is generated prior to the reaction and requires a stoichiometric amount of an organometalic reagent or main group element. These include the use of a Grignard reagent as the nucleophile (aryl and alkyl magnesium halides used in the Kumada coupling)[18], Reformatsky reagents (from α-haloacetate ester and zinc)[19], aryl, alkenyl and alkynyl zinc compounds as used in the Negishi coupling[10], organotin reagents in the Stille coupling[8,9] or the use of organoboron derivatives (as in the Suzuki coupling)[7]. These reactions will not be considered in the scope of this study as the use of large quantities of often expensive and toxic reagents cannot be tolerated from both an economical and environmental point of view in an industrial environment (although processes involving a Suzuki coupling have been implemented on a full-scale production plant[20,21]). The focus will, therefore, be placed on the direct arylation of active methylene compounds from which enolates are formed by deprotonation (addition of a base to the reaction mixture, see Scheme 1).

A large amount of research has also been dedicated to the arylation of active methylene compounds (as mentioned above) but using a preformed *ipso*-aryl cation in the form of a hypervalent orgonometallic complex. This type of reaction again employs a stoichiometric organometallic reagent and although these reagents are not attractive for the same reasons as given above, they are worth considering as in many respects these reagents are the stoichiometric forerunners of the catalytic use of transition metals. These reagents employ the same 2-electron switch mechanism as is used by phosphine complexes of palladium.

1.3.1 Hypervalent Iodine Compounds

Diaryliodonium salts (eg. Ph_2ICl) have been reacted with a number of active methylene or methane compounds. Generally, the *C*-arylated product predominates, although *O*-arylation has been observed[22]. The types of nucleophile that have been successfully *C*-

arylated include the readily enolisable β-diketones[22-24], β-ketoesters[25], and malonic esters[26,27]. Readily enolisable ketones, cyano ketones, esters and aliphatic nitro compounds have also been successfully arylated on the α-carbon[28,29].



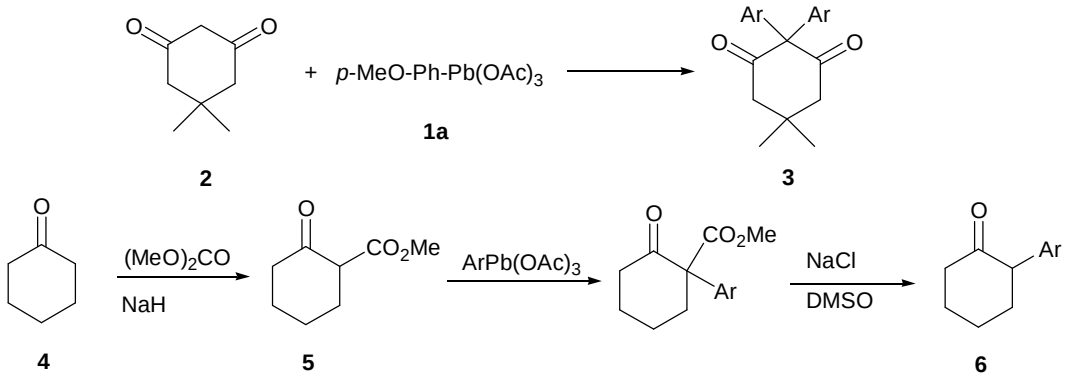
Scheme 8. Iodine (+I)/(-I) mediated enolate arylation reaction

The diaryliodonium salts can, theoretically, be seen as the oxidative addition product between an iodo arene and an aryl halide to use the analogy with transition metal catalysis (Scheme 8). The iodine central atom is regarded as being in the +1 oxidation state. When this complex reacts with a metal enolate it expels the metal halide to form a diaryliodonium salt of the enolate. Reductive elimination leads to the arylated methylene compound and leaves the reduced aryl iodide (in which iodine is in its -1 resting state). Since the formation of the iodonium salt does not take place by simple oxidative addition of iodine into an aryl halide bond, iodine cannot be used catalytically and requires at least a full equivalent of the pre-formed iodonium reagent. The possibility exists, however, of recycling the iodoarene through oxidation to its iodoso counterpart and subsequent regeneration of the diaryliodonium species.

1.3.2 Aryllead Reagents

The use of aryllead triacetates as arylating reagents has been pioneered by Pinhey and co-workers[30,31]. $ArPb(OAc)_3$ reacts with arenes in trifluoroacetic acid medium to give bi-aryls[32] and gives *ortho*-*C*-phenylated products by reaction with phenols[33,34]. More important for the purposes of this work, is the reaction with β-diketones, β-keto esters

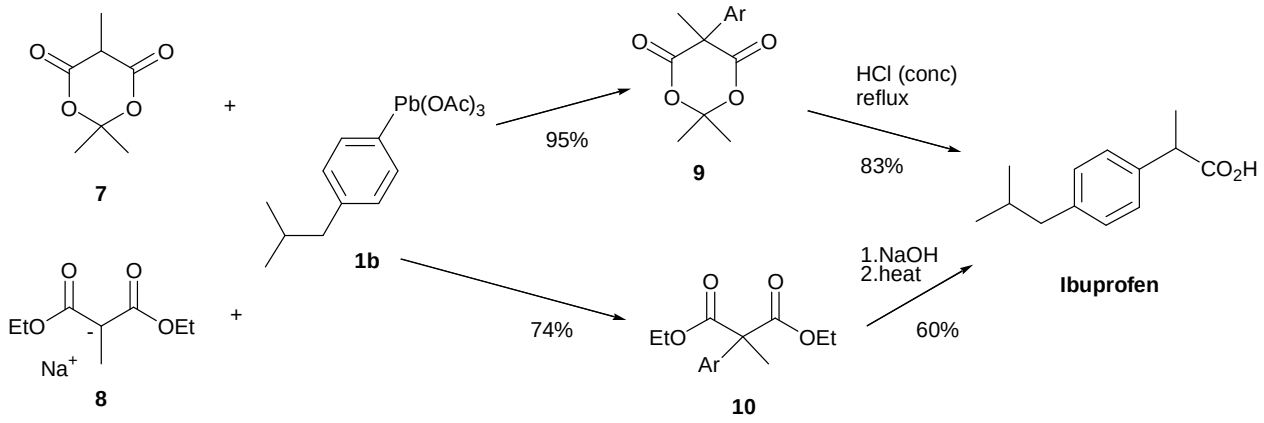
and malonic acid derivatives leading to α-arylated products[35-37]. *p*-Methoxyphenyllead triacetate **1** reacts with dimedone **2** in chloroform containing pyridine at 40°C to form 2,2-bis-*p*-methoxyphenyl-5-5-dimethylcyclohexan-1,3-dione **3** [35] (Scheme 9). 2-Arylcyclohexanones **6** may be prepared from cyclohexanone **4** by first preparing the β-ketoester **5** through treatment with sodium hydride and dimethyl carbonate followed by arylation with an aryllead triacetate and decarboxylation[36].



Scheme 9. Lead (III) mediated dimedone and cyclohexanone arylation

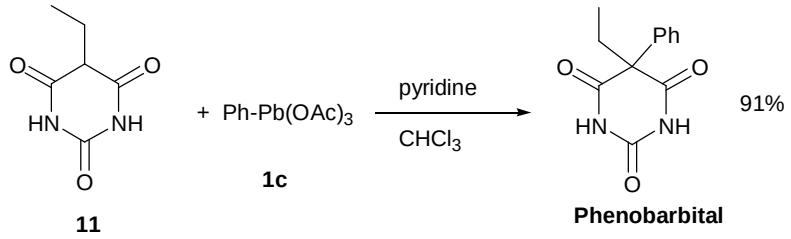
Another approach to obtaining α-arylated ketones is the arylation and base cleavage of α-hydroxymethylene ketones which proceeds in moderate to good yield[38] as well as enamine arylation[39].

Substituted malonic acid derivatives were found to react slowly under the same reaction conditions while the cyclic variants (substituted Meldrum's acids) gave high yields of the arylated products[37,40]. The synthetic usefulness of this reaction was demonstrated in a short and high yielding route to the important nonsteroidal anti-inflammatory drug, ibuprofen, from 2-methyl substituted Meldrum's acid **7** [37] (as shown in Scheme 10). The use of the sodium salt of substituted malonic acid esters in reaction with aryllead triacetates and pyridine overcame the initial problem of low reactivity observed for malonic acid esters[40] A similar yield for ibuprofen was demonstrated using the sodium salt of diethyl methylmalonate **8** [40].



Scheme 10. Synthesis of Ibuprofen from methyl Meldrum's acid **7** and diethyl methylmalonate **8**

Another synthetically useful application of this chemistry is the preparation of the anti-depressant drug, Phenobarbital, by direct phenylation of 5-ethyl barbituric acid **11** in high yield (Scheme 11)[37].



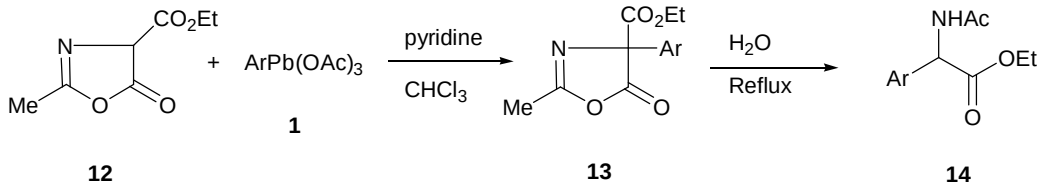
Scheme 11. Synthesis of Phenobarbital

An interesting feature of the aryllead arylation is the ability to form quaternary carbon centres. In almost all examples, tertiary carbanions reacted faster than the secondary counterparts[35-37,40]. For instance, Meldrum's acid and the sodium salt of diethyl malonate gave only very low yields of arylated products, while the phenyl, methyl or ethyl substituted starting materials were arylated in high yield in a facile reaction[37,40]. Barbituric acid could be arylated in good yield but again the reaction of the mono-arylated product was much faster as evidenced by the fact that the only product isolated was that of di-arylation even when only 1 equivalent of aryllead reagent was used[40].

It was later found that the use of chelating pyridine type bases as ligands or promoters for the reaction led to faster reaction rates and higher yields, even for rather inactive diethyl malonate and sterically hindered diethyl isopropylmalonate[40,41].

The lead chemistry was extended to ketone enolates, although primary and secondary enolates gave arylated products in low yield (<20%), tertiary centers were arylated in modest yields (up to 50%)[42].

This arylation technique was also applied to the preparation of α-aryl-*N*-acetylglycine derivatives by arylation of 4-ethoxycarbonyl-2-methyl-4,5-dihydro-1,3-oxazol-5-one **12** which is easily obtained from diethyl acetamidomalonate[42]. The arylated product is hydrolysed to yield the arylated *N*-acyl-glycine ethyl ester **14** (as shown in Scheme 12).



12 **13** **14**

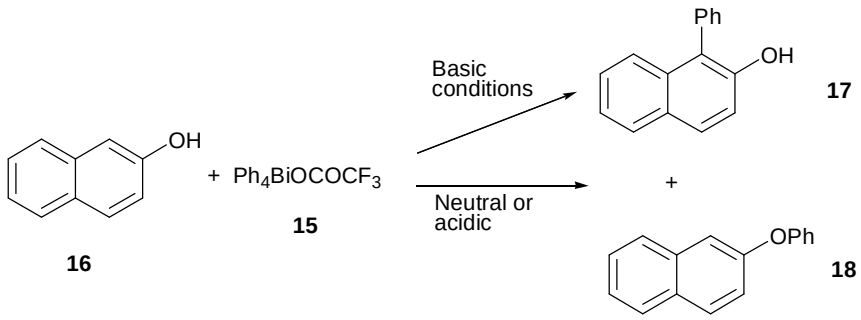
Scheme 12. Preparation of α-aryl *N*-acetylglycine ethyl esters **14** by aryllead chemistry

Nitroalkanes and nitronate salts also undergo α-arylation with aryllead triacetates in DMSO solution, the reaction being high yielding and general in the absence of steric hinderance[43].

1.3.3 Organobismuth Reagents

Organo bismuth compounds exist in two main forms namely a trivalent Bi(III) complex with a pair of non-bonded *s*-electrons or a pentavalent Bi(V) complex. Ph_3BiX_2 is the most common organobismuth reagent from which a number of arylation reagents have been established. The reaction of Ph_3BiCO_3 with a number of enolisable substrates such as phenols, cyclic β-keto esters and the pre-formed enolate of cyclohexanone led to α-phenylated products[44,22]. It was later found that Ph_5Bi was a

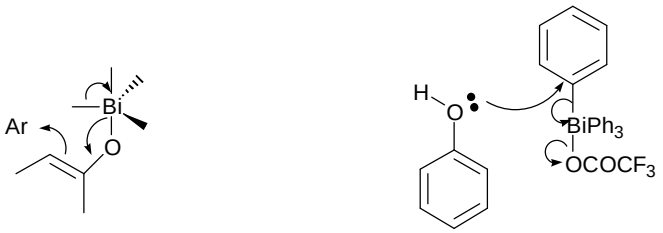
more selective phenylating reagent[45,44]. A competitive reaction to *C*-phenylation is the corresponding ether formation which was thought to be influenced by the electron withdrawing or donating nature of the fifth substituent in the intermediate bismuth complex. It was, however, concluded that *C* vs *O*-phenylation could be controlled by the presence of a base or acid (see Scheme 13).



Scheme 13. *C* vs. *O*-phenylation of 2-naphthol **16**

$Ph_4Bi(OCOCF_3)$ was found to be an excellent reagent for *ortho* or α-*C*-phenylation of a wide range of substrates such as phenols, enols, ketones, and β-diketones under basic conditions[46,27-29]. The same reaction under neutral conditions gave mixtures of *C* and *O*-phenylated products **17** and **18** while addition of an acid led to mainly the *O*-phenylated products **18**. It was subsequently found that the pivotal bismuth compound, Ph_3BiCl_2, was itself a good, high yielding reagent for *ortho* or α-*C*-phenylation in the presence of a suitable base[46,27].

Studies have shown that the *C*-phenylation reaction is not an ionic process, and that the intermediate is unlikely to undergo reductive elimination by a free-radical pathway, but does so by a non-synchronous concerted mechanism[47](Figure 1). ESR spectroscopy has also ruled out the possibility of a free-radical pathway[48]. The *O*-phenylation reaction of the other hand is believed to follow an aromatic S_N2-type pathway involving nucleophilic attack by the phenol at the bismuth bearing aromatic carbon[46]. This carbon has a partial positive charge resulting from the presence of an electron-withdrawing group on the bismuth atom.



C-phenylation

O-phenylation mechanism

Figure 1. *C* vs. *O*-phenylation mechanism

Although these early examples of enolate arylation were useful as synthetic tools and were quite general in the aryl fragments and enolisable substrates, the requirement for stoichiometric amounts of toxic and expensive reagents which had to be specifically prepared, made these techniques impractical. To avoid this, the reaction had to be made catalytic requiring a catalyst able to undergo a 2-electron shift to first insert into the aryl halogen bond (addition of 2 anionic ligands, see Scheme 14). The catalyst has to be returned to its initial oxidation state during product formation (reductive elimination of 2 anionic ligands). The catalyst should be able to perform this cycle many times to minimise the loading required.



Scheme 14. 2-electron shift reactions to allow for catalyst regeneration

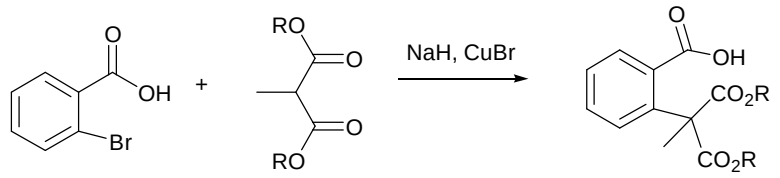
1.4 Transition Metal Catalysed Enolate Arylation

Early examples of the use of transition metals to perform the role of catalyst have been classified according to the type of metal catalyst used.

1.4.1 The use of Copper salts

The first example of a metal catalysed reaction between an aryl halide and an enolate was the so-called Hurtley reaction[49]. This reaction, which was reported as far back as

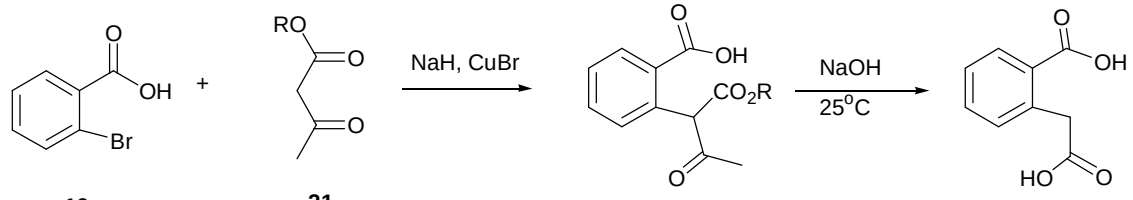
1929, involved the coupling reaction of *o*-bromobenzoic acid with the sodium salts of various β-dicarbonyl compounds in boiling ethanol in the presence of copper acetate. The reaction between *o*-bromobenzoic acid and acetylacetone, cyclic diketones, malonate esters, β-ketoesters, cyanoacetate esters and malononitrile have been studied by a number of groups[50-52]. Bruggink and McKillop investigated other reaction conditions and came to the conclusion that the reaction is best performed using an excess of the dicarbonyl compound with sodium hydride and 5-10mol% CuBr in the absence of solvent[51]. For larger scale reactions the reaction mixture could be diluted with toluene. Both *o*-bromo- and chlorobenzoic acid **19** gave high yields using these improved conditions.



19a **8** **20**

Scheme 15. Copper catalysed direct arylation substituted malonate esters with 2-bromobenzoic acid

Decarbonylation of the α-arylation product of dicarbonyl species (such as **22**, see Scheme 16) by a retro-Claisen mechanism has been observed under classical Hurtley reaction conditions[50-52]. This reaction is promoted by ethoxide or hydroxide ion and was not observed when the NaH method was used. Although this is a complication in most instances it has been used to prepare homophthalic acids **23** [52].

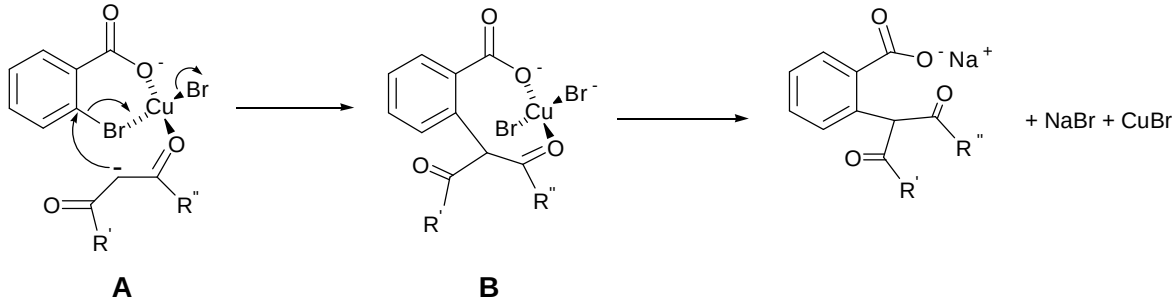


19a **21** **22** **23**

Scheme 16. Preparation of homophthalic acid by copper catalysed arylation followed by base-mediated retro-Claisen reaction

The reaction was found to be limited to enolates containing a β-carbonyl group although cyanoesters also gave moderate arylation yields. Reactions with other soft enolates like those obtained from nitroalkanes, dimethylsulfoxide or cyclopentadiene were unsuccessful.

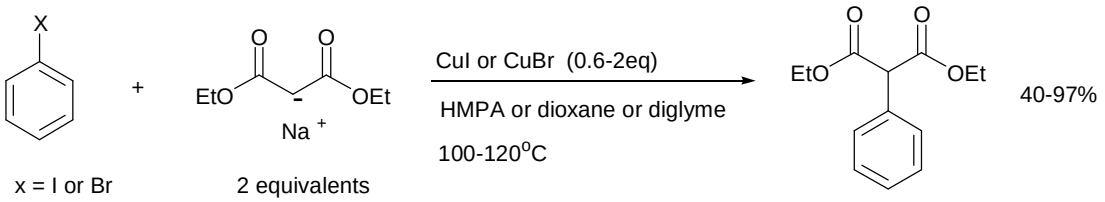
Apart from *o*-bromobenzoic acid and substituted variants thereof, 2-bromonicotinic acid could also be used but with more limited scope[53]. Attempts to utilise other *o*-haloaryl compounds, 2-BrC_6H_4X (X = CO_2Et, $CONH_2$, CH_2OH, NO_2, CHO, CN, SO_3H, CONHOH) in this reaction failed while low activity was observed with 2-bromophenylacetic acid[52]. The reaction is further limited to *ortho*-substituted bromobenzenes as the *meta* and *para* substituted isomers were unreactive[54]. From these results it was concluded that the reaction is dependant on the ability to form a copper chelate. The halide is activated towards nucleophilic displacement by polarisation of the C-Br bond by the copper chelate **A**, reinforced by electron withdrawal by the carboxylate group, and therefore making it a chelation assisted S_NAr mechanism (Scheme 17).



Scheme 17. Chelation assisted S_NAr mechanism

In 1981, Setsune *et al* reported the copper catalysed coupling of the sodium salt of diethyl malonate with unactivated aryl iodides and bromides[55]. The phenylated malonate ester **24** was obtained in between 60 and 70% yield in HMPA, diglyme and dioxane solution at 100-120^oC using 1.2 equivalents of CuI (Scheme 18). The yield of diethyl phenylmalonate **24** could be improved to as high as 97% by using 2 equivalents of both sodium diethylmalonate and CuI. The air-sensitive CuBr was found to be a more active catalyst and led to 60% **24** using only 0.5 equivalents catalyst while only

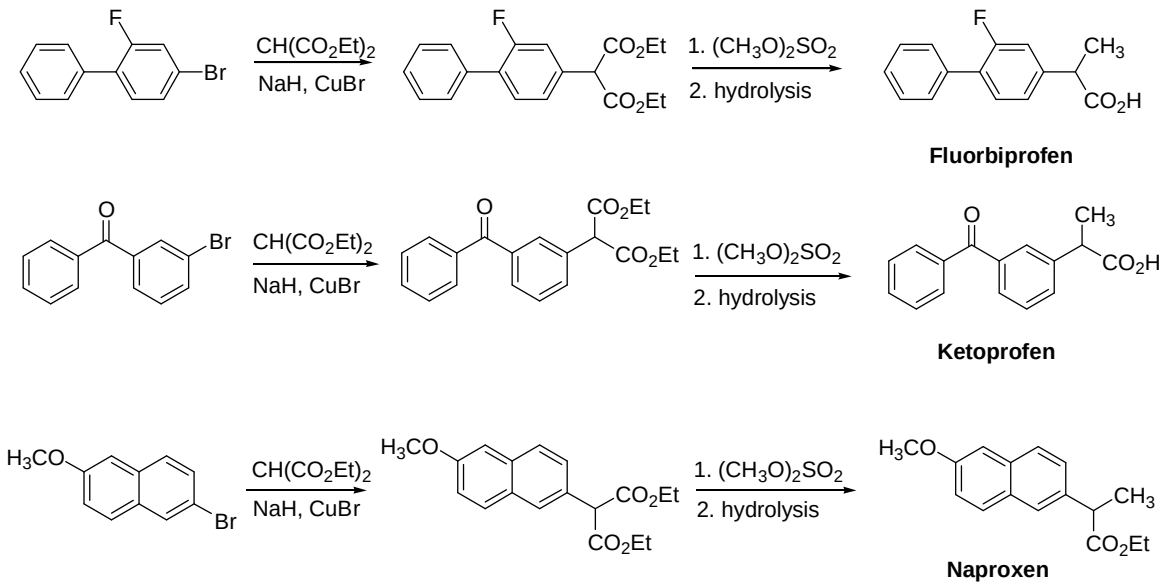
38% was achieved using CuI. The addition of triphenylphosphine as a ligand for copper severely retarded product formation. Bromobenzene was less active at 43% using 1.2 equivalent CuBr. In contrast to the observations made during the Hurtley investigations, electron withdrawing substituents like NO_2, $COCH_3$, CO_2CH_3 led to increased yields when in the *ortho* position and to lesser extent in the *para* position.



Scheme 18. Copper catalysed diethyl malonate arylation

Similar results were reported by Suzuki and Osuka for the sodium salt of ethyl cyanoacetate but yields were generally lower and required the use of 2 equivalents of sodium salt and CuI[56].

In 1992, Ugo *et al* described the application of the Setsune protocol for the preparation of a number of the α-arylpropionic acid anti-inflammatory agents[57]. The arylated malonate esters were methylated using dimethyl sulfate and potassium carbonate followed by caustic hydrolysis and decarboxylation upon acidification to yield α-arylpropionic acids. High enol to aryl bromide ratios were used and more than equimolar amounts of CuBr were required to prepare Fluorbiprofen in 46%, Ketoprofen in 70% and Naproxen in 36% total yield (Scheme 19).



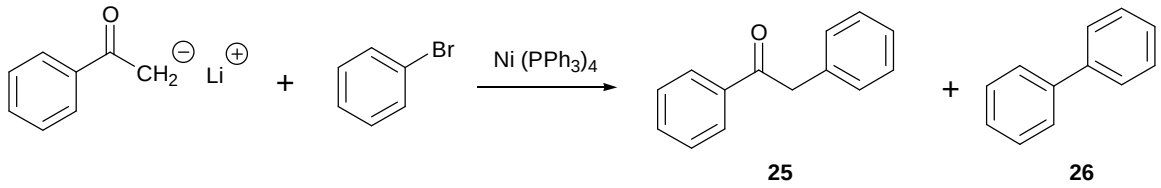
Scheme 19. Preparation of α-arylpropionic acid anti-inflammatory agents via copper-catalysed malonate arylation

The first example of a truly catalytic copper arylation of active methylene compounds was released by Miura *et al* in 1993[58]. Following on a successful CuI – PPh_3 catalysed arylation of terminal alkynes[59], it was found that catalytic amounts of copper (10mol%) were sufficient to obtain ethyl arylcyanoacetate in high yield from ethyl cyanoacetate and iodobenzene when the reaction was performed in DMSO solution using K_2CO_3. Lower yields were obtained with malononitrile and acetylacetone, diethyl malonate is thought to be unstable under the conditions (120^{o}C) explaining its omission from the report. Again the use of triphenylphosphine decreased the product yield.

Buchwald reported a copper catalysed arylation of diethyl malonate with aryl iodides using 2-phenylphenol as a co-catalyst (this will be further discussed in later chapters)[60].

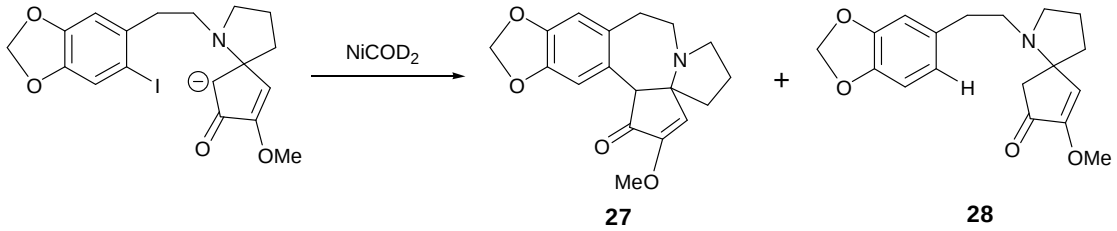
1.4.2 Nickel Catalysed Arylations

The first example of a nickel catalysed arylation reaction involving a non-organometallic carbon enolate was reported by Semmelhack in 1973[61]. The lithium salt of acetophenone was coupled with bromobenzene in the presence of tetrakis-(triphenylphosphine)Ni(0) (Scheme 20).



Scheme 20. Nickel catalysed arylation of acetophenone

This reaction was described as inefficiently catalytic as 14mol% catalyst gave only a 50% conversion of the aryl halide of which 65% was converted into benzylphenyl ketone **25** (~2-2.5 catalyst turnovers). The formation of biphenyl **26** was the major competing reaction (also referred to as homocoupling). The same group also described an intramolecular version of this reaction as part of the total synthesis of cephalotaxinone **27**[61,62] (see Scheme 21). Again the reaction yield was low (30% **27**) and stoichiometric nickel was used, in this instance the major competing reaction was the reductive dehalogenation of the substrate (to give **28**) which is related to homocoupling and predominates where steric hindrance prohibits the latter reaction.

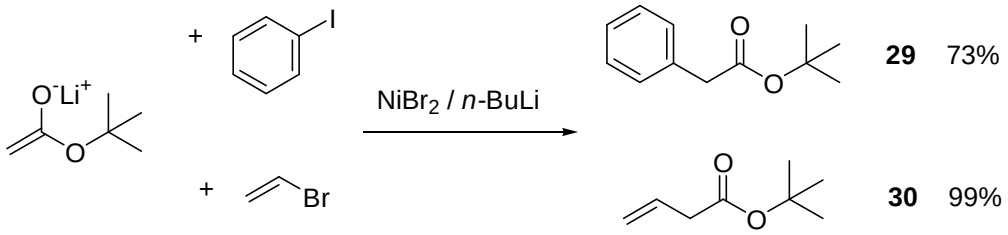


Scheme 21. Nickel catalysed ketone arylation applied to Cephalotaxinone synthesis

It was noted by the authors that the same reaction could be performed more successfully by a $S_{RN}1$ mechanism by generating the aryl radical either by alkali metal reduction (KNH_2, Na/K in liquid NH_3, 45% yield) or irradiation (94% yield). These results may explain why the nickel catalysed enolate arylation attracted little attention at that time.

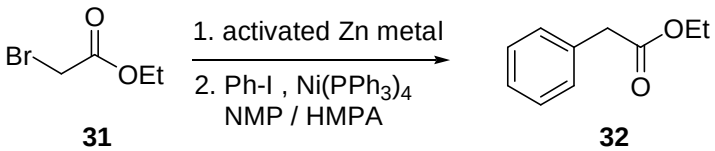
The next example of a nickel metal catalysed arylation reaction was by Millard and Rathke in 1977 [63]. They reported nickel catalysis in the vinylation and arylation of lithium ester enolates. $NiBr_2$ was used in stoichiometric amount and was treated with *n*-butyllithium prior to introduction of the vinylbromide or iodobenzene and the

preformed lithium salt of *tert*-butyl acetate. The vinylation yields were as high as 99% (**30**) while the arylation using iodobenzene proceeded in 73% yield (**29**) while bromobenzene could be coupled in only 41% yield and chlorobenzene was virtually inactive (Scheme 22). The catalytic nature of this reaction was demonstrated by obtaining a 70% vinylation yield while using 20mol% $NiBr_2$. Although it is expected that a Ni(0) species is the active catalyst (by reduction with *n*-butyllithium), tetrakis(tri-*n*-butylphosphine)Ni(0) was not an active catalyst.



Scheme 22. Nickel-catalysed arylation and vinylation of *t*-butyl acetate

In 1979 Fauvarque and Jutand reported on the catalysis of the arylation of the Reformatsky reagent ($BrZnCH_2CO_2Et$)[19]. The reaction is reported to proceed smoothly when using a soluble Ni(0) complex in polar aprotic solvent (Scheme 23). Good yields for ethyl phenylacetate **32** were obtained after 3 hours at 45°C by using 10mol% tetrakis(triphenylphosphine)Ni(0) and a 2:1 ratio of enolate to aryl halide. Aryl iodides, bromides and chlorides are all active under the conditions although the best yields were obtained using aryl iodides. The choice of the aprotic solvent, which is used in a 1:1 mixture with dimethoxymethane (in which the organo-zinc reagent is prepared), is important to make the nickel species homogenous. HMPA and NMP were found to be the best solvents. The most active catalyst was found to be $Ni(PPh_3)_4$ and was best prepared *in situ* by reducing $NiCl_2(PPh_3)_2$ with ethylmagnesium bromide in the presence of 2 equivalents of triphenylphosphine. The same group reported the use of palladium in the same reaction but, in general, yields were lower - especially when using aryl bromides and chlorides.



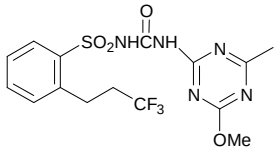
Scheme 23. Ni(0) – catalysed arylation of the Reformatsky reagent

1.5 Palladium Catalysed Arylations

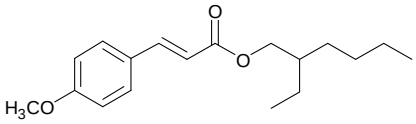
1.5.1 The Heck Reaction

The palladium catalysed arylation and alkenylation of olefins, known as the Heck or Mizoroki-Heck reaction, was discovered by Mizoroki[64] in 1971 and by Heck[65] in 1972. Heck developed this reaction in a number of fundamental papers followed by numerous other researchers to a point where the Heck reaction is now an indispensable tool in organic chemistry. Several reviews have been written on the subject and a wealth of information is known about the reaction mechanism and the catalytic cycle[66-75]. Heck olefination has found several applications in the production of fine chemicals[76].

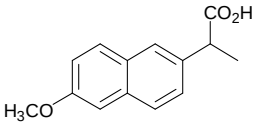
Examples are:



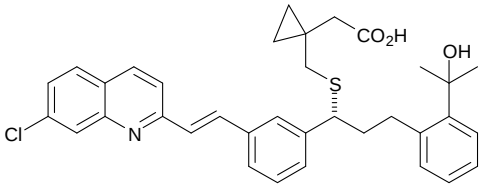
Prosulfuron™ (herbicide)



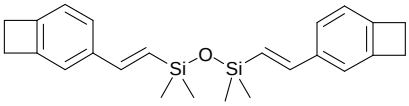
2-Ethylhexyl *p*-methoxycinnamate or OMC (UV-B sunscreen)



Naproxen™ (non-steroidal anti-inflammatory drug, NSAID)



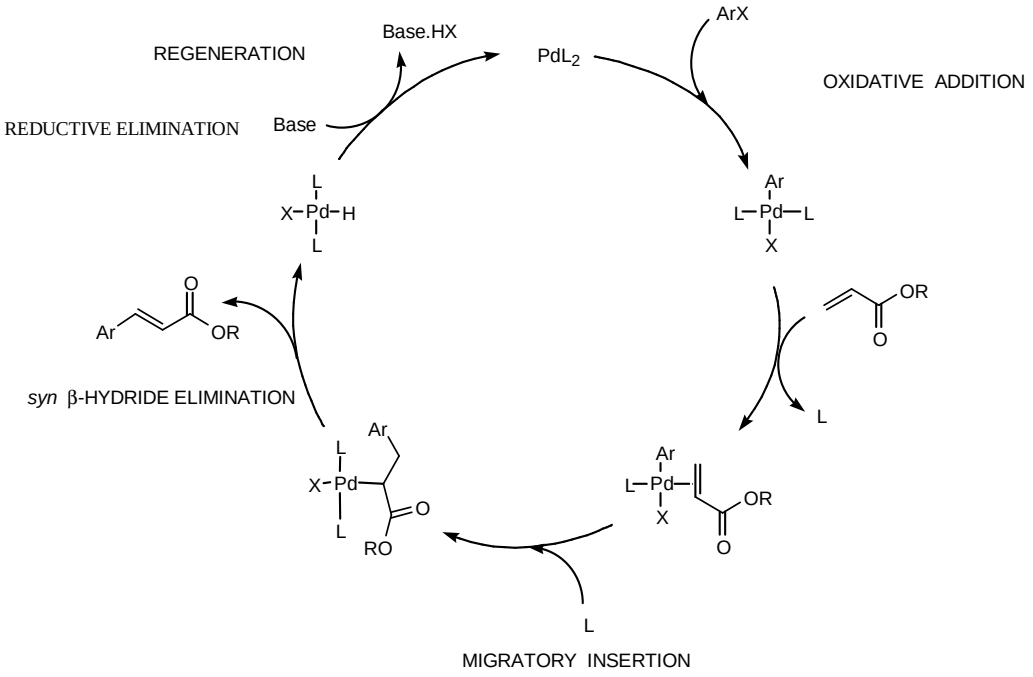
Singulair™ (anti-asthma drug)



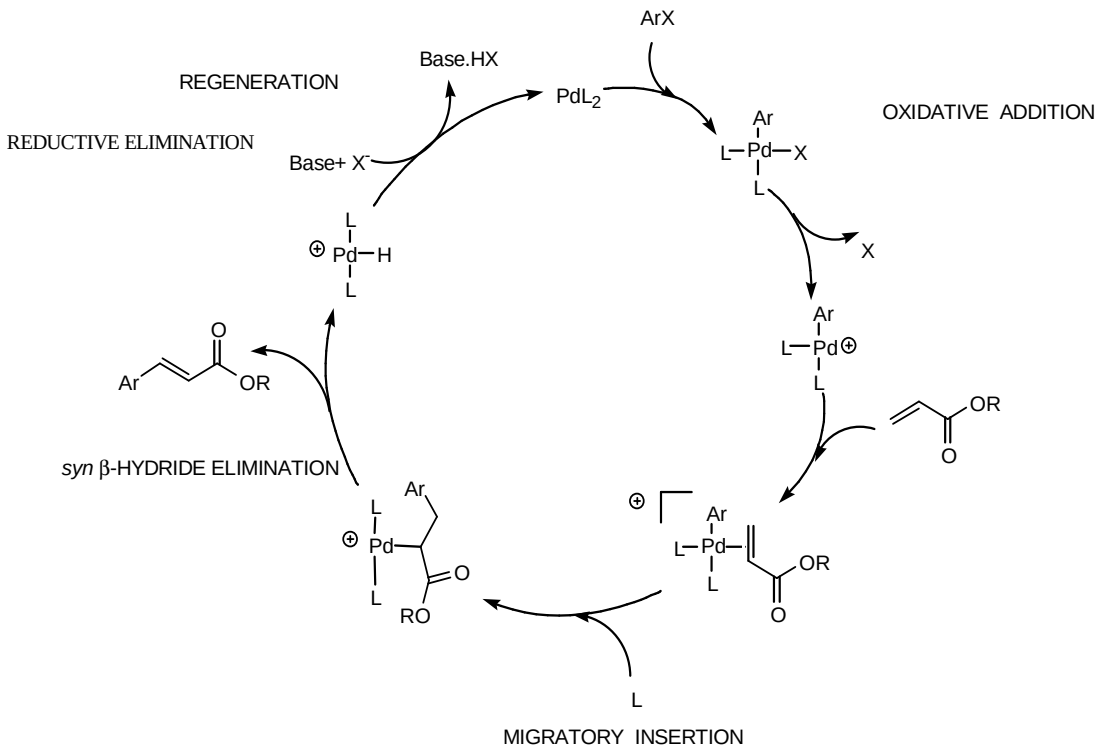
Cyclotene™ (monomers for coatings of electronic components)

Scheme 24. Example of fine chemicals produced using a Heck procedure

Reactivity in the Heck reaction relies heavily on the ability of Pd(0) species to undergo oxidative addition to Ar-X bonds to form a ArPd(II)X speices. A number of mechanistic possibilities have been proposed to fit experimental data of which the traditional (Scheme 25) and the cationic mechanism (Scheme 26) are the best known.

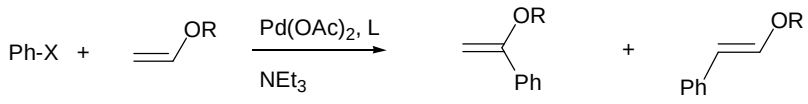


Scheme 25. Traditional mechanism of the Heck reaction



Scheme 26. Cationic mechanism for the Heck reaction

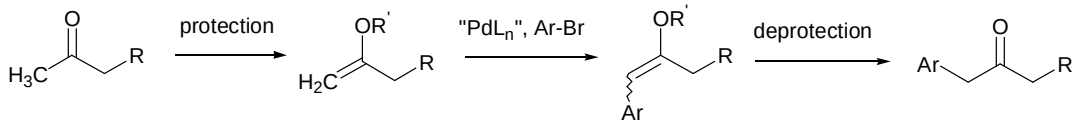
The β-substitution (insertion at the terminus of the alkene) is observed for olefins with electron withdrawing substituents (Michael acceptors) while α-selectivity (insertion at the more substituted end of the alkene) is common for electron-rich olefins such as enol ethers. The use of either mono-phosphines or chelating ligands may however alter the regioselectivity in especially electron-rich olefins[74] (Scheme 27).



Major	Minor	L = monodentate phosphine
Minor	Major	L = bidentade phosphine

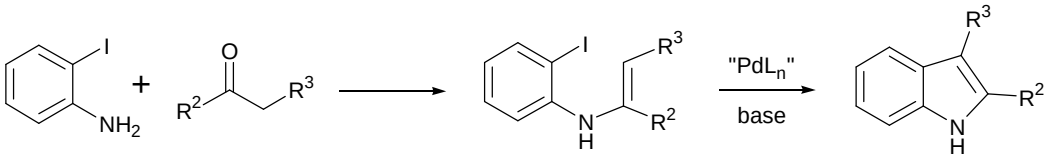
Scheme 27. Regioselectivity in the arylation of enol ethers

Palladium catalysed arylation of masked ketones has been achieved using a Heck-type approach. Enol ethers and silyl enol ethers are common Heck substrates and form the arylated enol ether which is the protected form of an α-arylketone[77-79,74] (Scheme28).



Scheme 28. Ketone arylation via Heck reaction of an enol ether

A novel synthesis of 2,3-disubstituted indoles via a palladium catalysed annulation between iodoaniline **33** and ketones was published by Chen *et al* [80] (Scheme 29). This approach depends on *in situ* enamine **34** formation followed by intramolecular Heck reaction to form the indole **35**. The scope of ketones that may be used in this reaction is broad as the intramolecular Heck reaction is more facile and less affected by steric hindrance than the intermolecular variant.

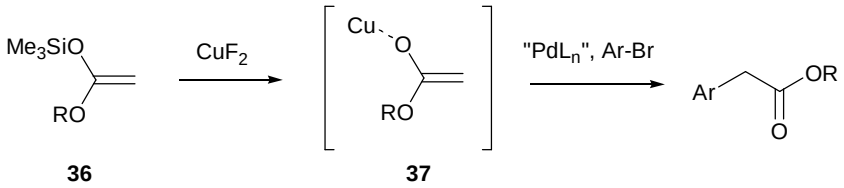


33 **34** **35**

Scheme 29. Intramolecular Heck reaction in the formation of 2,3-substituted indoles **35**

1.5.2 Palladium Catalysed Arylation through Transmetallation of Covalent-bonded Enolates

Another approach involving enols or ketene acetals to effect enolate arylation is through transmetallation of covalent-bonded enolates (Si, Sn,etc., enol ethers). It is interesting to note that Agnelli and Sulikowski[81] were able to couple trimethylsilylketene acetals **36** with aryl triflates or halides in the absence of the previously used thallium acetate[82] or tributyltin fluoride[83]. They used CuF (stoichiometric amounts) to form the copper enolate **37** from the silylketene acetal which was arylated in the presence of a palladium complex (Scheme 30).

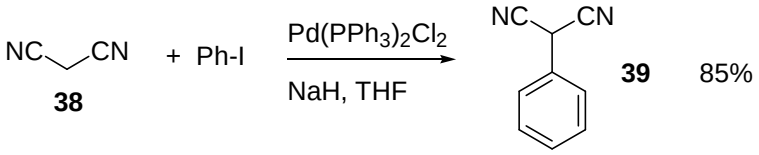


36 **37**

Scheme 30. Copper mediated palladium catalysed silylketene acetal arylation

1.5.3 Palladium Catalysed Enolate Arylation

In 1984 Takahashi and co-workers published results on the arylation of malononitrile **38** using a palladium catalyst[84,85]. This was the first example of a palladium catalysed intermolecular coupling involving a soft dicarbonyl type enolate. They used 14mol% of $(PPh_3)_2PdCl_2$ and prepared the malononitrile anion *in situ* with sodium hydride (Scheme 31). Refluxing in THF for 4 hours gave good yields (80-90%) of the corresponding arylmalononitrile **39**. The examples are limited to aryl iodides with the exception of an activated aryl bromide which required higher catalyst loading and gave lower yield (~50%). The methodology developed was applied in the synthesis of dioxabrinanes[86,87]. The analogous nickel catalysts were inactive.

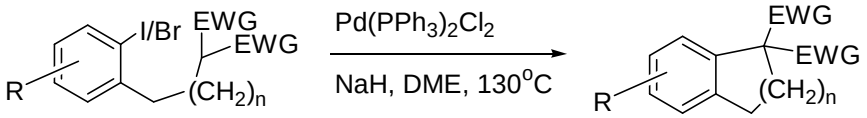


38

Scheme 31. First palladium catalysed arylation of malononitrile **38** by Takahashi

The work of Takahashi was followed up by Ciufolini *et al* in 1988 with an intramolecular variant of the Takahashi procedure on a variety of dicarbonyl compounds[88]. β-Ketoesters, β-diketones, cyanoacetates, malononitriles, malonate esters and α-sulfonyl esters were coupled in moderate yields with aryl iodides giving 10-15% higher yields than aryl bromides. It was reported further that, except for malononitrile and cyanoacetate esters, none of the substrates were active in intermolecular reactions with aryl halides. Another major limitation of these reactions was the use of DMF as solvent and high temperatures (135^{o}C) which could explain lower yields as many dicarbonyl compounds are known to decompose at elevated

temperature. The conditions employed by Takahashi were, therefore, superior from both a technical and environmental point of view.



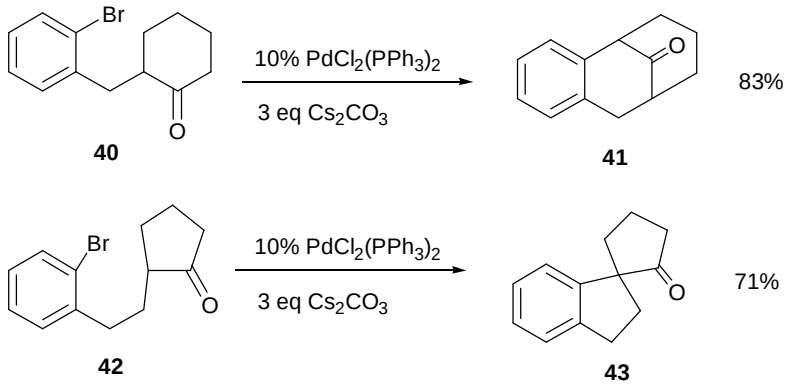
EWG = CO_2R, CN, COR, SO_2R; n = 1 or 2

Scheme 32. Palladium-catalysed intramolecular arylation of β-dicarbonyl compounds

1.6 Recent Development in Palladium Catalysed Arylation

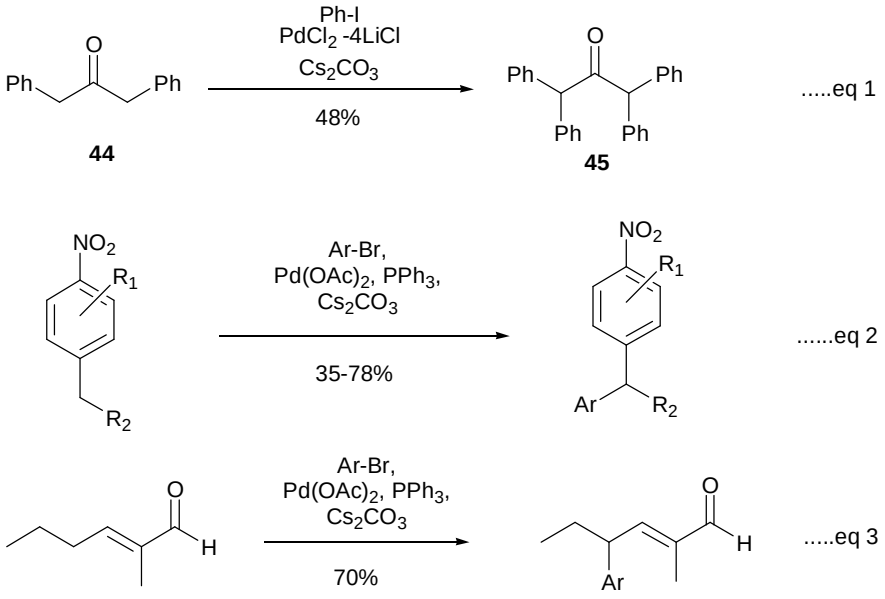
Almost a decade later, enolate arylation and specifically ketone arylation appeared to attract much attention as no less than 5 papers on the subject were released in 1997 [89-93].

Murutake and Natsume published the palladium catalysed intramolecular arylation of aliphatic ketones[93]. A number of 2-bromobenzyl-substituted cycloalkanones (like **40**, see Scheme 33) were converted into the bridged tricyclic species **41** while 2-bromophenethyl and 3-(2-bromophenyl)-propyl cyclohexanones gave the spiro compounds (**42** to **43**). 10mol% $PdCl_2(PPh_3)_2$ and 3 equivalents Cs_2CO_3 in hot toluene or THF were used and moderate to good yields of the arylated products were attained with dehalohydrogenation being the major side reaction.



Scheme 33. Palladium catalysed intramolecular ketone arylation

Miura and co-workers reported an example of an intermolecular diarylation of a ketone using an unligated Pd(II) species[89]. The coupling reaction between 1,3-diphenylacetone **44** and iodobenzene gave 1,1,3,3-tetraphenylacetone **45** in 48% yield using 5 mol% $PdCl_2$-4LiCl and Cs_2CO_3 (see Scheme 34, eq 1).



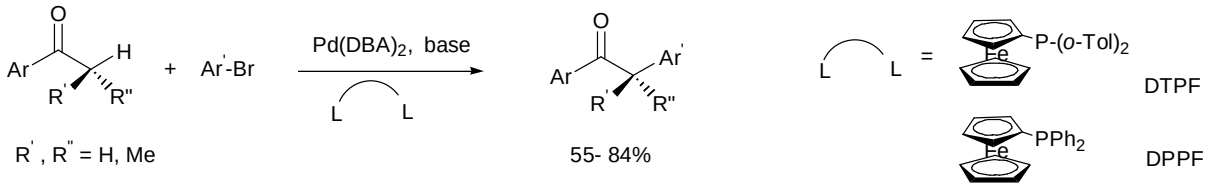
Scheme 34. Palladium catalysed arylation of *p*-nitrobenzyl compounds and α,β-unsaturated aldehydes

This work was followed up in 1998 with the arylation of *p*-nitrobenzyl compounds (Scheme 34, eq 2) and α,β-unsaturated carbonyl derivatives (eq 3) by aryl bromides using $Pd(OAc)_2$ and PPh_3[94,95]. The α,β-unsaturated carbonyl derivatives were selectively arylated in the γ-position even when the α-position was open for arylation (eq 3).

Also published in 1997 were two similar papers by the research groups of Buchwald and Hartwig[90,91]. These reports were preceded by successes achieved by both groups in the fields of palladium catalysed aromatic amination and etherification reactions.

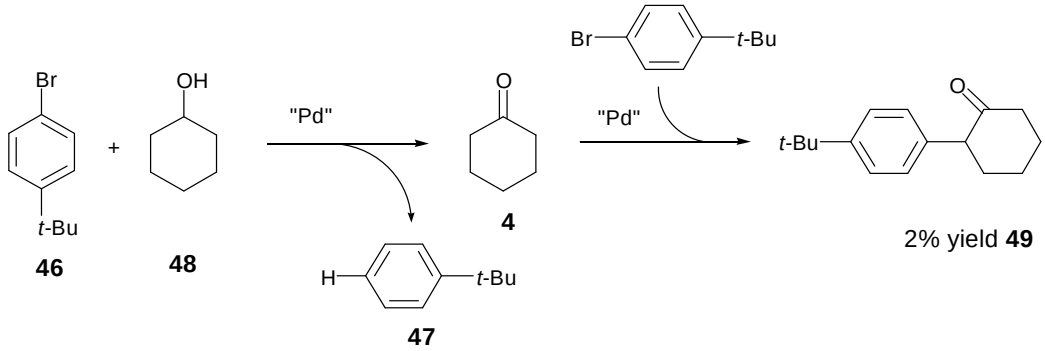
It was during an amination reaction performed in acetone medium that Hartwig observed *C*-arylation as a side-reaction[2]. This discovery prompted an appreciation of the similarity of the p*K*a values of arylamines and ketones[96] and the reactions of a

number of aryl methyl ketones with aryl iodides and bromides were investigated. High yields of the monoarylated ketone were obtained by using $Pd(dba)_2$ (dba = dibenzylidene acetone) and bis(diphenylphosphino)ferrocene (DPPF) and the tolyl derivative thereof (DTPF) (Scheme 35). $KN(SiMe_3)_2$ was used as the base but it was later found that sodium *tert*-butoxide could be used to similar effect.



Scheme 35. First ketone arylation by Hartwig *et al*

Buchwald was able to perform similar reactions using the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand and more effectively by using 2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (Tol-BINAP)[90]. Ketone arylation was also discovered by accident in the Buchwald laboratories: after successfully coupling electron-deficient aryl bromides with *in situ* prepared sodium alkoxides using $Pd_2(dba)_3$ and Tol-BINAP, ketone arylation was detected during a failed attempt to couple an electron-rich aryl bromide with a sodium alkoxide (Scheme 36). During this reaction the aryl bromide **46** was reduced to the arene **47** with concomitant oxidation of the alcohol (cyclohexanol **48**) to the corresponding ketone (cyclohexanone **4**). The observation in this reaction of a small amount of the α-arylketone **49** prompted the further investigation of this reaction to optimise the preparation of α-arylketones.

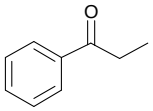
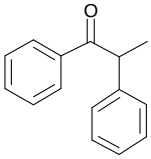
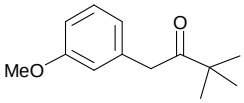
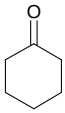
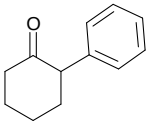
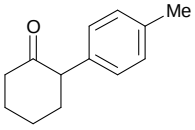
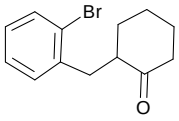
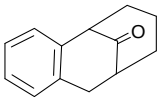
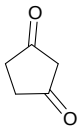
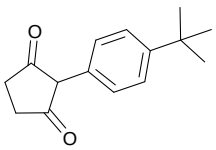
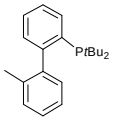


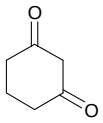
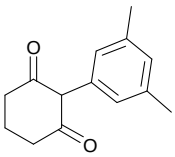
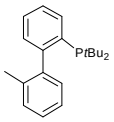
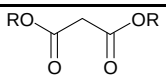
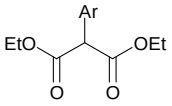
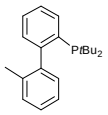
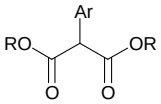
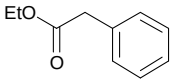
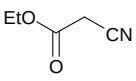
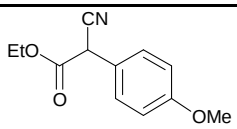
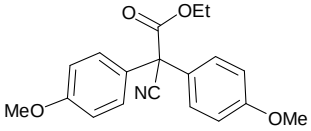
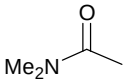
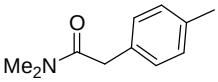
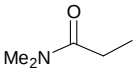
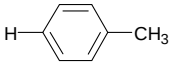
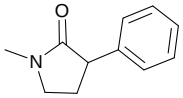
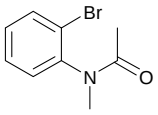
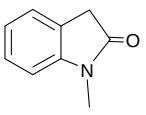
Scheme 36. Arylation of cyclohexanone **4** during palladium catalysed ether formation

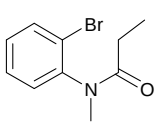
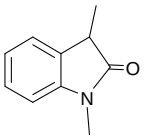
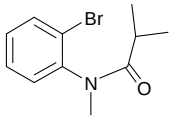
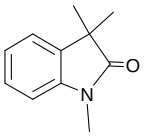
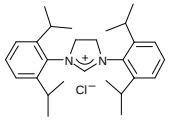
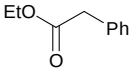
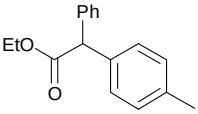
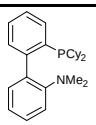
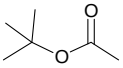
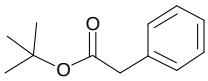
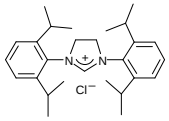
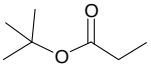
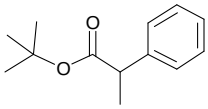
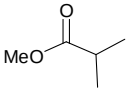
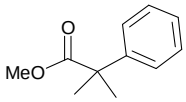
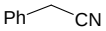
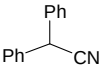
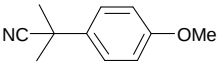
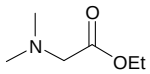
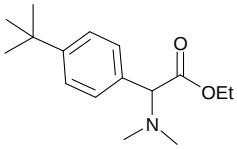
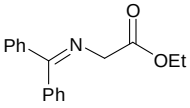
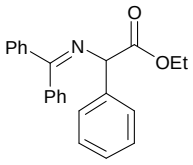
Since these initial groundbreaking publications several more papers have been published describing numerous examples of enolate arylation by using several new and existing bulky and electron rich phosphine ligands under varying reaction conditions. The arylation of malonate esters and cyclic diketones has also been described [97-100], followed by papers describing, amongst others , the arylation of cyanoacetate esters [101,97], amides (intra and inter molecular)[102,103], nitriles[104,105], nitroalkanes[106], esters[107-109] and even protected amino acid derivatives[108,110,111].

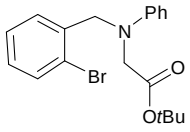
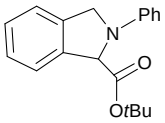
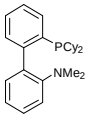
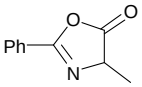
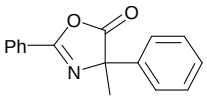
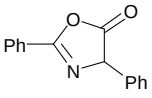
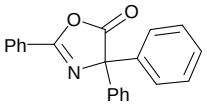
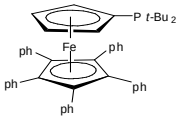
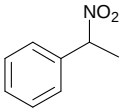
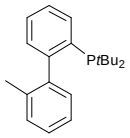
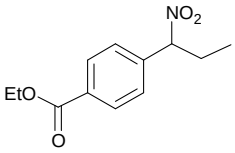
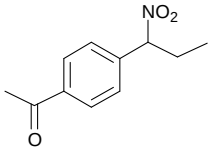
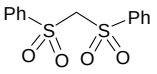
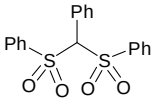
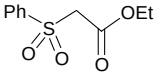
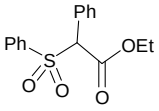
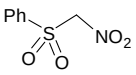
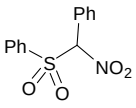
The different classes of enolate precursors that have been arylated by palladium complexes are depicted in **Table 1**.

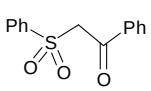
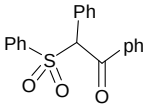
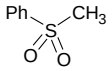
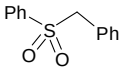
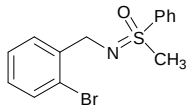
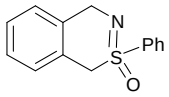
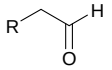
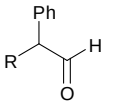
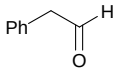
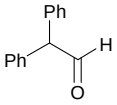
Table 1. Examples of the arylation reactions of various types of enolates with aryl bromides

Entry	Substrate	Product and yield (diarylation in parenthesis) *		Ligand	Base	Reference
	KETONES					
1			98%	None	NaO*t*Bu	Hartwig 1999[99]
2			68%	None	NaO*t*Bu	Buchwald 2000[100]
3			73%	*t*-Bu_3P	NaO*t*Bu	Hartwig 1999[99]
			Ar-Cl 59%	*n*-$BuPAd_2$	K_3PO_4	Beller 2002[1]
4			83%	PPh_3	Cs_2CO_3	Murataki 1997[93]
5			96%		K_3PO_4	Buchwald 2000[100]

Entry	Substrate	Product and yield (diarylation in parenthesis) *			Ligand	Base	Reference
6				84%		K_3PO_4	Buchwald 2000[100]
	MALONATE ESTERS						
7				80%	*t*-Bu_3P	NaO*t*Bu	Hartwig 1999[99]
	R = Ethyl	Ar = Phenyl					
8		Ar = 4-*t*-Bu-Phenyl		92%		K_3PO_4	Buchwald 2000[100]
9	R = *t*-Butyl	 R = *t*-Butyl Ar = Phenyl	Ph-Br Ph-Cl	89% 88%	*t*-Bu_3P	NaH	Hartwig 2002[97]
10	R = Ethyl		Ph-I Ph-Br	87% 78%	*t*-Bu_3P	Cs_2CO_3	Kondo 2001[98]
	CYANOACETATES						
11			Ar-Br Ar-Cl	89% 90%	*t*-Bu_3P	Na_3PO_4	Hartwig 2002[97]
12				(93%)			
	AMIDES						
13				72% (10%)	BINAP	KHMDS (2 eq.)	
14				-	BINAP	KHMDS (2 eq.)	
15				49 (9)	BINAP	KHMDS (2 eq.)	Hartwig 1998[102]
16				60%	BINAP	NaO*t*Bu	

Entry	Substrate	Product and yield (diarylation in parenthesis) *			Ligand	Base	Reference
17				52%	BINAP	NaO*t*Bu	
18				75%	BINAP		
19				99%	 (SIPr)	NaO*t*Bu	Hartwig 2001[103]
20				99%	PCy_3		
	ESTERS						
21				85%		LiHMDS	Buchwald[107] 59
22				87%		LiHMDS	Hartwig 2001[108]
23			Ph-Br Ph-Cl	75% 71%	SIPr	NaHMDS	
24				87%	t-Bu_3P	$LiNCy_2$	Hartwig 2002 [109]
	NITRILES						
25				47%	PPh_3	Cs_2CO_3	Miura 1998[104]
26	CH_3CN			(62%)	BINAP	NaHMDS	
27				85%			Hartwig 2002[105]
	AMINO ACID DERIVATIVES						
28				84%	t-Bu_3P	K_3PO_4	Hartwig 2001[108]
29			Ph-Br Ph-Cl	88% 82%	t-Bu_3P	K_3PO_4	

Entry	Substrate	Product and yield (diarylation in parenthesis) *		Ligand	Base	Reference
30			79%		LiO*t*Bu	Buchwald 2002[110]
31			85%	Ad_2P*t*Bu	K_3PO_4	Hartwig 2003[111]
32			55%	Ad_2P*t*Bu	K_2CO_3	
33			94%	 (Q-phos)	K_3PO_4	
	NITROALKANES					
34	Nitroethane (2eq)		90%		Cs_2CO_3	Buchwald 2002[106]
35	Nitropropane (2eq)		86%		Cs_2CO_3	
36	Nitropropane (1eq)		80%		Cs_2CO_3	
37	Nitromethane	Low yield	-			
38	2-nitropropane	No reaction	-			
39	Phenylnitromethane	No reaction	-			
	SULFUR STABILISED ANIONS					
40			77%	PPh_3	NaH	Beletskaya 2002[112]
41			72%	PPh_3	NaH	
42			72%	PPh_3	NaH	

Entry	Substrate	Product and yield (diarylation in parenthesis) *		Ligand	Base	Reference
43			30%	PPh_3	NaH	Beletskaya 2002[112]
44			0	PPh_3	NaH	
45			93 88	BINAP	Cs_2CO_3 K_2CO_3	Bolm 2003[113]
	ALDEHYDES					
46	 R = *n*-C_6H_{13}	 R = *n*-C_6H_{13}	77%	*t*-Bu_3P	Cs_2CO_3	Miura 2002[114]
47			82%	*t*-Bu_3P	Cs_2CO_3	

* unless otherwise indicated aryl bromides were used

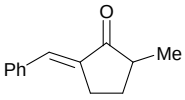
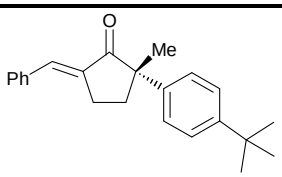
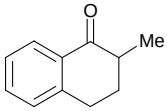
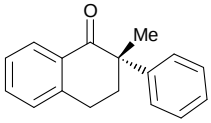
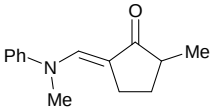
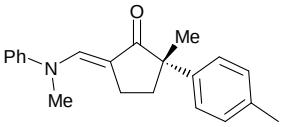
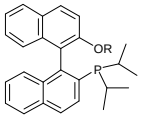
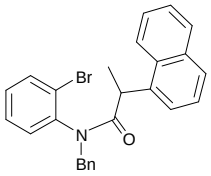
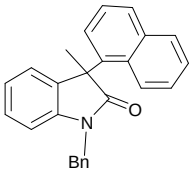
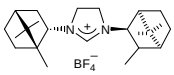
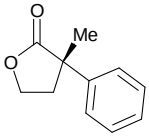
The wide range of enolates employed of which the carbonyl and dicarbonyl precursors have pK_a values varying from 12 to 35 [96] requires the use of bases with varying strength, the strength of the base being tailored to the pK_a. The varying electronic properties of the enolates influence the electron density of the metal in the catalyst complex and therefore require the use of ligands with different electron donating properties to allow for an efficient catalytic cycle.

Enolates as nucleophilic reagents are typically generated and used at low temperature but palladium catalysed arylation reactions often require elevated temperatures at which these enolates are prone to take part in self-condensation. This problem is of particular importance when the more active ketone and ester enolates are used. Dicarbonyl species, on the other hand, are often unstable at elevated temperatures. The requirement for a catalytic species that becomes active at lower temperature is, therefore, obvious.

The nature of the aryl halide contributes to the complexity of the reaction. Oxidative insertion of the palladium complex into the aryl halide bond is influenced by the electronic nature of substituents as well and the strength of the aryl halide bond. Arylation reactions involving aryl chlorides typically require the use of a highly electron-rich phosphine ligand while the ligand requirement for aryl bromides are less stringent[1]. The complexity of the enolate arylation reaction is demonstrated by the variability of bases, ligands and conditions employed, some of which are illustrated in Table 1.

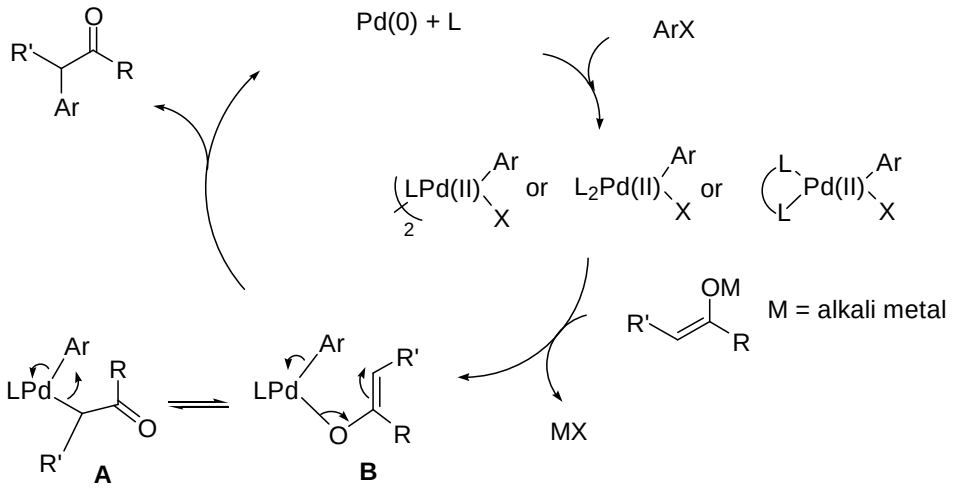
A few examples of stereo-selective arylation reactions using a chiral phosphine or imidazolinium carbene ligand have also been reported (see Table 2). Since the aryl group introduced enhances the acidity of the product relative to the substrate, deprotonation of the product occurs under the reaction conditions and therefore the examples of chiral induction are limited to the formation of a quaternary stereogenic centre by arylating an asymmetric tertiary carbon. Since enolate arylation is most prevalent in the formation of secondary and tertiary centres, examples of chiral arylation reactions are limited.

Table 2. Examples of asymmetric enolate arylation

Entry	Substrate	Product and yield (diarylation in parenthesis)		Ligand	Base	%ee	Reference
1			75%	$Pd(OAc)_2$ / *S*-BINAP	NaO*t*Bu	98%	Buchwald 1998[115]
2			66%		NaO*t*Bu	73%	
3			84%	$Pd_2(dba)_3$ /  R = CH_2(1-naphth)		93%	Buchwald 2002 [116]
4			80%	$Pd(dba)_2$ / 		71% (opt. rot. +)	Hartwig 2001[103],
			86%	$Ni(COD)_2$/ $ZnBr_2$/ *S*-BINAP	NaHMDS	>97%	Buchwald 2002[117]

1.7 Mechanistic Considerations

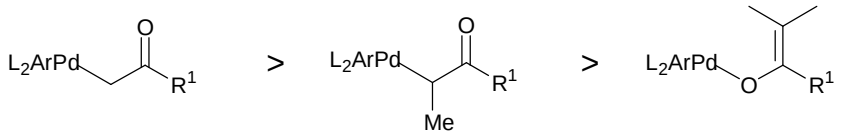
A plausible catalytic cycle for the palladium-catalysed arylation reaction of enolates is shown below (Scheme 37). The Pd(0) complex oxidatively adds into the aryl halide bond to form an aryl-palladium(II) halide complex. The preformed enolate associates to this complex by displacing the coordinated halide. The palladium enolate complex so formed collapses back to the original Pd(0) complex through formation of the aryl-enolate bond in a process termed reductive elimination (Scheme 37).



Scheme 37. Proposed catalytic cycle for enolate arylation reactions

The palladium enolate complex can assume a number of possible structures. In the case of monocarbonyl compounds the enolate could be either C-bound or O-bound to the palladium (**A** and **B** in Scheme 37). The anions of β-dicarbonyl compounds can assume the η^2-O,O-bound or η^1-C-bound states. Hartwig et al[118,105,119,120] investigated the reductive elimination step by preparing and isolating aryl-palladium enolate complexes and allowing these to react by heating to ascertain if these were possible reaction intermediates.

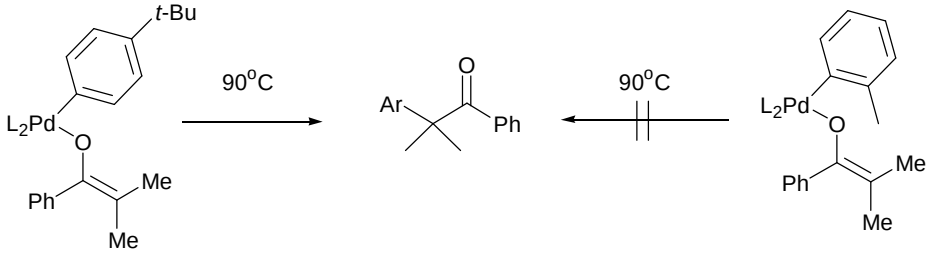
It was found that ketone enolate complexes bearing the 1,2-bis(diphenylphosphino)-benzene (DPPBz) ligand were stable enough to isolate[118]. The complex derived from a methyl ketone was more stable than from an ethyl ketone which was, in turn, more stable that that of an isopropyl ketone, suggesting that steric considerations may be a key factor in the reductive elimination of these complexes. Both methyl and ethyl ketone complexes were *C*-bound while the isopropyl ketone enolate was *O*-bound, suggesting that the *C*-bound formation is preferred and the *O*-bound intermediate only forms when the *C*-bound form becomes prohibitively congested (as shown in Figure 2).



L_2 = DPPBz [1,2-bis(diphenylphosphino)-benzene]

Figure 2. *C* vs *O* connectivity of palladium-enolate complexes

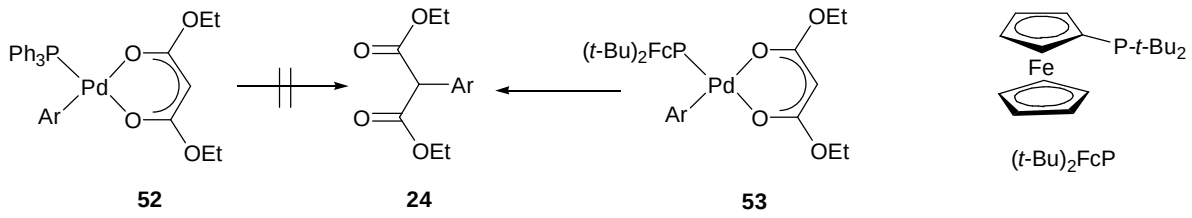
Reductive elimination proceeded in high yield with *C*-bound palladium enolates with both sterically unhindered and hindered aryl groups. The fact that the *O*-bound isopropyl phenyl ketone enolate also gave the coupled product in high yield with an unhindered aryl group **50** but not with a hindered aryl group **51** (Scheme 38), led Hartwig *et al*[118] to the conclusion that reductive elimination only proceeds through the *C*-bound enolate. The extra steric congestion introduced by the sterically hindered aryl group prevented the *O*-bound enolate from rearranging to the more crowded *C*-bound form, precluding arylation.



50 L_2 = DPPBz **51**

Scheme 38. Reductive elimination of hindered palladium–enolate complexes

Arylation of the more stabilized enolates such as those derived from malonate esters and other 1,3-dicarbonyl type compounds is, typically, more demanding than enolates stabilized by only one electron withdrawing group. Although deprotonation of these dicarbonyl species does not require strong and air-sensitive bases, their ability to form stable complexes with palladium complicates the product forming reductive elimination step[99,119].



Scheme 39. Reductive elimination during malonate arylation

The palladium complexes of the anion of diethyl malonate were prepared and were found to be η^2-O,O-bound when either PPh_3 or the sterically hindered di-*tert*-butyl ferrocenylphosphine (FcP(*t*-Bu)$_2$) was used (as depicted in Scheme 39). The PPh_3 ligated complex **52** did not undergo reductive elimination even with the addition of extra PPh_3. In contrast, the FcP(*t*-Bu)$_2$ ligated complex **53** gave the arylated malonate ester **24** in ~90% yield. It is postulated that the presence of a sterically hindered ligand is required to promote reductive elimination, presumably through rearrangement to the more reactive, less stable η^1-C-bound state. This is in agreement with the observation that malonate esters have only been arylated successfully using phosphine ligands bearing tertiary butyl groups.

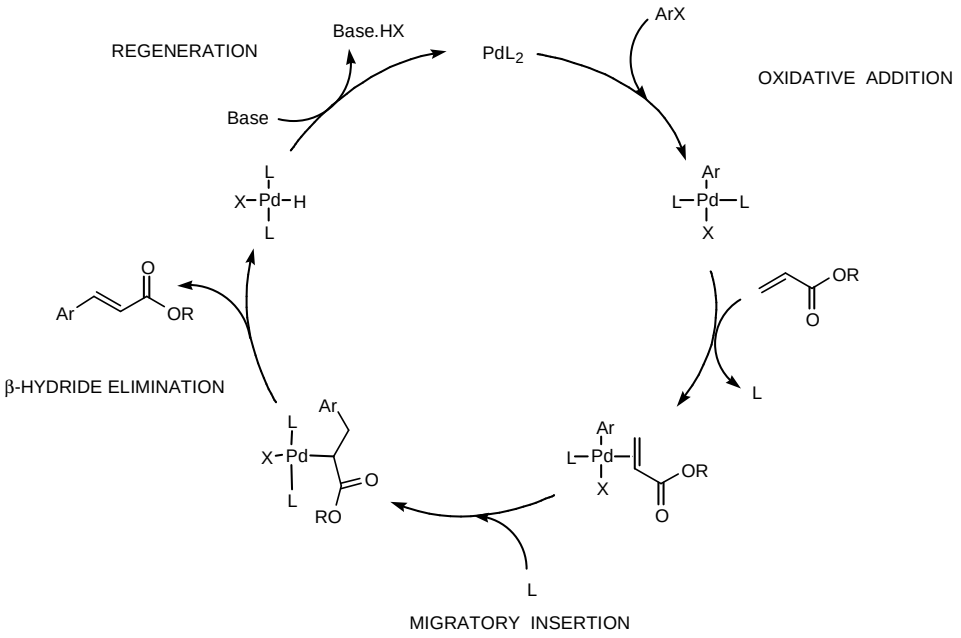
CHAPTER 2

INVESTIGATIONS INTO THE HECK REACTION

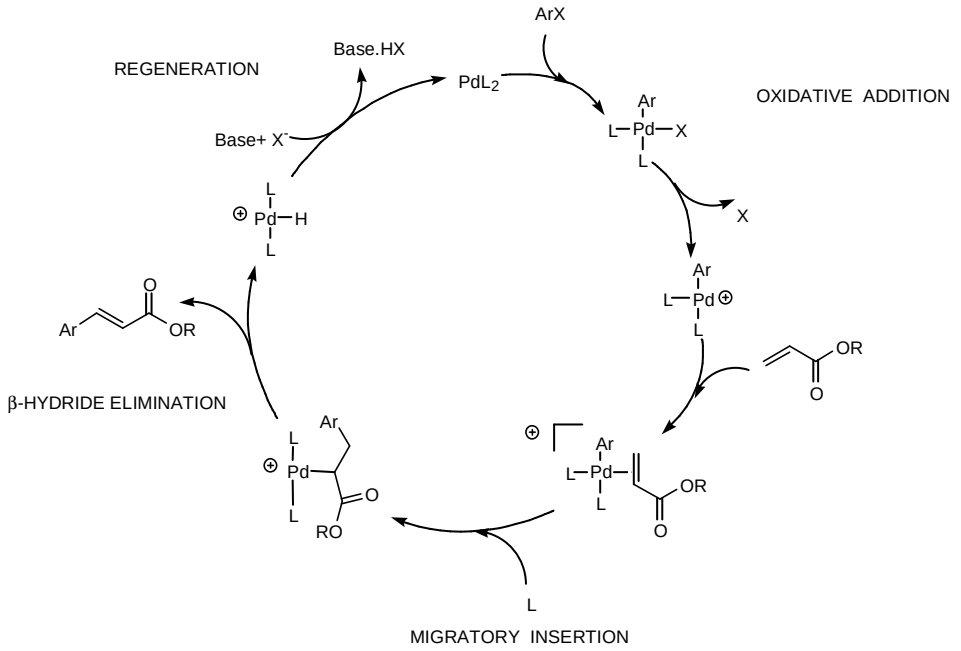
The palladium catalysed arylation and alkenylation of olefins, known as the Heck or Mizoroki-Heck reaction, was discovered independently by Mizoroki[64] in 1971 and by Heck[65] in 1972. Heck developed this reaction in a number of fundamental papers followed by numerous other researchers to a point where the Heck reaction is now an indispensable tool in organic chemistry. The Heck reaction is probably the most studied of the palladium catalysed arylation reactions and a number of comprehensive reviews have been written on the subject and a wealth of information is known about the reaction mechanism and the catalytic cycle[66-75].

A plethora of aryl and olefinic substrates have been studied under numerous variations of conditions and catalysts. Due to the generality of the reaction and the wealth of information known about the reaction, it has been used to benchmark the activity of transition metal catalysts as well as newly designed ligands.

Reactivity in the Heck reaction relies heavily on the ability of the Pd(0) species to undergo oxidative addition to Ar-X bonds to form a ArPd(II)X speices (as shown in Scheme 40 (also see Scheme 25, Chapter 1). The oxidative addition reaction rate depends mainly on the strength of the Ar-X bond which has to be broken. The order of reactivity is therefore I> OTf > Br > Cl [121]. The alkene forms a η^2-complex with the palladium complex. The formation of a new carbon-carbon bond is the next step and is called migratory insertion (Scheme 40). A number of mechanistic possibilities have been proposed, but it is most likely that ArPdX (Scheme 40) or $ArPd^+$ (Scheme 41) adds to the double bond in a concerted process[74].



Scheme 40. Traditional mechanism of the Heck reaction

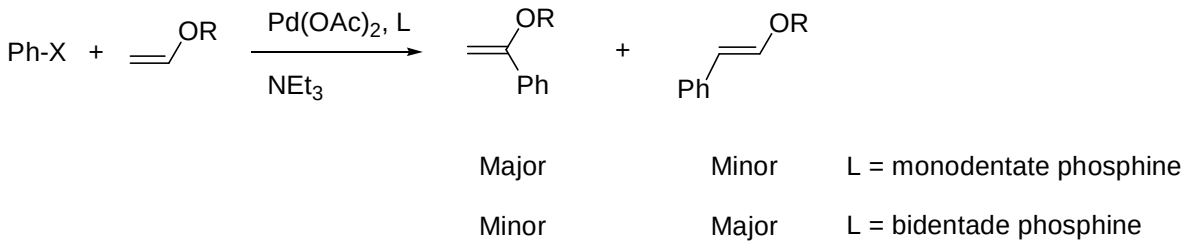


Scheme 41. Cationic mechanism for the Heck reaction

The palladium has to lose one ligand to free a coordination site for the alkene. If the leaving ligand is a neutral one, like a phosphine, a non-polar route is followed while when an anionic ligand leaves a cationic or polar route is followed[122-124] (see differences in Scheme 40 and 41). The cationic palladium intermediate may insert into the alkene electrophilically whereafter the aryl group undergoes a 1,3-shift. Another

theory is that the aryl group attacks the η^2-alkene to form $ArCH_2CHRPdX$ or $ArCH_2CHRPd^+$. These theories have to explain the specific regioselectivity obtained with different olefinic substrates.

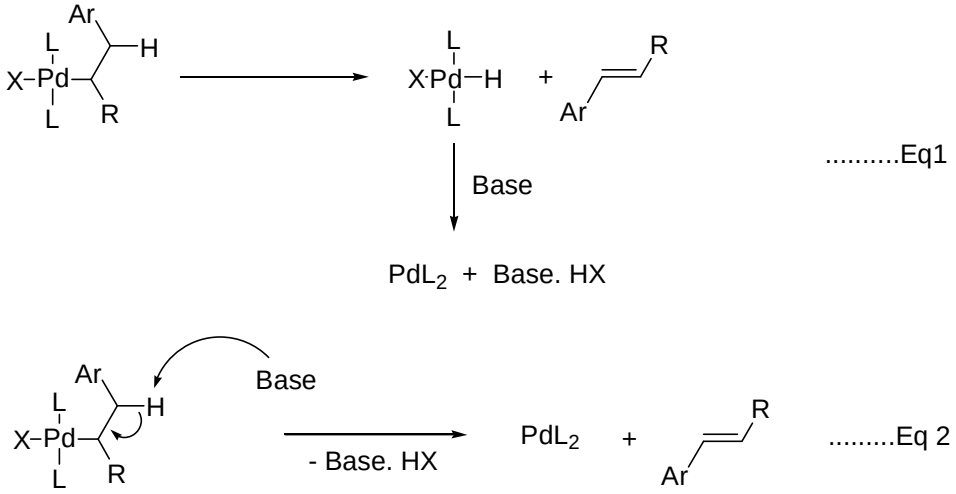
The β-substitution (insertion at the terminus of the alkene) observed for olefins with electron withdrawing substituents (Michael acceptors) is in line with attack by the aryl anion while α-selectivity (insertion at the more substituted end of the alkene) is common for electron-rich olefins such as enol ethers where the attack is likely to be originated by a cationic palladium intermediate. However, there are many discrepancies to these theories and researchers are not in agreement on the exact mechanism. The data published so far on the regioselectivity of arylation with both neutral and cationic aryl-palladium complexes shows that the palladium prefers to attach itself to the atom with the higher electron density *ie* the α-position of Michael olefins and the β-position of enol ethers. Substitution therefor occurs mainly at the position of lower electron density *ie* the β-position of Michael olefins and the α-position of enol ethers. The use of either mono-phosphines or chelating ligands may however alter the regioselectivity in especially electron-rich olefins (Scheme 42)[74].



Scheme 42. Regioselectivity in the arylation of enol ethers

The last step in the cycle is the release of the newly formed olefin and the recovery of the original Pd(0) species. Again there are several possibilities of which only two will be considered. The first possibility is β-hydride elimination (which is common in palladium catalysed reactions) which leads to the formation of the olefinic product and the X-Pd-H complex which is quickly scavenged by base releasing Pd(0) (Scheme 43,

Equation 1). The other alternative is the deprotonation of the intermediate product followed by a classical reductive elimination releasing both the product and the Pd(0) complex at the same time (Equation 2).



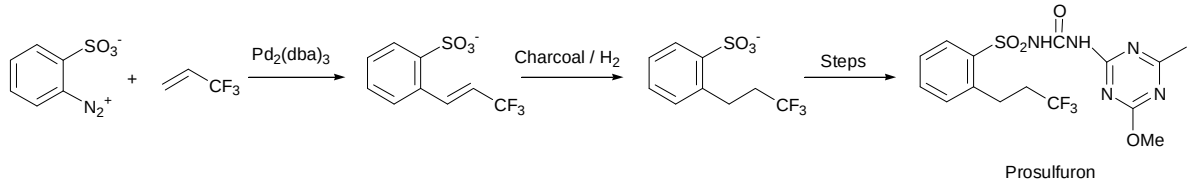
Scheme 43. β-Hydride elimination vs. reductive elimination

2.1 Industrial Applications of the Heck Reaction

Due to the maturity of this reaction, it has also found the most industrial applications of the arylation type reactions[76]. It is therefore insightful to study the development of this reaction from laboratory to industrial stages. As the development of other related palladium catalysed reactions have often followed the same trends as the Heck reaction, this could be used as a model study for the commercialisation of other arylation reactions.

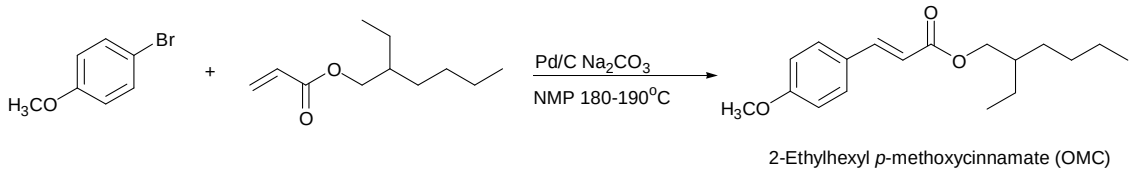
Heck olefination has found several applications in the production of fine chemicals[76].

Examples of Heck olefination implemented in industrial processes are provided below:

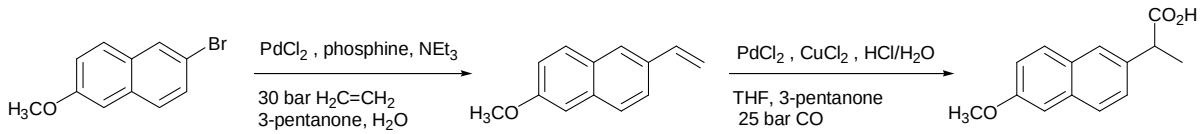


Prosulfuron

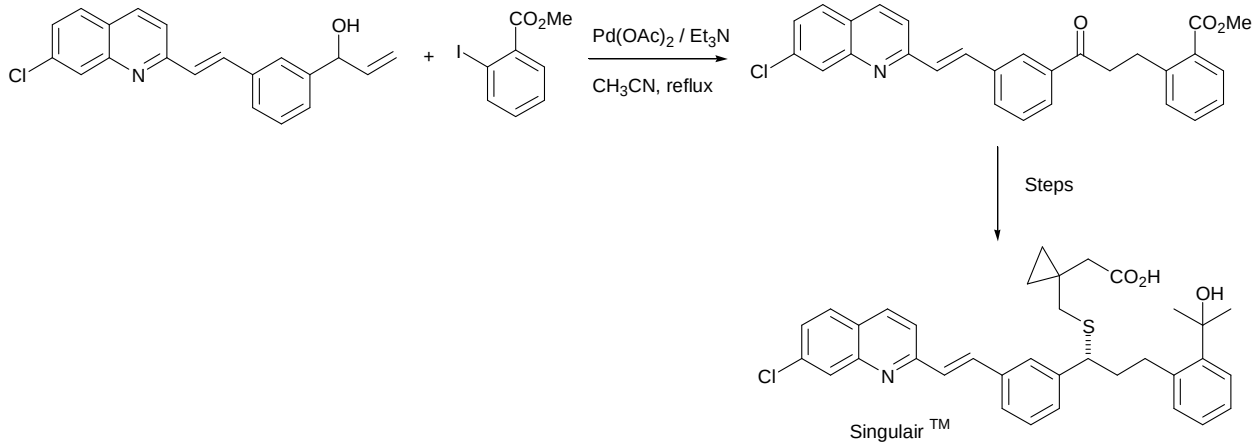
Scheme 44. Prosulfuron™ (herbicide)[125]



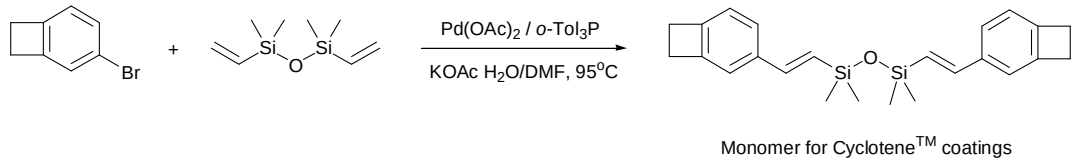
Scheme 45. 2-Ethylhexyl *p*-methoxycinnamate or OMC (UV-B sunscreen)[126]



Scheme 46. Naproxen™ (non-steroidal anti-inflammatory drug, NSAID)[127]



Scheme 47. Singulair™ (anti-asthma drug)[128,129]



Scheme 48. Cyclotene™ (monomers for coatings of electronic components)[130]

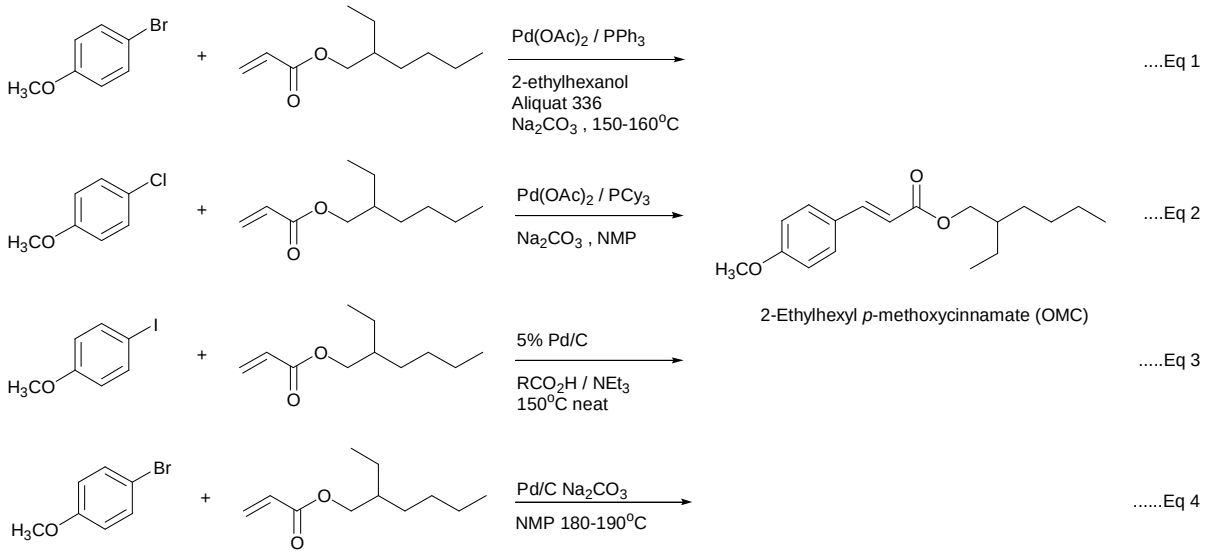
In this thesis only the synthesis of the cinnamates (Scheme 45) will be discussed in detail.

Octyl methoxycinnamate (OMC) or 2-ethylhexyl 4-methoxycinnamate is an important UV B sunscreen agent. Several synthetic routes have been developed of which many

are patented. These procedures range from the aldol-type reactions like the Claisen condensation between esters and anisaldehyde[131] or the Knoevenagel reaction[132,133] involving malonic acid, to the ketene route developed by BASF[134] or the more recent introduction of the Heck reaction[135-138] (a topic of this thesis) involving either iodo-, bromo- or even chloroanisole.

A number of companies have patented the Heck route to OMC using varying reaction conditions and catalyst systems as will be discussed below.

Bayer has patented a process to prepare 2-ethylhexyl *p*-methoxycinnamate and 2-isoamyl *p*-methoxycinnamate using a mixture of a Pd(II) salt and triphenylphosphine and a heterogenous base (namely sodium carbonate, see Scheme 49, eq 1)[137]. The reaction is performed either in the presence of 2-ethylhexanol as solvent or a phase transfer agent such as methyl tri-*n*-octylammonium chloride or polyethylene glycol. High yields are achieved by heating at 150-160^{o}C using palladium loadings of as low as 0.0025 mol%. The palladium is protected from precipitation as palladium black by using a relatively high loading of phosphine (typically a 40:1 ratio of triphenylphosphine to palladium).



Scheme 49. Patented Heck processes to OMC

Merck has disclosed a procedure for the preparation of cinnamic acid compounds by reacting an acrylic acid compound with an aryl chloride in the presence of ≤ 1mol % palladium (in either the 0 or +2 oxidation state) and a bulky aliphatic phosphine (such as tricyclohexylphosphine or tri-isopropylphosphine, Scheme 49, eq 2)[138]. The base employed was sodium carbonate in a polar solvent such as NMP. These reactions appear to proceed slowly and are low yielding when the examples quoted are examined.

Givaudan-Roure corporation has patented a process describing a procedure to prepare substituted cinnamic esters from aryl iodides and acrylate esters using low loadings of a heterogenous palladium catalyst (typically 5% palladium on charcoal, Scheme 49, eq 3)[136]. A carboxylic acid ammonium salt (such as the combination of acetic acid and triethylamine) is used as the base. In this process the reaction mixture is heated to ~150^{o}C in the absence of solvent to yield the Heck coupled product in excess of 90% isolated yield. The reaction of aryl bromides failed under these conditions unless acrylic acid was used in combination with 1 molar equivalent of a dialkylamine; a polar solvent such as NMP was used to dilute the semi-solid reaction mixture.

Another process that employs a palladium on charcoal catalyst was developed at the IMI institute for R & D in Israel (see Scheme 49, Eq 4)[76,126]. 4-Bromoanisole was coupled with 2-ethylhexylacrylate at high temperature (180-190^{o}C) in NMP solution with sodium carbonate as base. It is thought that the palladium could be homogenous by dissociation from the support, but is re-precipitated once the aryl bromide is depleted and can be fully recovered by means of filtration. This phenomena has also been observed by Arai[139] for supported palladium and Lipshutz[140] for nickel catalysts. Another advantage of this reaction is that it can tolerate low levels of water (it is claimed that up to 15% water is permissible and that it has an accelerating effect). This process is supported by the flourishing organobromine and bromine recovery industry in Israel that allows for the recycle of sodium bromide through bromine to 4-bromoanisole.

As part of this study, the preparation of cinnamic acid derivatives by the Heck reaction was further examined. The use of solvent-free phase transfer assisted conditions, heterogenous catalysts as well as the use of acrylic acid salts were the major focus areas in this part of the investigation.

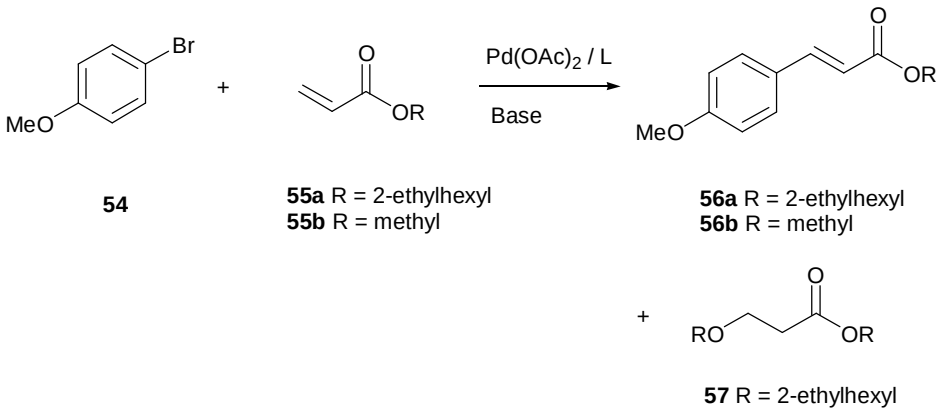
2.2 Homogenous Palladium Catalysis

The typical conditions required to couple an acrylate ester and a deactivated aryl halide like 4-bromoanisole involve a palladium source, either as Pd(0) or Pd(II), a phosphine ligand (either mono- or bidentate) and the use of a trialkylamine base in a high boiling solvent such as dioxane, DMF or NMP.

In an industrial environment the use an amine base and organic solvents causes undesired complications. Amine bases can be removed from the products by extraction with dilute mineral acid. Recovery of the amine would, however, require treatment with inorganic base followed by steam distillation or extraction and a drying step. Removal of solvent and recycling of an anhydrous solvent introduces additional process steps. The stringent specifications on the type and level of residual solvent in fine chemicals add further complications and restrictions.

The so-called Jeffery's conditions, at least in part, avoid these complications. These conditions involve the use of an inorganic base - typically sodium or potassium carbonate together with a phase transfer catalyst (PTC) with or without added solvent[141-143,71].

A patent by Bayer[137] in 1994, reports a process for the preparation of OMC using solvent-free conditions with trioctylmethylammonium chloride (Aliquat 336) as phase transfer agent and sodium carbonate. Alternatively the phase transfer agent could be replaced by using 2-ethylhexanol as solvent. As we were interested in an industrial Heck process some of the examples described in this patent were examined in our laboratories (Scheme 50, Table 3).



54

55a R = 2-ethylhexyl
55b R = methyl

56a R = 2-ethylhexyl
56b R = methyl

57 R = 2-ethylhexyl

Scheme 50.

Table 3. Homogenous Palladium Catalysed Heck Reactions

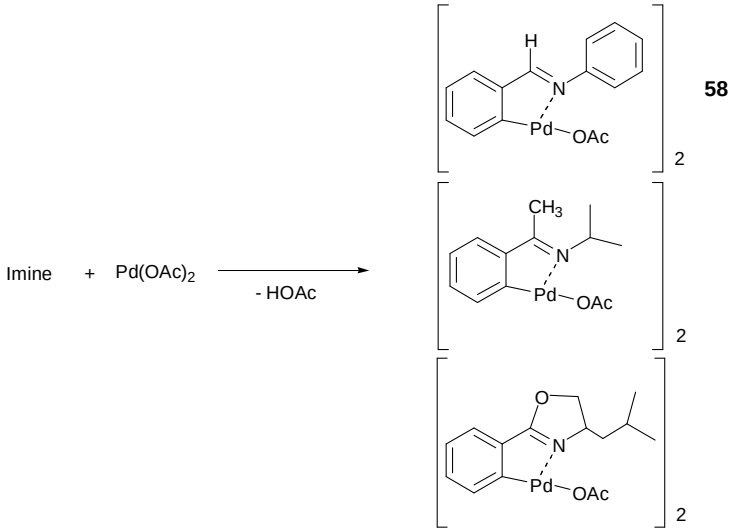
Entry	Acrylate	$Pd(OAc)_2$ mol%	Ligand (mol%)	Base	Solvent / PTC	Conversion of 54	Selectivity to 56 / 57
1	**55a**	0.01%	PPh_3 (0.4%)	Na_2CO_3	EHA	55%	**56a** 0, **57** n.d
2	**55a**	0.025%	PPh_3 (1.0%)	Na_2CO_3	PTC	76%	**56a** >90%
3	**55a**	0.025%	PPh_3 (1.0%)	Na_2CO_3	EHA (conc.)	34%	**56a** 39%, **57** 56%
4	**55a**	0.2%	Benzal aniline (1%)	Na_2CO_3	PTC	2%	**56a** >80%
5	**55a**	1%	$P(OEt)_3$ (~20%)	Na_2CO_3	NMP	30%	**56a** >90%
6	**55b**	0.2%	PPh_3 (8%)	Na_2CO_3	NMP	35%	**56b** 92%
7	**55a**	0.2%	PPh_3 (8%)	NEt_3	Neat	~10%	**56a** > 90%

* EHA = 2-ethylhexylalcohol, PTC = phase transfer catalyst = Aliquat 336, NMP = 1-methyl-2-pyrrolidinone , n.d. = not determined, Reaction temperature: 150-160^{o}C

When an example employing 2-ethylhexanol was repeated (Table 3, entry 1) it was discovered that in our hands very little of the desired coupling product was formed and, instead, the major product was that of conjugate addition of ethylhexanol into the acrylate **57**. When we repeated the reaction under more concentrated conditions (only 20% of the solvent) more of the desired Heck product **56a** was formed although the conjugate addition still accounted for 56% of acrylate consumption (Table 3, entry 3).

In the absence of additional 2-ethylhexanol as solvent using Aliquat 336 (trioctylmethylammonium chloride) a more positive result was obtained. A conversion of 76% was achieved at 150^{o}C for 20 hours using 0.025% palladium and 1% triphenylphosphine (an isolated yield of 65% OMC is claimed in the Bayer patent)[137] (Table 3, entry 2).

The ratio of phosphine to metal used in the patented procedure varied between 10:1 and 40:1. This high phosphine loading is believed to be necessary to stabilise palladium (especially in the zero oxidation state) as sub optimal co-ordination of palladium leads to precipitation of palladium black. This is the major factor limiting the turnover number of the palladium catalyst. We observed by gas chromatographic studies that during the reaction most of the triphenylphosphine is converted to triphenylphosphine oxide. The use of such high phosphine loadings is obviously not desired from a cost point of view as well as causing complications in product purification.



Scheme 51. Benzalaniline complexes with $Pd(OAc)_2$

Benzaldimines are known to form C-N palladacycles with palladium[144] (Scheme 51) and these catalysts have found application in the Heck chemistry of aryl iodides but examples with aryl bromides are limited to bromobenzene. In an effort to avoid the use of a phosphine ligand, a relatively simple imine, benzalaniline **58**, was used in the reaction between ethylhexyl acrylate and 4-bromoanisole under PTC conditions. Although selectivity toward the desired cinnamic acid compound **56a** was high, activity was disappointing (Table 3, entry 4). The low reactivity of the more electron-rich 4-bromoanisole is ascribed to slow oxidative addition which requires a highly

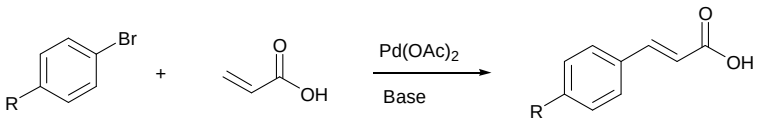
electron rich palladium complex. The lower electron density of the palladium/imine complex as compared to that of a palladium/phosphine complex may limit this type of ligand to aryl iodides and activated aryl bromides.

Triethylphosphite was also examined in this reaction to compare its activity to triphenylphosphine (Table 3, entry 5). It was found that a selective reaction to **56a** occurred although conversion was limited (~30%). It is thought that proper optimisation could lead to a comparable reaction with that observed when using triphenylphosphine. The use of trialkylphosphites (which have similar electron donating properties and cone-angles to their phosphine counterparts) has the added advantage that upon hydrolysis, phosphoric acid will be the only phosphorus containing effluent as compared to triphenylphosphine and triphenylphosphine oxide which are harmful to the environment and are difficult to separate from the product.

The low conversion numbers obtained when using either sodium carbonate in NMP or triethylamine both as base and solvent (Table 3, entries 6 and 7) even at much higher catalyst loading (0.2mol% vs 0.025mol%) demonstrates the effectiveness of the phase transfer catalyst to promote this reaction.

2.3 Heck Reactions on Acrylic Acid

The reactions between acrylic acid and bromobenzene and 4-bromoanisole were also investigated (Scheme 52, Table 4). This has the advantage of a water soluble product that, potentially, could be removed from the reaction mixture as an inorganic salt by extraction. Un-reacted aryl halide and the catalyst would stay in the organic phase and could, potentially, be recycled to minimise catalyst cost.



54a R=OMe
54b R=H

55c

59a R = OMe
59b R = H

Scheme 52. Heck Reactions of Acrylic Acid with Bromobenzene and 4-Bromoanisole

Table 4.

Entry	$Pd(OAc)_2$ mol%	Ligand (mol%)	Base	Solvent/ PTC	Conversion of 54	Yield 59
1	0.2	PPh_3 (8%)	Na_2CO_3	NMP	95% **54b**	79% **59b**
2	0.2	PPh_3 (8%)	Na_2CO_3	Xylene/PTC	100% **54b**	>90% **59b**
3	0.2	PPh_3 (8%)	Na_2CO_3	**54b** /PTC	-	29% **59b**
4	0.2	PPh_3 (8%)	Na_2CO_3	Xylene/ PTC	33% **54a**	20% **59a**
5	0.2	PPh_3 (8%)	Na_2CO_3	**54a**/ PTC	-	10-15% **59a**

NMP: 1-methyl-2-pyrrolidinone; PTC: phase transfer catalysis = Aliquat 336

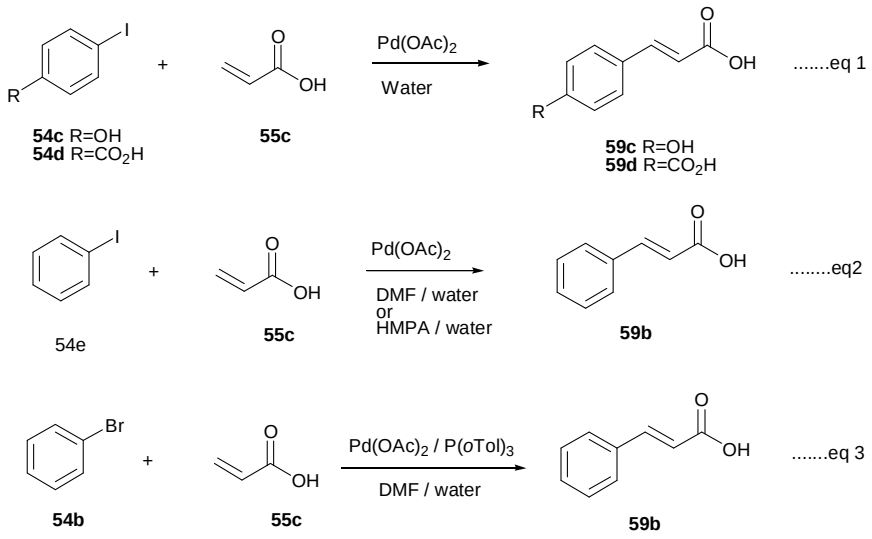
The reaction between acrylic acid and bromobenzene was conducted in NMP using $Pd(OAc)_2/PPh_3$ (Table 4, entry 1). Conversion of bromobenzene was 95% while the selectivity to cinnamic acid was 83% (yield of **59b** is 79%). The remainder of bromobenzene was converted to benzene by hydrodehalogenation. Two equivalents of acrylic acid were used of which some was consumed due to, presumably, polymerisation or decomposition.

This reaction was repeated under phase transfer conditions (Aliquat 336) using xylene as a solvent (Table 4, entry 2). Although the reaction mixture was a thick slurry, due to the large amount of sodium acrylate, complete conversion of bromobenzene and high selectivity to cinnamic acid was observed (90%).

The reaction was then repeated using an excess of bromobenzene, with the dual role of reagent and solvent (Table 4, entry 3). Unlike previous reactions where acrylic acid was added in excess, it was the limiting reagent. The conversion and yield could not be determined accurately by GC analysis as it was hampered by unreliable integration of the broad acrylic acid peak. Isolation was done by addition of water which led to

the formation of a thick suspension. After a difficult and tedious extraction a 29% yield of the desired product **59b** was achieved. Analysis of the organic layer by ^{31}P-NMR spectroscopy revealed that all PPh_3 had been converted to the oxide. More PPh_3, sodium carbonate and acrylic acid were added to the bromobenzene phase and reacted further. The Heck reaction proceeded and a further 21% cinnamic acid **59b** was formed (isolated yield). This showed that the catalyst was still active and that catalyst recycle was possible although product separation has to be improved to make this approach viable.

The reaction between 4-bromoanisole **54a** and acrylic acid was tested under phase transfer conditions (PTC, Aliquat 336) in xylene (Table 4, entry 4). The reaction proved to be more sluggish with the conversion limited to 33% after 16 hours at 140^{o}C. 4-Methoxycinnamic acid **59a** was isolated in 20% yield from this reaction, suggesting a fairly selective reaction (approximately 60%). The limitation of this reaction was, again, that a large amount of sodium acrylate formed which caused thick emulsions – especially when less polar solvents were used. The use of a biphasic system with a phase transfer agent would seem to be a solution for the physical problems encountered but we have been unsuccessful thus far in obtaining Heck products under such conditions.



Scheme 53. Examples of Heck reactions that have been performed in aqueous and partially aqueous medium

Heck reactions in the aqueous phase have been reported but examples are limited[145-148]. The reaction between acrylic acid and aryl iodides has been done in an entirely aqueous system provided that the aryl iodide is water soluble (*ie*. iodophenol or iodobenzoic acid, Scheme 53, eq 1). For water insoluble aryl iodides DMF / water and HMPA / water mixture were used (Scheme 53, eq 2). The reactions with iodo arenes were done with unligated palladium while the use of bromobenzene required the addition of P(*o*-Tol)$_3$[145](Scheme 53, eq 3). The last mentioned reaction showed a dramatic positive influence of the presence of water. In neat DMF solution the yield of cinnamic acid was only 12% while the addition of 10% or more water increased the yield to almost quantitative. This is explained by the fact that water, being a very polar solvent, should promote migratory insertion by forcing the reaction to follow the cationic pathway. Water has the ability to wash the metal centre clean of all other labile ligands such as halides and acetates, thus creating a cationic palladium intermediate which promotes the insertion into the double bond.

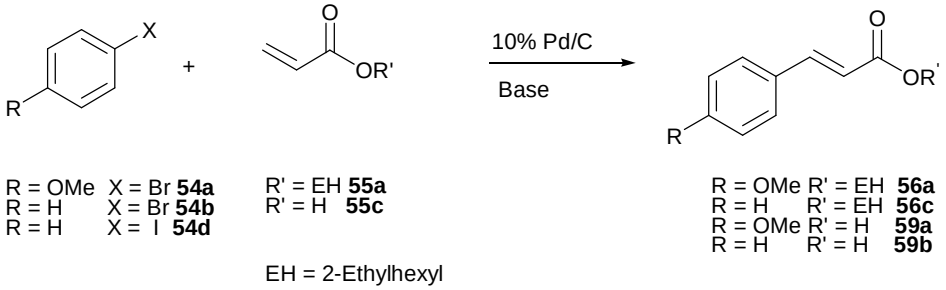
2.4 Heterogenous Palladium Catalysis

The use of a heterogenous catalyst in place of a homogenous catalyst has significant advantages since it can be removed easily from the reaction mixture and can, therefore, be recycled to lower the cost of production. Many attempts have been made to heterogenise homogenous metal catalysts by various techniques such as attaching ligands to polymeric supports, encapsulation of catalysts and using dendrimers to attach the active catalytic species. A number of such “heterogenous” metal catalysts, tailor-made for various catalytic conversions, are commercially available (such as Johnson Matthey’s FibreCat™ which employs a phosphine ligand tethered to an insoluble polymer support, Rexalyst™ from Polium Technologies which uses a high temperature soluble polymer linked ligand and Avecia’s Pd EnCat™ which is based on encasing palladium in highly cross-linked polyurea beads)[20].

A patent by Mallinckrodt[135] in 1990 first described the Heck reaction between an aryl iodide and an acrylate ester using a catalyst comprising palladium on a support and

trialkylamine base. A later patent by the Givaudan-Roure Corporation[136] improved this reaction by the use of an alkanoic acid ammonium salt formed from an alkanoic acid and a primary, secondary or tertiary amine base. The patent is limited to aryl iodides except in the reaction of acrylic acid with bromoanisole. Reetz has noticed a similar enhancement by the addition of a similar ionic pair in the form of *N*,*N*-dimethylglycine in the reaction of bromobenzene with styrene[149].

An example described in this patent involving ethylhexyl acrylate **55a** and iodobenzene **54d** was successfully repeated in our laboratories and was followed up by a series of experiments using different arylhalides as well as acrylic acid (Scheme 54, Table 5). Iodobenzene conversion of higher than 90% was achieved in 2 hours at 150°C with selectivity to the Heck product **56c** being >90% (Table 5, entry 1).



Scheme 54. Heck reactions of 2-ethylhexyl acrylate **55a** catalysed by palladium on carbon

Table 5. Palladium on Carbon Catalysed Heck Reactions

Entry	Metal	Base	Solvent	Acrylate	Conversion of 54	Product Yield
1	10%Pd/C (0.2% Pd)	NEt_3/ Acetic acid	Neat	**55a**	100% **54d**	>90% **56c**
2	10%Pd/C (0.2% Pd)	NEt_3/ Acetic acid	Neat	**55a**	30% **54b**	15% **56c**
3	10%Pd/C (0.2% Pd)	Na_2CO_3	NMP	**55a**	41% (2h 180°C) **54a** 88% (16h 180°C)	33% **56a** 55% **56a**
4	10%Pd/C (0.2% Pd)	Na_2CO_3	NMP / water	**55a**	100% **54a**	60% **56a**
5	10%Pd/C (0.2% Pd)	Na_2CO_3	PTC	**55a**	53% **54a**	23% **56a** (isolated yield)
6	10%Pd/C (0.1% Pd)	Na_2CO_3	NMP	**55c**	n.d. **54b**	~30% **59b** (isolated yield)
7	10%Pd/C (0.2% Pd)	Na_2CO_3	NMP	**55c**	35% **54a**	26% **59a** (isolated yield)

Entry	Metal	Base	Solvent	Acrylate	Conversion of 54	Product Yield
8	10%Pd/C (0.2% Pd)	Na_2CO_3	NMP / water	**55c**	88% **54b**	55% **59b** (isolated yield)
9	10%Pd/C (0.2% Pd)	Na_2CO_3	NMP / water	**55c**	75% **54a**	62% **59a** (isolated yield)
10	10%Pd/C (0.2% Pd)	Na_3PO_4	NMP / water	**55c**	75% **54a**	70% **59a** (isolated yield)
11	10%Pd/C (0.2% Pd)	Na_2CO_3	Xylene / PTC	**55c**	Very little reaction **54b**	**59b**
12	10%Pd/C (0.2% Pd)	Na_3PO_4	Xylene / water / PTC	**55c**	No reaction **54a**	**59a**

NMP: 1-methyl-2-pyrrolidinone, OMC: octyl methoxycinnamate, PTC: phase transfer catalysis =aliquat 336

The above reaction was attempted using bromobenzene **54b** instead of iodobenzene (Table 5, entry 2). Heating at 150^{o}C for 60 hours gave ~30% conversion of **54b** in an unselective reaction (only ~15% of **59c** was formed). The reaction of 4-bromoanisole **54a** was not attempted as this would most likely lead to an even less successful reaction (based on the unsuccessful reaction with **54b**).

The patent[136] clearly states that although acrylic acid could be coupled with 4-bromoanisole using 1 equivalent of dibutylamine, no reaction was observed when either sodium or potassium carbonate was used. Since sodium carbonate could be used when using a homogenous catalyst in the reaction of acrylate esters and acrylic acid, it appeared to be unreasonable that it would not be effective when using a heterogenous catalyst system. Therefore a number of reactions using sodium carbonate in combination with a 10% palladium on carbon catalyst were performed in our laboratories (Table 5, entries 3-11).

The reaction between **54a** and 2-ethylhexyl acrylate **55a** in NMP using sodium carbonate and palladium on carbon gave a 41% conversion of **54a** after 2 hours at 180^{o}C (Table 5, entry 3). The selectivity towards octylmethoxycinnamate (OMC) **56a** was determined to be 80% (**56a** yield of 33%). Further heating for 16 hours led to complete consumption of the acrylate while only 88% of bromoanisole was converted. Some decomposition might have led to the lowering of selectivity to 62% (55% **56a**).

A reference[76] to an OMC process used by IMI institute for research and development from Israel, suggested that the use of 15% water in NMP accelerated the reaction between ethylhexyl acrylate **55a** and **54a**. In our hands the presence of water led to large scale hydrolysis of the product formed (**56a** → **59a**) while not inhibiting the Heck reaction (Table 5, entry 4). This reaction had to be done in a pressure reactor as the presence of water at the reaction temperature of 185^{o}C led to an autogenous pressure of 7 bar.

The same reaction in the absence of solvent under PTC also produced **56a** (Table 5, entry 5). From GC analysis the conversion of **54a** was 53% while nearly all acrylate **55a** had been converted. Isolation by distillation gave a 23% yield of OMC **56a**. This would suggest that the reactions done at high temperature and high concentration (solvent less) are prone to acrylate losses, presumably down a polymerisation pathway.

The reactions of both bromobenzene **54b** and 4-bromoanisole **54a** with acrylic acid **55c** were conducted using sodium carbonate, Pd/C and NMP to give cinnamic acid **59b** and 4-methoxycinnamic acid **59a** in 30% and 26% yield (Table 5, entries 6 and 7). When these reactions were repeated using 15% water in NMP, which made the reaction mixtures less viscous, aryl halide conversion was higher and the isolated yield increased to 55% and 62% respectively (Table 5, entries 8 and 9). By replacing sodium carbonate with tri-sodium phosphate, the reaction of **54a** with **55c** was further improved and a conversion of 75% and an isolated yield of 70% of 4-methoxycinnamic acid **59a** was achieved (Table 5, entry 10). All attempts at replacing NMP by using a water immiscible solvent and PTC were, however, unsuccessful.

In summary, the Heck reaction for the preparation of 4-methoxycinnamic acid **59a** or OMC **56a** can be performed using a heterogenous palladium catalyst and by either using acrylic acid or an acrylate ester. When an acrylate ester is used the reaction could be performed solvent-free with a PTC although the yield is inferior to that obtained when using NMP. The reaction of acrylic acid requires NMP as solvent while the presence of 15% water is beneficial to the reaction.

There has been an ongoing debate around the true nature of supported metal catalysts. Evidence exists that the catalytic activity observed in some reactions could be ascribed to dissolved or leached metal. A similar phenomenon was noticed by Arai *et al* [139] during a study on the use of supported palladium in the Heck reaction of iodobenzene **54e** and methyl acrylate **55b** in NMP solution. They concluded the level of palladium in solution accumulates with time and that a maximum of 55% of dissolved palladium (for Pd/C) was detected after 1 hour. They did, however, also find that it was almost entirely re-deposited on the support upon consumption of the aryl iodide. The effect was less drastic when using either bromo or chlorobenzene. Although significant quantities of palladium leached into solution and conversion of the aryl halide was high, the dominant reaction was dehalogenation with the maximum selectivity observed for the cinnamate ester was a mere 22%. Mehnert *et al*[150] reported higher selectivities using palladium-grafted mesoporous MCM-11 (Pd-TMS11) for both bromobenzene (82% at 39% conversion) and chlorobenzene (40% at 16% conversion).

These published results, support our own good results obtained for iodobenzene and the lower selectivity for bromobenzene and 4-bromoanisole when using a palladium on carbon catalyst under various conditions. The 62% selectivity to OMC **56a** at 88% conversion of 4-bromoanisole obtained by using 10% Pd/C with sodium carbonate in NMP (entry 8) and the 70% isolated yield of 4-methoxycinnamic acid **59a** with 75% conversion of 4-bromoanisole with sodium phosphate base in wet NMP (entry 10), do however, appear to be an improvement on the published results.

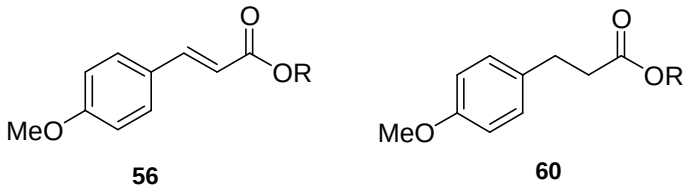
2.5 Nickel Catalysed Reactions

One of the pioneers of transition metal catalysed reactions, Lipshutz, has recently studied the use of nickel deposited onto carbon extensively[140]. A recent article by Lipshutz *et al*[140] deals with the nature of the Ni/C catalyst and interesting observations regarding the origin of the catalytic activity in amination and Kumada reactions were made. It was concluded that the catalytic activity could be attributed to homogenous

nickel. It was estimated that up to 78% of the adsorbed nickel was available, but unlike the supported palladium catalysts, the leached nickel is located almost entirely within the charcoal matrix, since only very low levels of nickel were found in the filtered reaction mixture by ICP at any time during reaction. The excellent adsorption properties of the support allows for recovery of almost all nickel by final filtration. Lipshutz found that the amount of phosphine added in the reaction did not influence the extent of nickel leaching. The presence of the ligand did, however, play the same role as it would in a truly homogenous reaction.

However, the use of nickel as a catalyst in Heck chemistry has been briefly reported with limited results published[151,152]. It appears that the major limitation in the use of nickel is the difficulty in maintaining nickel in the zero oxidation state, something that is of little concern when using palladium. It does appear that the use of a Ni(0) species is not sufficient to maintain nickel in the zero oxidation state and that alternative reducing agents are required for in-situ reduction. This can, typically, also limit the turnover number of the catalytic species.

The use of a stoichiometric amount of a reductant, like zinc metal powder, in the reaction of an acrylate ester with an aryl halide, leads to the formation of a large proportion of "saturated Heck product" **60** (as depicted in Figure 3) in addition to some of the expected Heck product **3**.



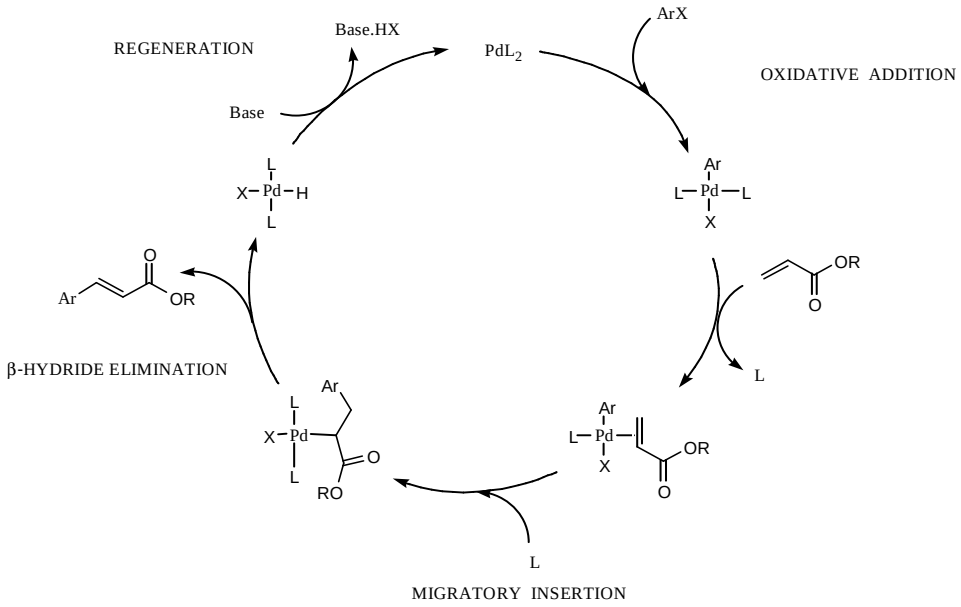
56 **60**

Heck Product "Saturated Heck" Product

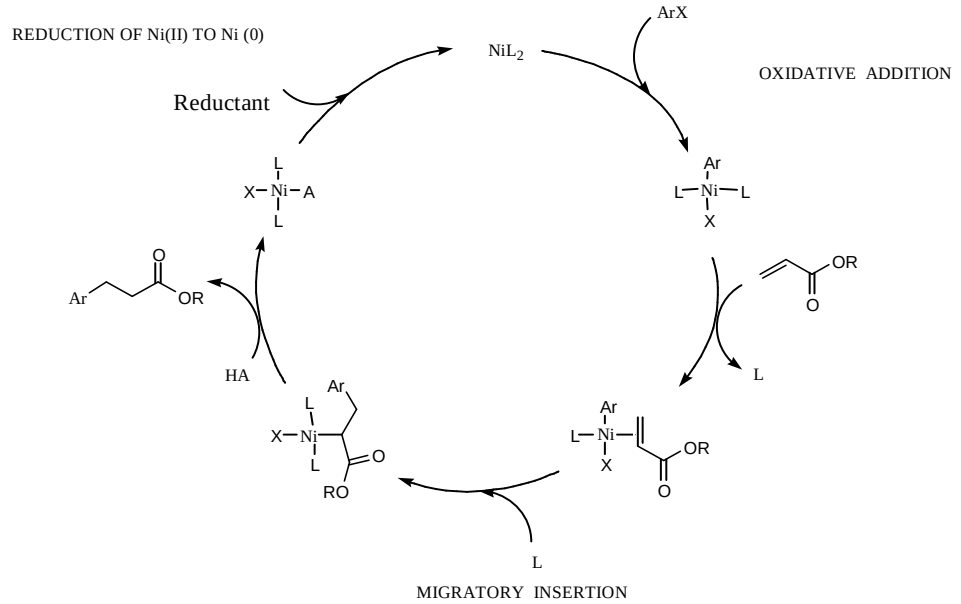
Figure 3.

Since the formation of the "saturated Heck product" only happens when the olefin is a Michael acceptor, and not when using styrene as the olefin, a mechanism involving the Michael addition of $ArNiBr(PPh_3)_2$ to the acrylate ester has been proposed[74](compare the traditional Heck reaction mechanism with the proposed mechanism, Scheme 55

and 56). During the catalytic cycle Ni(0) oxidatively adds to the aryl halide which then adds to the acrylate ester in a Michael sense. The nickel leaves as Ni(II) and needs to be reduced to Ni(0) to complete the cycle. When a palladium catalyst is used, a similar route is followed but the Heck product is formed by β-hydride elimination and Pd(0) is released after deprotonation with a base.



Scheme 55. Traditional Mechanism of the Heck Reaction

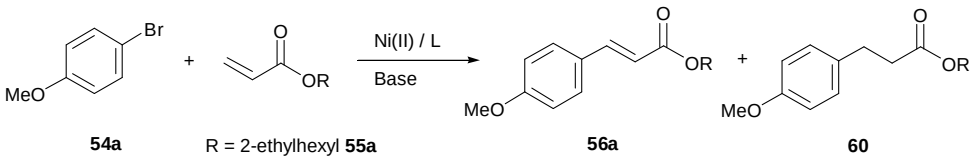


Scheme 56. Proposed Mechanism for the Formation of the Saturated Heck Product

A number of experiments were performed by us using $NiCl_2$ and excess triethylphosphite in the absence of zinc metal (Scheme 57, Table 6). It has been demonstrated that Ni(0) is formed by heating Ni(II) in the presence of $P(OEt)_3$. The conversion rate of 4-bromoanisole **54a** (which is deactivated toward oxidative addition) was surprisingly high. The major product was, however, like in the zinc reactions, the "saturated Heck product" **60**. Some Heck product **56a** was also formed and it did appear that the amount of saturated product formed could be correlated to the amount of $P(OEt)_3$ used. When 10 equivalents or more of $P(OEt)_3$ was used the product was almost exclusively **60** while when the amount of $P(OEt)_3$ was limited the relative percentage of Heck product **56a** increased (Table 6, entries 1-4). The conversion did, however, decrease as the amount of $P(OEt)_3$ was decreased. This suggests that this reaction is not limited at the oxidative addition stage but that the olefin insertion and reductive elimination / β-hydride elimination step are sluggish. The Michael addition of the aryl nickel complex is dominant but requires the presence of a reducing reagent to regenerate Ni(0).

In an experiment involving benzalaniline **58** and $NiCl_2$ (Table 6, entry 5) the Heck product **56a** was the major product but the conversion was very low considering the catalyst loading of 50%, the product representing only a single catalytic cycle.

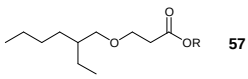
A reaction was performed using a nickel and triphenylphosphine system under phase transfer conditions to compare triphenylphosphine to $P(OEt)_3$ (Table 6, entry 7). The conversion of **54a** was limited to 30% and the Heck product **56a** predominated the saturated product **60**. It would therefore appear that the Heck reaction was not promoted by the presence of excess ligand while conversion of the aryl halide and formation of the saturated product was promoted by facilitating the turnover of nickel in the catalytic cycle ($P(OEt)_3$ being more active than PPh_3 as a reductant).



54a R = 2-ethylhexyl **55a** **56a** **60**

Scheme 57. Nickel catalysed reaction between 4-bromoanisole **54a** and 2-ethylhexyl acrylate **55a**

Table 6. Nickel Catalysed Heck Reactions

Entry	Catalyst (mol%)	Ligand (mol%)	Base	Solvent	Conversion of 54a	Ratio of 56a to 60
1	$NiCl_2$ (~5%)	$P(OEt)_3$ (~50%)	Na_2CO_3	PTC	n.d	1:16 (~35%)
2	$NiCl_2$ (~12%)	$P(OEt)_3$ (100-120%)	Na_2CO_3	NMP	90%	1:30
3	$Ni(POEt_3)_4$ (4%)		K_2CO_3	NMP	5%	1:2.6
4	$Ni[P(OEt)_3]_4$ (4%)	$P(OEt)_3$ (~120%)	NBu_3	NBu_3	100%	N/A **60** was formed in 20%
5	$NiCl_2$ (~50%)	Benzalaniline **58** (55%)	K_2CO_3	THF/NMP	30%	5:1
6	$Ni(PPh_3)Cl_2$ (1%)	PPh_3 (10%)	Na_2CO_3	2-ethyl-hexanol	30% 100% of **55a**	7:6 70% **57**  **57**
7	$Ni(PPh_3)Cl_2$ (5%)	PPh_3 (50%)	Na_2CO_3	PTC	n.d.	7:4 (~30%)

NMP: 1-methyl-2-pyrrolidinone; PTC: phase transfer catalyst = Aliquat 336, n.d. = not determined.

A procedure for nickel catalysed Heck reactions has been developed by Sugi[153]. It involves a reaction carried out in NMP and uses sodium carbonate as base. The nickel catalyst was formed from a mixture of $NiCl_2$ and triphenylphosphine (2 equivalents of PPh_3 relative to $NiCl_2$). The reaction has to be done at elevated temperature (160^oC +) to facilitate the conversion of Ni(II) to Ni(0).

A nickel catalysed Heck procedure for aryl chlorides which includes an in-situ halogen exchange to convert the aryl chloride into an aryl iodide has been developed[154]. The procedure uses a combination of both nickel and palladium and the authors claim that the halogen exchange is catalysed by palladium to convert the aryl chloride into a better Heck substrate. This, however, contradicts the fact that the oxidative addition occurs readily with nickel while the later stages of the reaction (regeneration of the active Ni(0) species) proved to be problematic. It is therefore proposed that the Heck

reaction is actually palladium catalysed while the nickel plays a role in the Finkelstein reaction (the exchange of one halide for another)[155].

No example for the use of a heterogenous nickel catalyst in the Heck reaction has been found.

2.6 Preparation and Testing of Novel Phosphorus based Ligands

In the search for improvements to existing Heck protocols, we set out to examine the use of a number of novel ligands. Our earlier investigations using aromatic imine ligands did not appear promising (see Table 3, Scheme 51). Subsequently, we focused our attention on phosphorus based ligands and specifically on novel types of ligands or those not previously known in Heck coupling.

Sterically hindered trialkyl and triaryl phosphites are known to be highly active ligands for the Suzuki coupling[156-158], and even show activity in the coupling of aryl chlorides[156]. Triaryl phosphites, especially those with added steric bulk and electron-density to increase the cone-angle as well as electron-density of the phosphorous atom, have also been shown to be active ligands for palladium catalysed Heck reactions of activated aryl chlorides and deactivated aryl bromides[159]. Beller reported turnover numbers of >10 000 in the reaction between styrene and 4-bromoanisole using a catalyst comprising $Pd(OAc)_2$ and tri-(2,4-di-*t*-butylphenyl)-phosphite **61**[159]. Turnover numbers were even higher when excess ligand was used (between 10 and 100 to Pd).

In view of the success of the bulky Beller phosphites in the Heck reaction, we set out to devise a cheaper and more accessible alternative. 2-*t*-Butyl-4-methoxyphenol (better known as butylated hydroxy anisole or 3-BHA) is a well known anti-oxidant which is freely available. A triaryl phosphite with 3-BHA as the aryl substituent was proposed to have similar cone-angle and electron-donating properties to **61**. We set out to examine the ligand properties of the "BHA phosphite" **62** which was prepared by reaction of 3 equivalents of 3-BHA with PCl_3 (Figure 4).

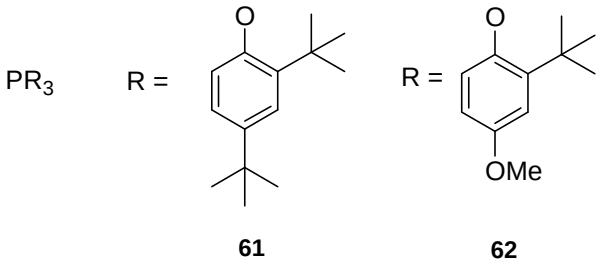
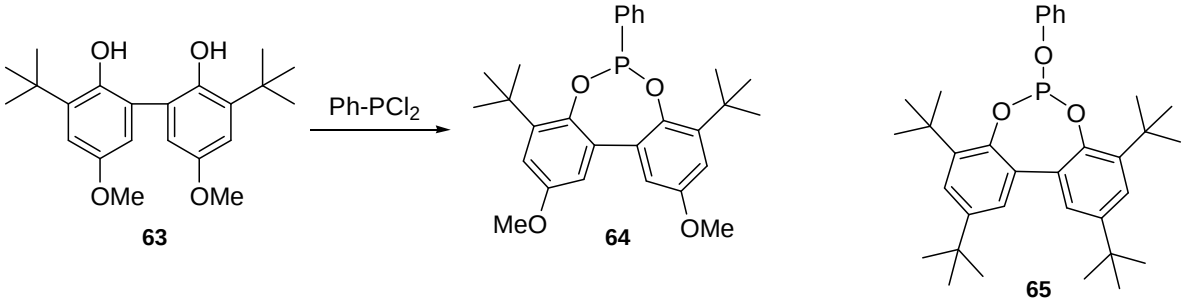


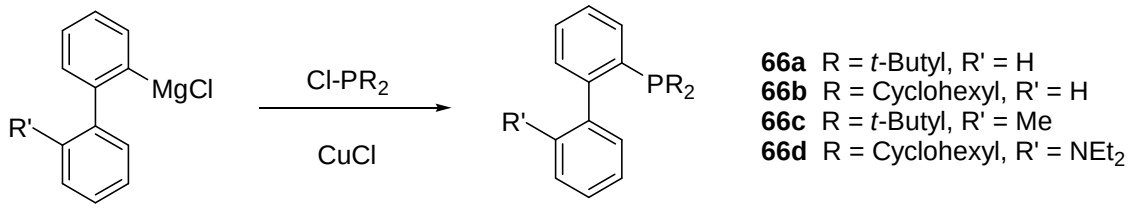
Figure 4. Tri-aryl phosphite ligands

A similar phosphite type ligand **64** where the orientation of the *tert*-butyl groups is constrained to a limited area of space was prepared from dichlorophenylphosphine and a "dimer" of 3-BHA **63** (Scheme 58). A similar structure **65** has been used by Union Carbide Corporation as a ligand to improve the rhodium catalysed hydroformylation of branched olefins[160].



Scheme 58. Preparation of **64**

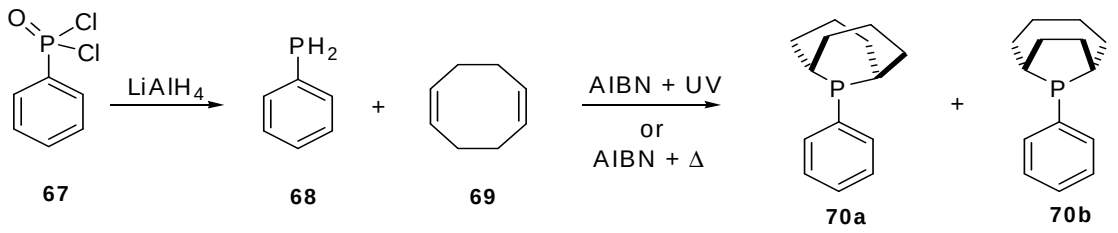
We further examined the preparation of conformationally restricted bulky phosphine ligands which were based on the "Buchwald" ligand series, namely the dialkylphosphinobiaryl type ligands **66** (see Scheme 59). The literature preparation of these ligands typically involves the coupling an existing dialkylphosphine chloride with a Grignard reagent of the biaryl moiety[161] (Scheme 59). This approach is limited by the availability of the dialkylphosphine chlorides (which are tedious to prepare). We, therefore, examined a different strategy by which the aryl/biaryl phosphine is first prepared followed by phosphine addition to unsaturated systems (see Scheme 60 and 61).



66a R = *t*-Butyl, R' = H
66b R = Cyclohexyl, R' = H
66c R = *t*-Butyl, R' = Me
66d R = Cyclohexyl, R' = NEt_2

Scheme 59. Buchwald type ligands

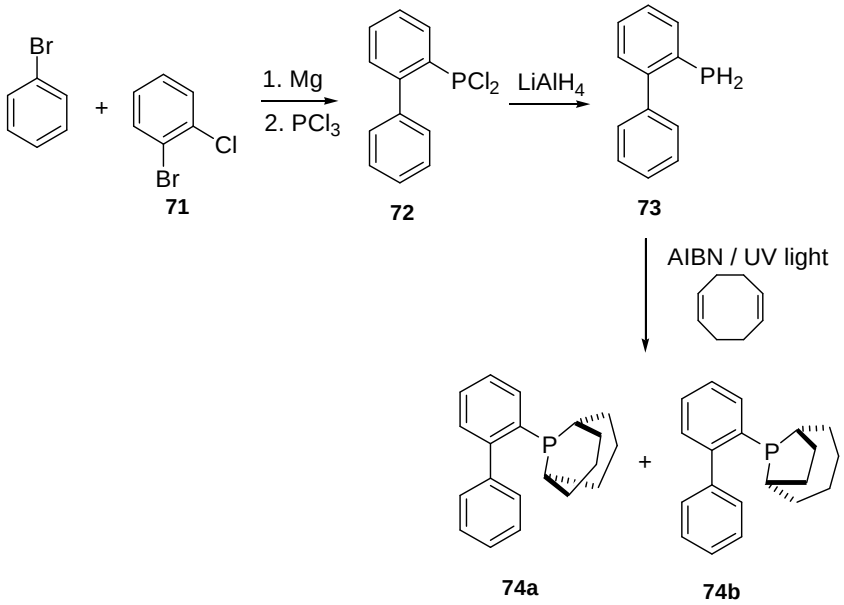
The radical addition of aliphatic phosphines (specifically cyclohexylphosphine) to a cyclic diene (specifically cyclooctadiene, Scheme 60), either thermally or photochemically mediated, has been published[162]. Phenylphosphine **68** was prepared by reduction of dichlorophenylphosphine oxide **67** using $LiAlH_4$. Distilled cyclooctadiene **69** was reacted with a two-fold excess of phenylphosphine in the presence of catalytic AIBN at 95-100°C in toluene solution. The reaction was slow and unselective with a number of peaks appearing in the ^{31}P-NMR spectrum. Stirring at room temperature for 3 days did however result in near to complete conversion of 1,5-cyclooctadiene. Apart from unreacted phenylphosphine **68**, 9 other phosphine peaks were observed by ^{31}P-NMR spectroscopy (all of significant size). Vacuum distillation removed phenylphosphine and toluene (150°C, 10mbar) and a fraction was collected (170°C, 0.5mbar) which contained only two components (by ^{31}P-NMR spectroscopy). This fraction was determined to be a 2:1 mixture of components having ^{31}P chemical shift of 9.3 ppm and -21.7 ppm respectively by ^{31}P-NMR spectroscopy. The major phosphabicyclononane product was determined (by ^{13}C-NMR) to be the symmetrical isomer **70a** while the minor product was the unsymmetrical isomer **70b** (Scheme 60). The reaction between cyclohexylphosphine and **69** is reported to give a 60:40 ratio of peaks at 13.2 ppm and –25.7 ppm[162]. The distillation bottoms contained a number of components which could be higher boiling 1:2 / 2:2 adducts of phenylphosphine and cyclooctadiene. This, however, was not verified.



Scheme 60. Phenylphosphine **68** addition to cyclooctadiene **69** to prepare phenyl phosphabicyclononanes **70a/b**

After a three-month period, the mixture was analysed again and the relative amounts of the two components had changed to a 4:1 mixture (from a 2:1 mixture). Addition of *tert*-butylhydroperoxide to the NMR sample resulted in an exothermic reaction and the peaks shifted from –21.7ppm and 9.3ppm to 41.0ppm and 66.5ppm respectively, which is in agreement with the conversion of a tertiary phosphine to phosphine oxide.

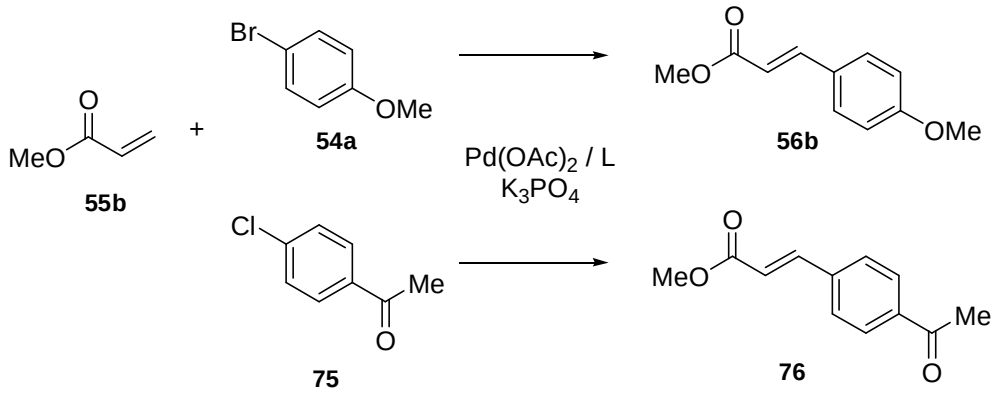
The same procedure was applied to 2-biphenylphosphine **73** in order to prepare a "Buchwald" type ligand. 2-Biphenylphosphine **73** was prepared from phenylmagnesium bromide and 2-chlorobromobenzene **71** and trapping the biphenyl Grignard with PCl_3 followed by lithium aluminium hydride ($LiAlH_4$) reduction of the dichlorophosphine **72** (Scheme 61). Distillation gave **73** in high purity.



Scheme 61. Preparation of biphenyl phosphabicyclononanes **74a** and **74b**

Reaction with cyclooctadiene in the presence of AIBN and irradiation with a sunlamp over 3 days (~ 12x3 hour irradiation periods) gave full conversion of the primary phosphine **73** to a number of components. Major peaks (by ^{31}P-NMR spectroscopy) were observed at 44.5 ppm/-19.8ppm/-17.6ppm and 9.2ppm. It is believed that **74a** and **74b** were formed and correspond to the -19.8 and 9.2ppm peaks due to the similarity with **70a** and **70b**. Oxidation of the NMR sample with *tert*-butyl hydroperoxide gave peaks at 65.5 ppm and 41.3ppm similar to that observed for the phenyl phosphine analogues **70**, the major component having a ^{31}P NMR shift of 38ppm. Due to the low volatility of the components, purification by fractional distillation failed. Column chromatography however caused oxidation of the product. The preparation of this ligand was not further pursued.

These ligands (**62**, **64**, and **70** as a mixture of isomers) were tested in combination with $Pd(OAc)_2$ in the Heck reaction between methyl acrylate **55b** and either 4-bromoanisole **54a** or 4-chloroacetophenone **75** (Scheme 62).



Scheme 62. Heck coupling of methyl acrylate **55b** with **54a** and **75**

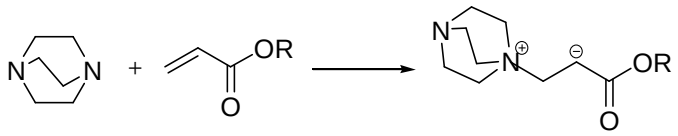
Although **62** (as a 2:1 mixture with 1mol% $Pd(OAc)_2$) only showed low activity in the reaction between **54a** and **55b** (14% of **56b** formed after 40h at 110^{o}C) much more promising results were achieved in the reaction with the electron-deficient aryl chloride **75** (70% of **76** was formed after 2h and 77% after 40h). Ligand **64** was found to be inefficient in promoting the reaction with **55b** and was not tested further.

The phenylphosphine / cyclooctadiene adducts **70a** and **70b** also showed activity with 41% **56b** formed in 40h while **76** was formed in 68 and 77% yield after 2 and 16h respectively. These results are promising as the yields of the Heck products **56b** and **76** were superior to those obtained under the same conditions when using P*t*Bu$_3$, P*o*Tol$_3$, **66a** or **66b** as ligands.

It is apparent that there is the potential for the development of a series of ligands which activate palladium for use in the Heck reaction. Simple 3-BHA derived phosphites and phenylphosphine/cyclooctadiene adducts are of particular interest in this regard. The use of these ligands in Heck chemistry will be pursued at a later date.

2.7 Heck Reactions Involving Nucleophilic Bases

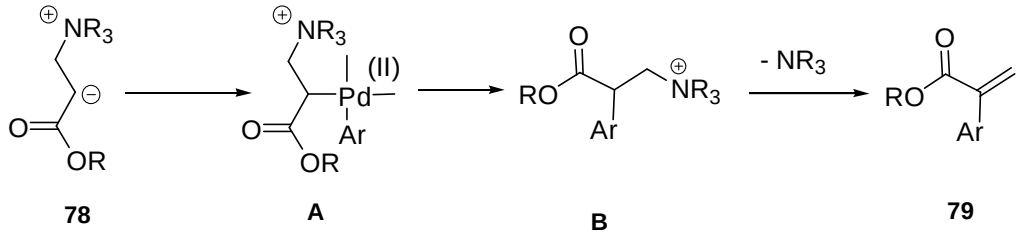
The traditional Heck reaction conditions employ a trialkylamine as the base. Triethylamine is the most common base, while tributylamine is often used when higher reaction temperatures are used. Bases are, however, chosen based on their basicity and not their nucleophilic properties.



77 **55** **78**

Scheme 63. Conjugate addition of DABCO to acrylate

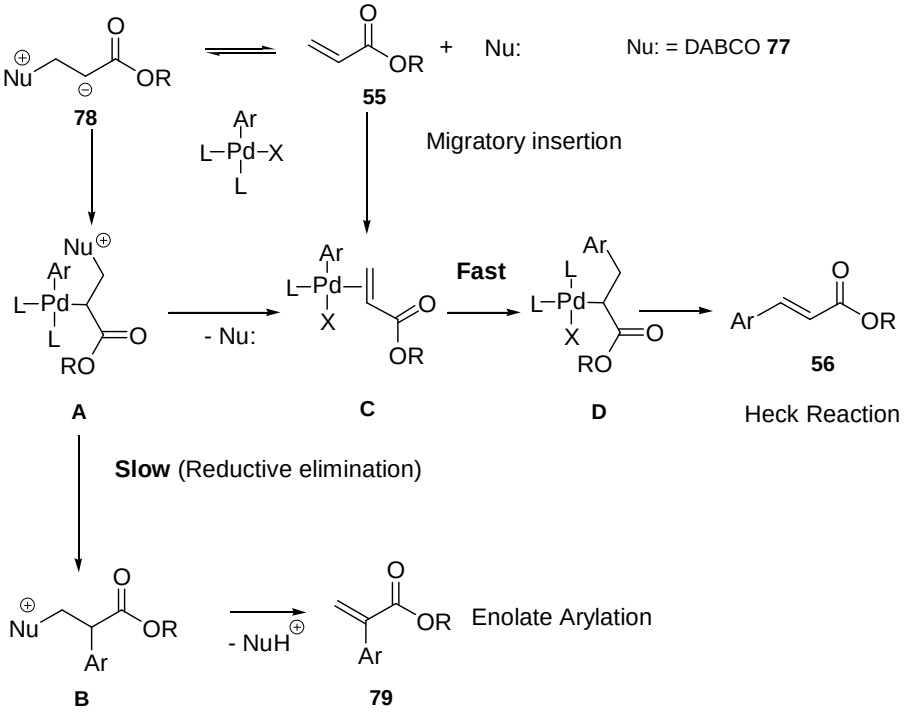
Nucleophilic bases like DABCO **77** are known to add to acrylate esters in a conjugate sense (as shown in Scheme 63) as is exemplified by the Baylis-Hillman reaction[163]. It was anticipated that the use of a nucleophilic base, known to add conjugatively into acrylate esters, in a Heck reaction might lead to a reversal of regioselectivity by favouring substitution in the alpha-position of an acrylate ester (Scheme 64).



Scheme 64. Proposed Concept of Modified Heck Reaction using a Nucleophilic Amine

The formation of intermediate **A** from **78** by reaction with an aryl-palladium(II) complex could conceivably lead to the formation of **B** (as in enolate arylation) which on elimination of the nucleophilic amine would give the 2-arylated acrylate **79**.

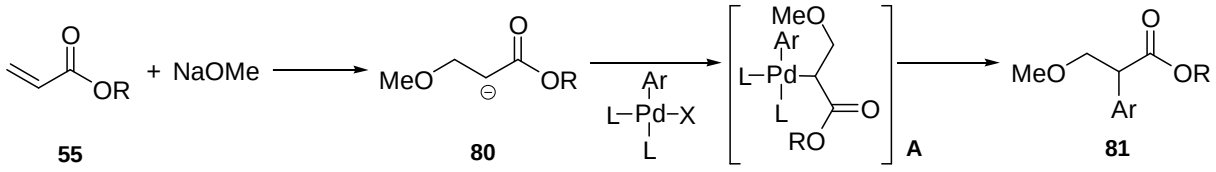
On the basis of the proposed concept, a number of reactions on bromobenzene and methyl acrylate involving DABCO were performed in our laboratories employing different catalysts and conditions. Most of the reactions were slow, compared to when using an inorganic base or triethylamine, and yielded exclusively the normal Heck product, methyl cinnamate **56c**.



Scheme 65. Competition between Heck Mechanism and Enolate Arylation Mechanism

The most likely explanation for the formation of the β-substituted product **79** is achieved by comparing the relative reaction rates involved (see Scheme 61). The association of the enolate to the palladium complex (formation of **A**) and the reductive elimination (**A**→**B**) steps during enolate arylation is suspected to be rate limiting (see Chapter 3, Section 3.2)[120]. In the Heck mechanism the alkene coordination to the palladium complex (formation of **C**) is thought to be a slow process especially when a neutral pathway is followed while the migratory insertion and hydride elimination (**C**→**D**→**56**), on the other hand, are likely to be fast. With the addition of a nucleophile to an acrylate ester being reversible and the reductive elimination step slow or blocked, the normal Heck product **56** will predominate.

In a similar manner sodium methoxide can also add conjugatively to an acrylate ester to generate the alpha enolate of a 2-methoxypropanoate ester **80** (as depicted in Scheme 66). If such a methoxide/acrylate adduct was to associate to an aryl-palladium species it could be postulated that an alpha arylacrylate **81** would be formed via an enolate arylation mechanism involving reductive elimination.



55 **80** **A** **81**

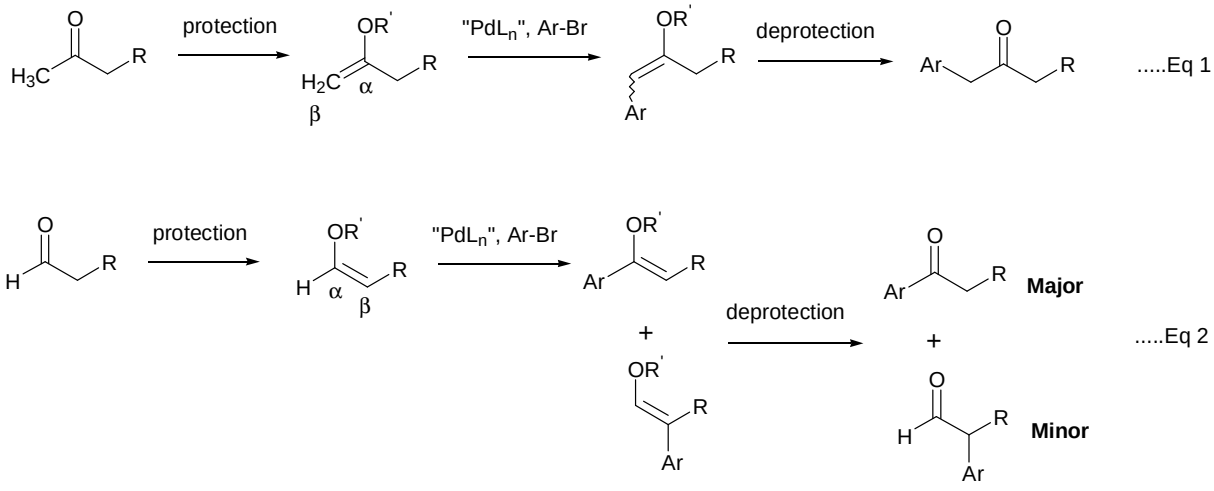
Scheme 66. Proposed concept of conjugate addition of methoxide to acrylate esters followed by enolate arylation

A reaction between methyl acrylate and bromobenzene with sodium methoxide as base was attempted using a $Pd(OAc)_2$ / 2-(di-*tert*-butylphosphino)-biphenyl **66a** catalyst system. Again the major product formed was methyl cinnamate **56** with no sign of the desired product.

The use of alkoxide bases that can reduce palladium via β-hydride abstraction, methoxide and ethoxide, is discouraged as this lead to formation of palladium black as well as aryl halide reduction and biphenyl formation.

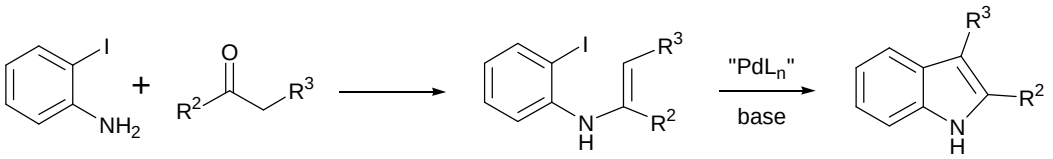
The failure of enolate arylation and the preference for the Heck reaction is similar to that observed when DABCO was used as nucleophilic base. Once again the association of the enolate to the Pd(II) complex or the reductive elimination step must be disfavoured and the addition of the nucleophilic base reversable (see Scheme 65, Nu = OMe).

Since the Heck mechanism appears to predominate when an arylation reaction could follow a Heck route or an enolate arylation route, ketone arylation has been performed in a Heck-type approach by masking the ketone as an olefinic substrate. Enol ethers and silyl enol ethers are common Heck substrates and form the arylated enol ether which is the protected form of an α-arylketone[77-79,74](Scheme 67). Due to the selectivity in the formation of the enol-ether from a dialkyl ketone, the least substituted arylketone will be formed. In the case of enol-ethers derived from an aldehyde the reaction is complicated by the fact that both the α and β-positions of the enol ether are available for substitution (Scheme 67, eq 2). Since the α-position of enol ethers is often more reactive, the major product is an enol protected aryl alkyl ketone. Alkenes with a β-substituent are less favourable Heck substrates and therefore the use of an enol ether is broadly limited to ketones with one methyl group and a more bulky substituent, or a substituent lacking a proton α to the carbonyl (Scheme 67, eq 2).



Scheme 67. Ketone and aldehyde arylation via Heck reaction on enol ethers

A novel synthesis of 2,3-disubstituted indoles **85** via a palladium catalysed annulation between iodoanilines **82** and ketones **83** was published by Chen *et al* [80](Scheme 68). Although, at first glance, the procedure appears to be an enolate arylation, it does in fact involve a Heck reaction. During the reaction an enamine **84** is formed *in situ* which than takes part in an intramolecular Heck reaction to form the indole. The scope of ketones that may be used in this reaction is broad as the intramoleclar Heck reaction is more facile and less affected by steric hindrance.



82 **83** **84** **85**

Scheme 68. Intramolecular Heck reaction in the formation of 2,3-substituted indoles

2.8 Conclusion

During this investigation into the preparation of cinnamic acid derivatives by different Heck reaction protocols a number of important conclusions were made. The development of a practical and economically feasible procedure for, especially, OMC had to fulfill a number of specifications, of which the cost of the catalyst was the most critical. It was found that low palladium levels could be used (0.01-0.025mol% $Pd(OAc)_2$) when it was stabilised with a relatively high phosphine loading (40 equivalents of PPh_3 to Pd). Reactions could also be performed in the absence of solvent and using an inorganic base. These reactions required the use of a phase transfer agent while the use of a long chain alcohol (to facilitate contact between the inorganic base and non-polar acrylic acid ester in a highly viscous slurry) resulted in acrylate consumption via conjugate addition of the alcohol. The problems associated with the use of high levels of phosphine could, in part, be solved as the replacement of PPh_3 with $P(OEt)_3$ (which can be oxidised and hydrolysed to phosphoric acid and ethanol) was proven in principle.

Although good results were obtained with iodobenzene using solvent-free conditions (presence of PTC), heterogenous catalysis (10% Pd/C) was less effective for aryl bromides. Better results were obtained when a polar solvent (like NMP) was used. Unlike literature claims that small amounts of water accelerated the reactions in NMP, we found that it led to nearly quantitative hydrolysis of the formed cinnamic acid ester. It was also found that fair to good yields of cinnamic acids could be obtained from acrylic acid using Pd/C in NMP or NMP/water mixtures.

The Heck coupling of acrylic acid could also be performed using a homogenous palladium catalyst. A high yield of cinnamic acid was obtained with $Pd(OAc)_2/PPh_3/Na_2CO_3$ when xylene and a PTC were used. These reaction conditions would allow for removal of the product in a water wash while allowing the catalyst and unreacted aryl halide to be recycled in the xylene phase. Unfortunately, results were less promising when 4-bromoanisole was used instead of bromobenzene.

The use of phosphine-free catalytic systems, including the use of the heterogenous supported palladium catalysts is possible since none of the steps in the general Heck cycle (oxidative addition, migratory insertion and β-hydride elimination) are totally dependant on the presence of a strongly bound ligand. Non-ligated palladium is inherently reactive enough for insertion into an aryl-X bond especially when X = I. When X = Br and especially Cl, the rate of oxidative addition is, however, low and is greatly aided by electron donating phosphine ligands.

The most serious drawback of the phosphine-free systems is the inherent instability of the catalytic cycle. Mismatch of reaction rates of individual stages could cause collapse of the catalytic cycle and catalyst deactivation.

Due to the lack of strongly bound neutral ligands these systems proceed via the cationic route through de-ligation of the anionic ligands and therefore are best performed in polar solvents like DMF, NMP as well as in aqueous media.

Success with heterogenous palladium and other non-ligated catalysts relies heavily on finding the specific reaction conditions most suited for each system. The use of phase transfer agents, halide salt promoters, mixed amine and inorganic bases, ionic liquids and aqueous systems are topics under investigation to improve the application to bromo and chloro arenes.

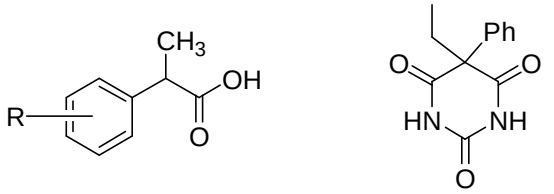
In another attempt at making the Heck approach to cinnamic acid esters more economically viable by lowering the cost of the catalyst nickel catalysed reactions were investigated. Nickel catalysed Heck reactions are known but require the use of a stoichiometric amount of zinc dust as a reductant to maintain nickel in the zero oxidation state. When we used triethylphosphite as ligand with $NiCl_2$ we found that, although the acrylate was coupled to the aryl moiety, the double bond had been reduced to give a 3-arylpropionic acid ester as the major product. A direct relation between the amount of reduced product as well as conversion of the aryl halide and the amount $P(OEt)_3$ was observed. The use of PPh_3 lead to less of the 3-arylpropionic acid ester as it is a less efficient reductant for Ni(II). The reluctance of Ni(II) to be converted to Ni(0) *ie.* reductive elimination of the Heck product, was the major limiting factor for the use of nickel in the Heck reaction. It is believed that at elevated temperature, higher concentrations of Ni(0) would be achievable.

In an attempt to use Heck chemistry to achieve α-arylation of esters, experiments were performed to change the regioselectivity of acrylate arylation. The use of nucleophilic bases, to add in a Michael sense to the acrylate, failed to afford the 2-substituted acrylate product. It is thought that although the nucleophilic base adds conjugatively to the acrylate substrate, this reaction is reversible and since reductive elimination of the enolate-Pd-aryl complex is slow, the normal Heck pathway predominates and leads to almost exclusively the more favoured β-substituted acrylate.

CHAPTER 3

STUDIES INTO THE ARYLATION OF VARIOUS ENOLISABLE SUBSTRATES

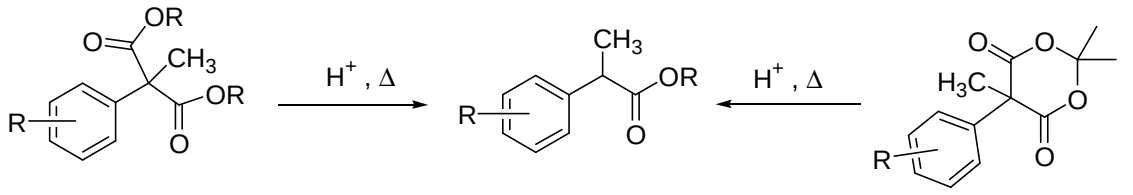
The arylation of the more electron rich enolates of dicarbonyl compounds like 1,3-diketones or malonate esters opens up potential routes to several industrial important products especially the arylpropionic acid anti-inflammatory drugs and phenobarbital (Figure 5) and are therefore of particular interest to researchers in industry and academia alike.



Arylpropionic Acids **Phenobarbital**

Figure 5.

The arylation of aliphatic esters is, potentially, a very interesting and powerful conversion which could provide the most atom-efficient route to the arylpropionic acid anti-inflammatory drugs. The arylated ester intermediate is, however, also accessible through decarboxylation of arylated malonates or Meldrum's acid derivatives (Scheme 69).



Arylated Malonate Ester **Arylated Meldrum's Acid**

Scheme 69. Preparation of arylated ester by decarboxylation of arylated malonate ester or Meldrum's acid

Examples of arylation utilising palladium catalysis for the arylation of the more stabilised enolates of dicarbonyl compounds like 1,3-diketones or malonate esters are rare[99,91,100,90]. The same reaction with related species like Meldrum's acid and barbituric acid has not been investigated. In theory, these conversions are more complicated since these species are able to form stable complexes with the metal which does not allow reductive elimination to take place. This promotes the pathway for competitive reactions like β-hydrogen elimination and subsequent reduction of the aryl

halide. For example, acetylacetone is known to form remarkably stable complexes with palladium[164](Figure 6). It does, however, seem that, in the case of malonate esters, high steric bulk induced by the use of tertiary-butylphosphine ligands can induce reductive elimination resulting in the desired arylated malonate.



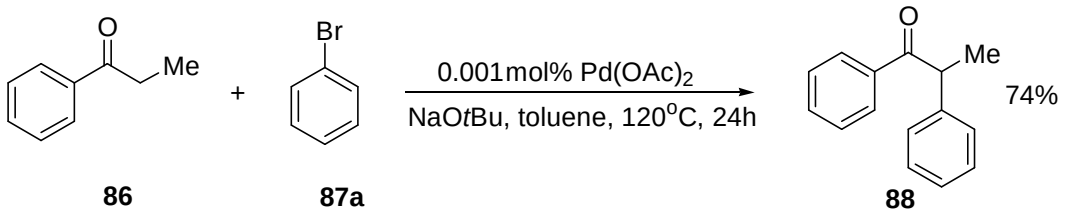
(pyridyl)Pd(PPh_3)(acac) (pyridyl)Pd(PEt_3)$_2$(η^1-acac)

Figure 6. Palladium acetylacetone complexes

3.1 Arylation Reactions of Ketones and 1,3-Diketones

The first examples of palladium catalysed enolate arylation published by the research groups of both Hartwig and Buchwald, dealt with ketone substrates[91,90]. The alkyl aryl ketones, in particular, propiophenone **86**, were the preferred substrates since complicating factors such as regioselectivity and mono- and diarylation selectivity are avoided. The extra stability imparted by the phenyl group as well as the low self-condensation tendency of propiophenone has made it a privileged enolate arylation candidate.

Our early investigations also centred around reactions of this substrate **86** (Scheme 70). After several experiments with different conditions it was found that the best results were obtained by using NaO*t*Bu as base, toluene as solvent, $Pd(OAc)_2$ as the palladium source and a temperature of 110^{o}C. This was later confirmed in publications by Buchwald who used very similar conditions[100]. They discovered that the reaction between propiophenone and bromobenzene did not require the addition of ligands as $Pd(OAc)_2$ (at levels as low as 0.001 mol%) on its own led to a facile arylation reaction (Scheme 70). The ligand-free reactions are, however, not general although a few other examples were published[100].

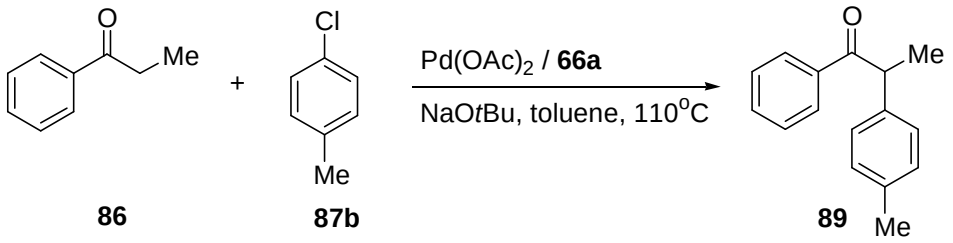


Scheme 70. Arylation of propiophenone by low levels of unligated palladium

We found that NaH could also be used in the propiophenone arylation reaction provided that deprotonation (and hydrogen evolution) was complete prior to the addition of $Pd(OAc)_2$. Deprotonation was carried out by heating to 100°C for 5 minutes until hydrogen formation ceased. This was done to prevent catalytic hydrodehalogenation of bromobenzene to benzene by hydrogen in the presence of a palladium catalyst. An arylation yield (**88**) of 93% (full consumption of bromobenzene **87a**) was achieved in 1 hour at 110°C with the use of 1.25 molar equivalents of propiophenone and 0.3 mol% palladium. The high arylation yield points to the fact that the arylation reaction is faster than the competitive reactions (hydrodehalogenation to benzene and homocoupling to biphenyl only accounted for 7% of bromobenzene consumption).

The comparable reaction using NaO*t*Bu as base performed similarly with a yield of 94% after 2 hours of heating although bromobenzene conversion was not complete (<5% remained).

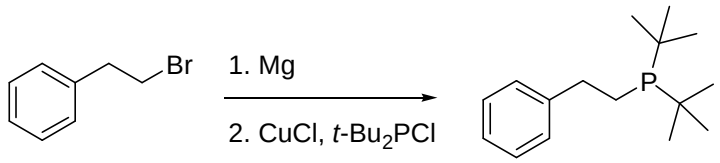
While unligated palladium proved to be an efficient catalyst for the reaction between propiophenone and aryl bromides, aryl chlorides required the use of a bulky and electron-rich phosphine ligand. The reaction between propiophenone **86** and 4-chlorotoluene **87b** was attempted with 1mol% $Pd(OAc)_2$ under similar reaction conditions to these employed for the reaction with bromobenzene (Scheme 71). The arylation yield was a mere 3% after 16 hours of heating. Full conversion of the aryl chloride to **89** was achieved after 30 minutes of heating when 2-(di-*tert*-butylphosphino)-biphenyl (**66a**) was used as ligand.



86 **87b** **89**

Scheme 71. Arylation of propiophenone with 4-chlorotoluene

The use of 2-(di-*tert*-butylphosphino)-phenylethane (**90**) as ligand gave a similar result with complete aryl chloride consumption within 1h of heating. **90** was prepared from phenethyl magnesium bromide and di-*tert*-butylphosphine chloride in a CuCl catalysed reaction (Scheme 72).



90

Scheme 72. Preparation of **90**

A ligand prepared during the investigation of the Heck reaction (see Chapter 2), phenyl phosphabicyclononane **70a/b**, proved to be inactive in this reaction.

Beller recently published results of ketone arylation reactions with non-activated and deactivated aryl chlorides such as 4-chlorotoluene **87b** and 4-chloroanisole **87e** [1]. It was found that the use of highly electron-rich and sterically hindered phosphine ligands holds the key to successful arylation reactions when using aryl chlorides. Of several sterically hindered phosphine ligands that were tested, *n*-butylbis(1-adamantyl)-phosphine (*n*-BuPAd$_2$) was found to be the most effective with a 97% arylation yield achieved in the reaction between propiophenone and 4-chlorotoluene at a catalyst loading of 0.05mol%.

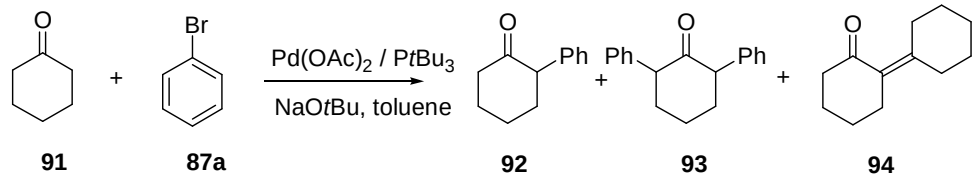
The use of a nickel salt as the catalyst in the arylation reaction of propiophenone was investigated in our laboratories. Several attempts with both 2mol% Ni(OAc)$_2$ and Ni(acac)$_2$ failed to yield any of the desired arylation product **88** when bromobenzene

87a was used. Significant amounts (by qualitative GC) of **88** were, however, produced when iodobenzene was used instead of bromobenzene with both $Ni(OAc)_2$ and $Ni(acac)_2$ as catalysts (the yields were not determined and both reactions suffered from side-reactions that accounted for significant propiophenone consumption).

When $Ni(OAc)_2$ was, however, ligated with **66a** and reduced in situ to Ni(0) with zinc metal (Ni:**66a**:Zn = 1:2:3) arylation with bromobenzene took place and 34% of **88** was formed. No reaction was observed with $Ni(PPh_3)_4$ (prepared *in situ* from $Ni(PPh_3)_2Cl_2$ + $2PPh_3$ + Zn).

The requirement for strong basicity in these palladium catalysed arylation reactions was demonstrated by the failure of K_3PO_4 (anhydrous and powdered) to mediate propiophenone arylation (even when the more polar 1,4-dioxane was used to ensure higher solubility of the inorganic base).

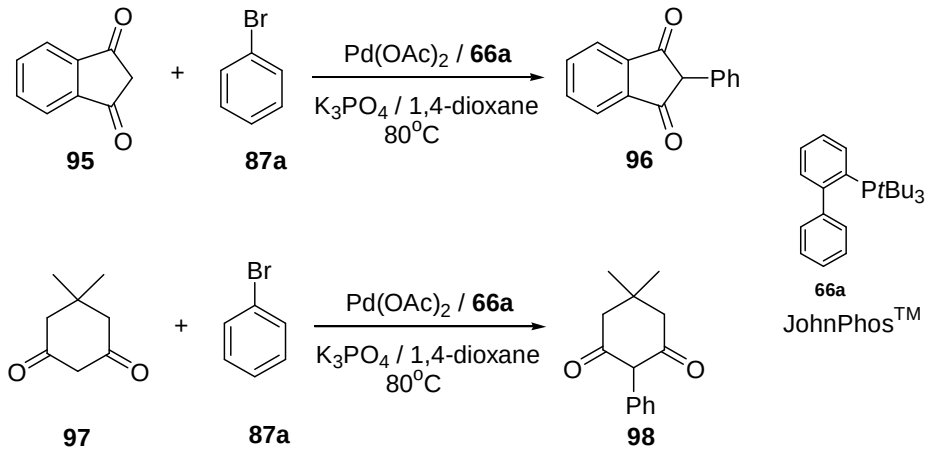
The importance of the correct choice of base for each specific substrate was demonstrated in the arylation of cyclohexanone **91** with bromobenzene and $Pd(OAc)_2$. The use of NaO*t*Bu in the reaction between cyclohexanone and bromobenzene resulted in rather low conversion of the ketone (36%). The use of an excess of bromobenzene led to significant amounts of the α,α'-di-arylated product **93** even while unreacted cyclohexanone was still present (Scheme 73). Higher reaction temperatures (100-110°C instead of 60°C) and longer reaction time also led to the formation of di-arylation product **93** as well as self-condensation product **94**.



Scheme 73. Arylation reaction of cyclohexanone **91**

When the reaction was repeated using K_3PO_4, the reaction was much faster even though mixing was hampered by the formation of a thick slurry. A bromobenzene conversion of >90% was achieved after 3 hours at 110°C (1.5 molar equivalents of cyclohexanone) while the selectivity towards monoarylation (**92**) was high (6.5:1 **92:93**). Mixing in the reaction was improved by using 1,4-dioxane as solvent. Bromobenzene conversion was 88% after 2 hours at 105°C while the mono to di-arylation ratio was 4:1 (**92:93**). The mono-arylation product **92** was isolated in 64% yield after purification by column chromatography. Buchwald and co-workers reported similar results, also by using K_3PO_4 in toluene[100].

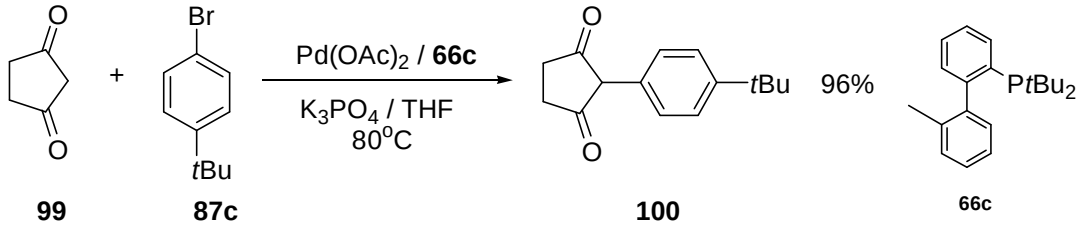
NaO*t*Bu also was not a suitable base for reactions of 1,3-diketones as the reaction of 1,3-indandione **95** with bromobenzene **87a** in the presence of $Pd(OAc)_2$ and P*t*Bu$_3$ failed to yield any arylated product (see Scheme 74). The reaction was severely hampered by the formation of a thick emulsion upon addition of the base and it is thought that the catalyst was deactivated by chelation of the metal with the enolate generating a species analogous to that illustrated in Figure 6.



Scheme 74. Arylation of 1,3-indandione **95** and dimedone **97**

When the reaction was repeated using K_3PO_4 instead, the arylation reaction proceeded smoothly with full conversion of bromobenzene in 2 hours at 80°C yielding exclusively 2-phenyl-1,3-indandione **96**. Dimedone (5,5-dimethylcyclohexane-1,3-dione) **97** was arylated with similar efficiency under the same conditions. High

yielding reactions of cyclohexane-1,3-dione and cyclopentane-1,3-dione with aryl bromides were reported by Buchwald, also using K_3PO_4 in either dioxane or THF solution[100](Scheme 75). 2-Di-*tert*-butylphosphino-2'-methylbiphenyl **66c** was used as ligand while the closely related 2-(di-*tert*-butylphosphino)-biphenyl ligand (JohnPhos™) **66a** was used in the current investigation. It was noted that, although arylation of cyclic diketones was feasible, all attempts with the acyclic counterparts failed – presumably due to the formation of stable complexes of the enolates with palladium.

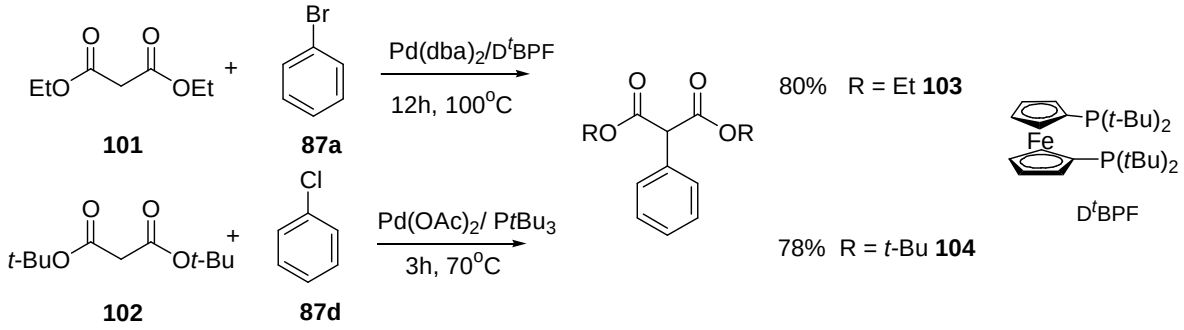


Scheme 75. Arylation of cyclopentane-1,3-dione by Buchwald[100]

In summary it appears that, while the palladium catalysed arylation of propiophenone with aryl bromides was successful in the absence of a phosphine ligand, the same reaction with aryl chlorides required the presence of an electron-rich phosphine ligand to promote oxidative addition to the aryl chloride bond. An additional requirement for a sterically hindered ligand arises when highly stabilised β-dicarbonyl enolates are arylated to promote reductive elimination. The choice of base is an important factor in the success of enolate arylation reactions as it appears that the use of a milder base (such as K_3PO_4) for more acidic substrates is advantageous. The build-up of high concentrations of the enolate during the reaction seems to negatively affect the arylation reaction rate. Optimal conditions seem to be achieved when deprotonation and arylation rates are matched.

3.2 Arylation Reactions of Malonic Acid Derivatives

Following on the successful arylation of the cyclic dicarbonyl compounds, the arylation of malonate esters (which have similar electronic properties to β-dicarbonyl substrates) was investigated. The stabilizing effect of the two carbonyl groups of malonic acid derivatives (as is the case with β-dicarbonyl substrates) could make reductive elimination slow and an η^2-*O,O*-bound palladium complex of such a β-dicarbonyl stabilised anion could be too stable to participate in the catalytic cycle. Nevertheless, the early publications relating to ketone arylation by both Hartwig[99] and Buchwald[100] included one or two examples of malonate ester arylation. Buchwald reported a 92% yield for the reaction between 4-*t*-butylbromobenzene (**87c**) and diethyl malonate (**101**) while Hartwig published a similar result with bromobenzene (Scheme 76). Hartwig also reported a 78% yield for the reaction of chlorobenzene (**87d**) with di-*t*-butyl malonate (**102**) using 1,1'-bis(di-*t*-butylphosphino)ferrocene (D^{t}BPF) as the ligand for the palladium catalyst.



Scheme 76. Arylation of malonate esters as reported by Hartwig[99]

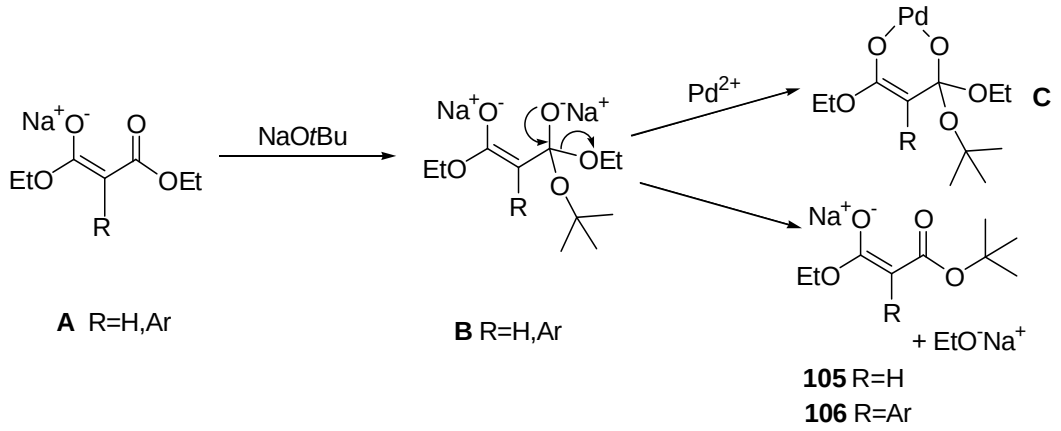
Conditions: 2mol% Pd; Pd:L = 1:1.25 for bromobenzene and 1:0.5 for chlorobenzene; 1.1 eq of malonate ester; 1.5 eq of NaO*t*Bu; reactions were conducted in dioxane solvent.

3.2.1 Palladium catalysed diethyl malonate arylation reactions

The reaction of bromobenzene with diethyl malonate using the $Pd(OAc)_2/P\textit{t}Bu_3$ catalyst system was repeated in our laboratory. When the reaction was conducted at 70^{o}C in THF solvent only 15% conversion of the malonate was achieved while ~50% of bromobenzene was consumed. When repeated in toluene solvent and at 110^{o}C, full conversion of bromobenzene and an 88% yield of diethyl 2-phenylmalonate **103** was achieved after only 30min.

In an attempt to improve the yield based on diethyl malonate (80% since it was added in 10% excess to bromobenzene) a reaction was performed in which a 10% excess of bromobenzene was used. Although full bromobenzene conversion was achieved, the diethyl malonate conversion remained at 80%. The addition of DMF to improve solubility of the malonate anion and to improve mixing during the latter stages of the reaction (when the large amount of NaBr formed hampers mixing) also did not result in improving malonate conversion beyond 80%. It would appear that side-reactions become competitive once the arylation reaction rate decreases due to low concentrations of substrate.

The use of 2 equivalents of base, to ensure full deprotonation of the substrate and product, retarded product formation (only 7% conversion of diethyl malonate). Upon the addition of another equivalent of diethyl malonate, the reaction rate increased and an overall malonate conversion of 39% was achieved as compared to 80% consumption when 1.2 equivalent of base is used. Attack of excess *t*-butoxide to the already deprotonated diethyl malonate **A** to form dianion **B** which can form a stable chelate complex with palladium **C** might explain this observation (Scheme 77).



A R=H,Ar

B R=H,Ar

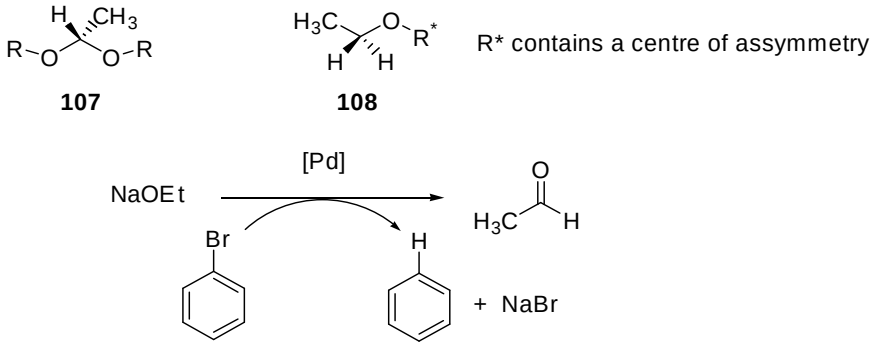
105 R=H
106 R=Ar

Scheme 77. Nucleophillic attack of malonate enolate by excess NaO*t*Bu

The observation that both diethyl malonate and diethyl phenylmalonate are transesterified with *t*-BuOH to yield mono *t*-butyl esters **105**/**106** in all reactions (albeit to the extent of only 5-10%) supports the formation of **B** (as likely intermediate during transesterification). This reaction would lead to the formation of sodium ethoxide and ethanol which are known to reduce aryl halides under palladium catalysis (see Scheme 78)[100]. The presence of ethanol, therefore, does explain hydrodehalogenation (to the parent arene) and homocoupling (to the biaryl) both of which involve the reduction of the aryl halide.

The use of the less nucleophilic sodium tris-(*t*-butyl)-methoxide should be examined to establish the role of nucleophilicity at essentially constant basicity.

When the reaction between bromobenzene and diethyl malonate in THF was repeated using 2-(di-*tert*-butylphosphino)-biphenyl **66a** very little arylation was observed although significant amounts of both bromobenzene and diethyl malonate were consumed. Isolation of the products from the reaction mixture and analysis by NMR spectroscopy revealed that apart from unreacted starting materials an unknown compound was present. Attempts at isolation and purification of this compound failed.



Scheme 78. Structural fragments of the unknown compound formed during phenylation of diethyl malonate using **66a**

When the reaction was repeated in toluene solvent, formation of the same by-product was observed although around a significant proportion of diethyl malonate was converted to the required phenylated product **103**. The use of a 1:1 ratio of palladium and ligand did lead to an increase in reaction rate (no further reaction after 1hour at 110^{o}C) but not in selectivity to **103**.

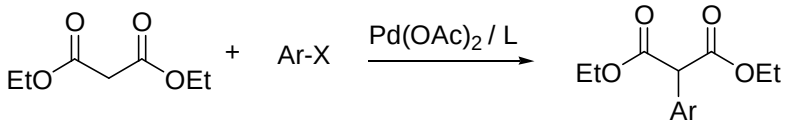
From both ^{1}H-NMR and ^{13}C-NMR analysis of the crude product it would appear that the unknown by-product contains an acetaldehyde acetal moeity **107**. The ^{1}H-NMR spectrum contains a quartet signal at 5.04ppm (1H) and a corresponding doublet at 1.38ppm (3H) while the ^{13}C-NMR spectrum contains a characteristic signal at 104ppm. The unknown compound also appears to contain a substructure such as **108** with R containing a centre of asymmetry since the CH_2 signal appears as 2 sets of doublets of quartets typical for a non-equivalent methylene as part of an ethyl substituent.

It is proposed that acetaldehyde is formed by a redox mechanism in which bromobenzene is hydrogenated and ethanol/sodium ethoxide is dehydrogenated. Acetal formation is therefore possible in the presence of free ethanol and hence the proposed acetaldehyde acetal reasonable. Combining the acetal structure with the ethoxide fragment in such a manner that a centre of asymmetry is created did not yield any reasonable structures.

The failure of the system using ligand **66a** to give high yields of **103** was surprising as the very closely related ligand **66c** was used by Buchwald to great effect in the reaction between diethyl malonate and 4-*tert*-butyl bromobenzene **87c** (see Scheme 75, 92% yield). They did, however, used K_3PO_4 as base, once again showing the limitations in the use of NaO*t*Bu. This ligand has also been shown to be active with aryl chlorides in ketone arylation reactions and, therefore, we investigated the malonate arylation reaction with chloroarenes instead (see Table 7).

The reaction with the electron-rich 4-chlorotoluene **87b** proceeded smoothly and 72% arylation yield (**103d**) was achieved while a small amount of the unknown compound was formed (Table 7, entry 5) using 1.1 equivalent of NaO*t*Bu. When chlorobenzene was the aryl halide, however, none of the unknown compound was formed while a 93% arylation yield was achieved (entry 6). It was observed that other side reactions like biphenyl formation and transesterification were also less prevalent when using chlorobezene as the substrate.

The amount of base required for high malonate conversion exceeded 1 equivalent as a lower malonate conversion (66%) was observed when only 1 equivalent base was used (80% conversion with 1.1 equivalents NaO*t*Bu (entry 7)). This suggests that a significant amount of base is consumed by deprotonation of the arylated malonate. In principle, 2 equivalents of base should be required to achieved 100% malonate conversion but (as was discussed earlier) this led to catalyst deactivation. Portion wise addition of base (to match the arylation rate) might give the desired effect.



101a **87a-g** **103a-g**

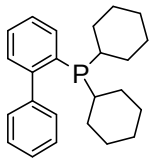
Table 7. Arylation reactions of diethyl malonate[a].

Entry	Aryl halide (equivalents)	Ligand	Base (equivalents)	Temp Solvent	Mol% Pd	Time	Yield of 103
1	Bromobenzene (0.9) **87a**	P*t*Bu$_3$	NaO*t*Bu (1.0)	70°C THF	2.0	16 h	15% **103a**
2	Bromobenzene (0.9) **87a**	P*t*Bu$_3$	NaO*t*Bu (1.0)	110°C Toluene	2.0	0.5 h	88% **103a**
3	Bromobenzene (1.1) **87a**	P*t*Bu$_3$	NaO*t*Bu (1.1)	110°C Toluene	2.0	1 h	78% **103a**
4	Bromobenzene (1.1) **87a**	**66a**	NaO*t*Bu (1.1)	110°C Toluene	2.0	1 h	33%[b] **103a**
5	4-chlorotoluene (0.8) **87b**	**66a**	NaO*t*Bu (1.1)	110°C Toluene	1.0	3 h	72%[c] **103d**
6	Chlorobenzene (0.8) **87d**	**66a**	NaO*t*Bu (1.1)	110°C Toluene	1.0	2 h	93% **103a**
7	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.0)	110°C Toluene	1.0	6 h	66%[d] **103a**
8	Chlorobenzene (0.8) **87d**	**66a**	NaO*t*Bu (1.1)	110°C Toluene	0.1	24 h	86% **103a**
9	Chlorobenzene (1.2) **87d**	PCy$_3$	NaO*t*Bu (1.2)	110°C Toluene	1.0	24 h	30%[e] **103a**
10	Chlorobenzene (1.2) **87d**	**66b**	NaO*t*Bu (1.2)	110°C Toluene	1.0	24 h	40% **103a**
11	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.5	0.5 h 1.5 h	90% **103a** 92%
12	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.1	1.5 h 17 h	91% **103a** 95%

Entry	Aryl halide (equivalents)	Ligand	Base (equivalents)	Temp Solvent	Mol% Pd	Time	Yield of 103
13	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	80°C Toluene	0.1	1.5 h 17 h 24 h	6.5% **103a** 87% 90%
14	Chlorobenzene (2.4) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.1	1.5 h 17 h	77% **103a** 96%
15	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.5)	110°C Toluene	0.1	1.0 h 1.5 h 24 h	71% **103a** 78% 97%
16	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.01	1.5 h 17 h 24 h	22% **103a** 52% 56%
17	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.1[f]	5 min 1 h	52% **103a** 98%
18	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.01[g]	18 h	10% **103a** +13% **109**
19	Chlorobenzene (1.2) **87d**	**66a**	NaO*t*Bu (1.3)	110°C Toluene	0.1[h]	1.5 h	90% **103a**
20	Chlorobenzene (1.2) **87d**	P*t*Bu$_3$	NaO*t*Bu (1.3)	110°C Toluene	1.0	17 h	33%[i] **103a**
21	Bromobenzene (0.8) **87a**	P*t*Bu$_3$	K_3PO_4 (2.3)	100°C Toluene	2.0	3 h	93% **103a**
22	4-chlorotoluene (0.8) **87b**	**66a**	K_3PO_4 (2.3)	100°C Dioxane	1.0	2 h	86% **103d**
23	4-chloroanisole (1.2) **87e**	**66a**	NaO*t*Bu (1.2)	110°C Toluene	1.0	18 h	82% **103e**
24	Ethyl 4-chloro benzoate(0.8) **87f**	**66a**	NaO*t*Bu (1.1)	110°C Toluene	1.0	1 h	85% **103f**
25	4Chloroacetophe none (0.9) **87g**	**90**	K_3PO_4 (2.7)	100°C Dioxane	1.0	20 h	76% **103g**

[a] Reaction Conditions: ratio of $Pd(OAc)_2$ to ligand is 1:2, 1ml solvent per mmol diethyl malonate, yield based on limiting reagent and determined by GC and ^{1}H-NMR spectroscopy of the isolated reaction mixture. [b] Pd/L was 1:1. [c] ~20% of the unknown compound (Scheme 78) was formed. [d] Preformed sodium salt of diethyl malonate was used. [e] 50% biphenyl was formed. [f] recycled catalyst: 20% of reaction mixture from entry 11 was used. [g] 2nd recycle, 10% of reaction mixture from entry 17 was used. [h] 1 week old catalyst solution was used. [i] Product was ethyl phenylacetate, 60% biphenyl formed.

The reaction between diethyl malonate and chlorobenzene was repeated using PCy_3 and cyclohexyl JohnPhos (**66b**, see Figure 7) but much lower arylation yields were achieved (entry 9 and 10). This again indicates that oxidative addition into the aryl chloride bond is accelerated by highly electron-rich ligands. The use of the phenethyl di-*tert*-butylphosphine ligand (**90**, see Scheme 72) in the reaction with 4-chlorotoluene **87b** was also unsuccessful although it did show promising activity when an activated aryl chloride, **87g**, was used (to yield **103g**, entry 25).



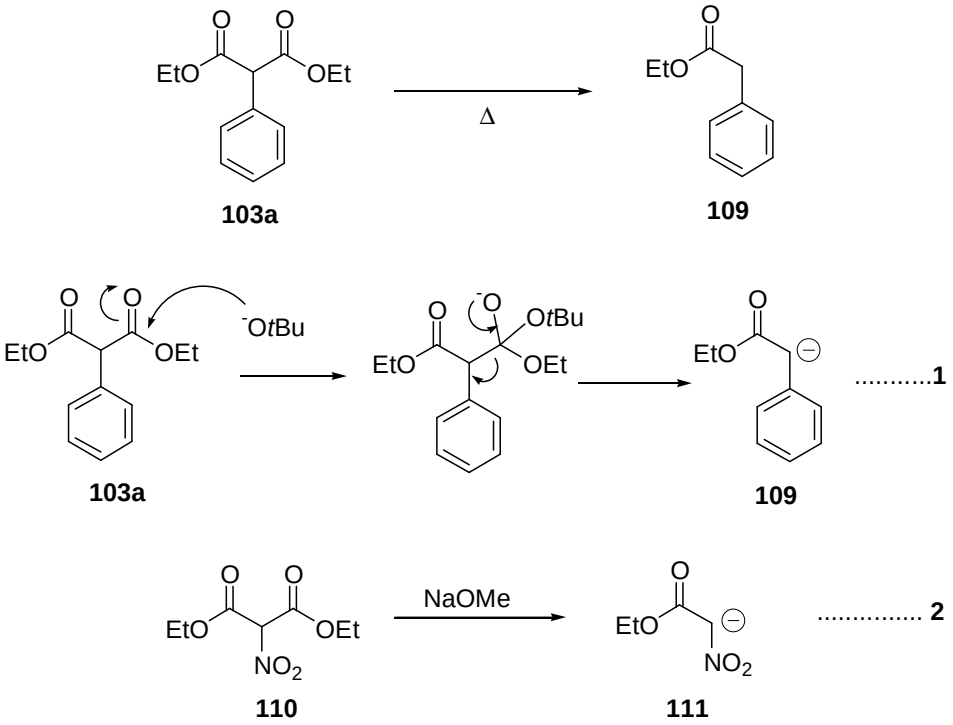
66b
Cyclohexyl JohnPhos™

Figure 7. Cyclohexyl JohnPhos™ ligand

A study was conducted to determine the effect of different reaction parameters on the outcome of the chlorobenzene reaction (entries11-19). When 0.5mol% palladium was used, full conversion was achieved within 30min at 110°C (entry 11). The same reaction performed with 0.1mol% palladium was slower and the same yield was achieved after 1.5 hours (entry 12). Lower reaction temperature led to a further decrease in reaction rate (17 hours required for 87% yield and 24 hours for 90%, entry 13). The use of 2.4 molar equivalents of chlorobenzene resulted in a slightly slower reaction (77% **103a** after 1.5 hours, entry 14) but a final yield of 96% **103a** was achieved. The use of more base (1.5 equivalents compared to 1.3) had a similar effect and led to the highest yield (97%, entry 15)

Further reduction in the catalyst loading (0.01mol%) resulted in a much slower reaction (only 22% yield after 1.5hours) and a 56% yield was achieved after 24 hours (entry 16). It was observed that, apart from the phenylated malonate **103a**, ethyl phenylacetate **109** was also present. The amount of **109** present increased upon further heating (total time of 40hours) and is believed to be formed by degradation of **103a**. Other researchers have found **109** to be the major product when these reactions are

conducted at 120^{o}C and has been described as a heat initiated dealkoxycarbonylation[98]. We propose that the formation of **109** is similar to the mono-decarboxylation of diethyl 2-nitromalonate **110** to yield ethyl 2-nitroacetate **111** which is mediated by NaOMe and is promoted by the stabilisation of the product anion due the presence of the nitro group (compare Scheme 79, equation 1 and 2). The 2-phenyl substituent of **103a** will have a similar stabilising effect[166-169].



Scheme 79. Formation of **109** from **103a**

It was observed that all the above reactions conducted with excess (1.2 equivalent) chlorobenzene remained yellow to orange and did not contain precipitated palladium black. The presence of residual aryl halide tends to prevent precipitation of palladium black by keeping it in the more stable +2 oxidation state. To test whether the catalyst was indeed still active, a portion of a reaction mixture (entry11) was used as the catalyst in another reaction (entry 17). The amount of catalyst used was the equivalent of 0.1mol% palladium (based on the initial loading). A very fast reaction resulted and a 52% yield after only 5min while a yield of 98% was calculated after 1 hour of reaction. A possible explanation for this high activity could be that the formation of

the active catalytic species is a slow process which is circumvented when using a recycled catalyst. The catalyst was recycled another time by using 10% of the reaction mixture in yet another reaction (effectively a 0.01mol% catalyst loading). However, only limited activity (entry 18) was observed.

The preparation of the catalyst was, typically, done by mixing $Pd(OAc)_2$ and **66a** in 1-2 ml toluene and heating to ~60^oC for 1-2min until all the palladium was dissolved and a yellow/orange solution was formed. Subsequent heating for a few minutes resulted in a reduction of the intensity of the colour. It was noticed that most of the colour of such solution disappeared during a storage period of 1 week at room temperature (not rigorously sealed or nitrogen purged) once again without precipitation of palladium black. The use this catalyst solution (0.1mol% Pd, entry 19) resulted in an identical reaction to that achieved with a freshly prepared catalyst (compare entry 12). This illustrates the stability of the ligated palladium species even in the presence of air.

It is uncertain whether the palladium is in the 0 or +2 oxidation state at this stage. A Pd(0) complex is required to initiate the catalytic cycle by oxidative addition to the aryl halide, but how Pd(0) is derived from the initially added Pd(II) is unclear. Although it is uncertain whether $Pd(OAc)_2$ could give rise a Pd(0) complex, the fact that a complex with similar activity and stability can be prepared by using a Pd(0) source such as $Pd(dba)_2$ instead of $Pd(OAc)_2$, suggest that a Pd(0) complex could be formed by mixing and brief heating of a mixture of $Pd(OAc)_2$ and 2 equivalents of ligand.

The use of P*t*Bu_3 as the ligand in the reaction of chlorobenzene led to unsatisfactory results - very little of **103a** was formed while the major product was **109** (33%, entry 20) after 17 hours of heating. Homocoupling to biphenyl accounted for most of the chlorobenzene converted. From this result and the failure of **66a** when using bromobenzene it would appear that these reactions are very sensitive with respect to the exact ligand employed. Hartwig has made a similar observation that the use of P*t*Bu_3 in diethyl malonate reactions with aryl chlorides suffered from generation of

significant amounts of arene from hydrodehalogenation while the same reactions with bromobenzene gave high yields of the arylated malonate esters[97,120].

Several other chloro arenes were reacted with diethyl malonate under similar reaction conditions. Good arylation yields were achieved with both 4-chloroanisole (**87e**) and ethyl 4-chlorobenzoate (**87f**, see entries 22-24) to yield **103e** and **103f**.

The use of K_3PO_4 as base also led to high arylation yield (see entry 21 and 22) when either toluene or dioxane was used as solvent. The use of Cs_2CO_3 and K_2CO_3 were, however, much less effective giving only low arylation yields. Hartwig recently published several examples of diethyl malonate arylation with aryl chlorides using K_3PO_4 in toluene solvent[97].

A few other research groups have published results for palladium catalysed arylation of diethyl malonate[170,171]. Djakovitch and Köhler claim to have achieved high yields of arylated products in reactions between diethyl malonate and various aryl bromides using heterogenous palladium exchanged NaY zeolite catalysts without the addition of any phosphine ligands[170]. In their report they also compare the results obtained with the heterogenous catalyst with that obtained using a mixture of $Pd(OAc)_2$ and PPh_3. We were unable, after several attempts, to obtain any arylated products when their procedures were repeated; even when using iodobenzene, no palladium catalysed arylation reaction occurred.

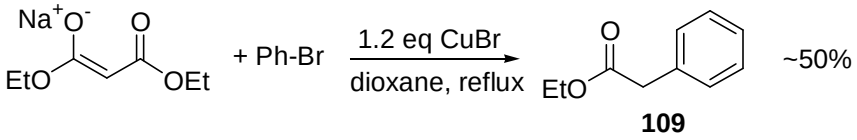
A similar report describes the use of sodium tetrachloropalladate in *N*,*N*-dimethylacetamide (DMAc)[171]. According to the authors, the use of heterogenous bases such as $Ca(OH)_2$ and $Ba(OH)_2$ resulted in high yields of diethyl phenylmalonate in the reactions of diethyl malonate with iodo-, bromo- and chlorobenzene. Once again, we were unable to repeat these results with the only reaction observed being homocoupling of the aryl halide.

These publications are in direct contradiction with our results and those obtained by the groups of Hartwig[99,97,120] and Buchwald[100] in which the use of highly electron-rich and bulky phosphine ligands were essential for successful reaction.

3.2.2 Copper catalysed diethyl malonate arylation

The use of copper catalysts in the arylation of diethyl malonate (as well as ethyl cyanoacetate and malononitrile) is well precedented[55,56,172,173,84,174,57,175-177]. Stoichiometric amounts of copper were used in all cases.

The reaction between sodium diethyl malonate and bromobenzene in dioxane was examined by us using 1.2 equivalents of CuBr and 5 equivalents malonate (Scheme 80). After 4 hours at reflux the mixture had the colour of precipitated copper metal and the yield of ethyl phenylacetate **109** was determined to be ~50% vs a reported yield of 70%[57].



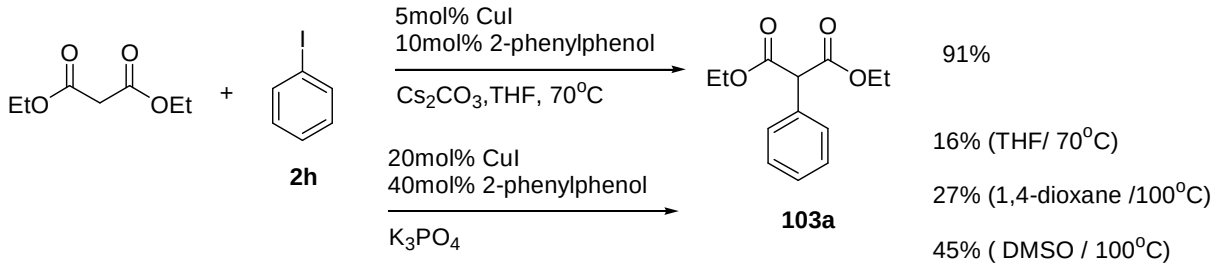
Scheme 80. Copper mediated arylation of diethyl malonate

Miura reported on the use of copper as a catalyst in the arylation reactions of ethyl cyanoacetate, acetylacetone and malononitrile with iodobenzene[58]. The yield of phenylated ethyl cyanoacetate was in excess of 80% when CuI or CuBr were employed at 10mol% loading. DMSO was the preferred solvent and K_2CO_3 was used as base. Reactions were conducted at 120^{o}C, the likely reason for the omission of malonate esters, which are prone to decomposition at this temperature (as was discussed earlier).

In 2002, Buchwald reported high yielding (>85%) malonate arylation reactions with aryl iodides using as little as 5% CuI [60] (see Scheme 81). These reactions did not require harsh conditions and were performed at 70^{o}C in THF as the solvent, allowing for a high level of functional group tolerance. The critical parameters for these

reactions were the use of Cs_2CO_3 as base and 2-phenylphenol as ligand for the copper catalyst.

We were, however, unable to repeat these results with the best result obtained by using K_3PO_4 in dioxane at 100°C (27% yield of **103a**) while only 16% of **103a** was formed in THF solvent. A higher yield (45%) was achieved by performing the same reaction in DMSO solvent at 100°C (Scheme 81).



Scheme 81. Copper catalysed diethyl malonate arylation

Cs_2CO_3 was not used as it was not available and was deemed to be too expensive to ever find industrial application. It appears that the choice of both inorganic base and solvent for each enolate type is crucial as K_2CO_3 was entirely ineffective for diethyl malonate arylation compared to the good results obtained by Miura in the reactions of ethyl cyanoacetate.

The use of copper catalysis in enolate arylation is described in more detail in Chapter 5.

3.2.3 Arylation Reactions of Meldrum's Acid and Barbituric Acid

After the successful arylation of malonate esters as well as 1,3-diketones we looked to arylate other highly stabilised enolates. Meldrum's acid and barbituric acid are cyclic variants of malonic acid derivatives but are significantly more acidic than their acyclic counterparts (Figure 8)[96].

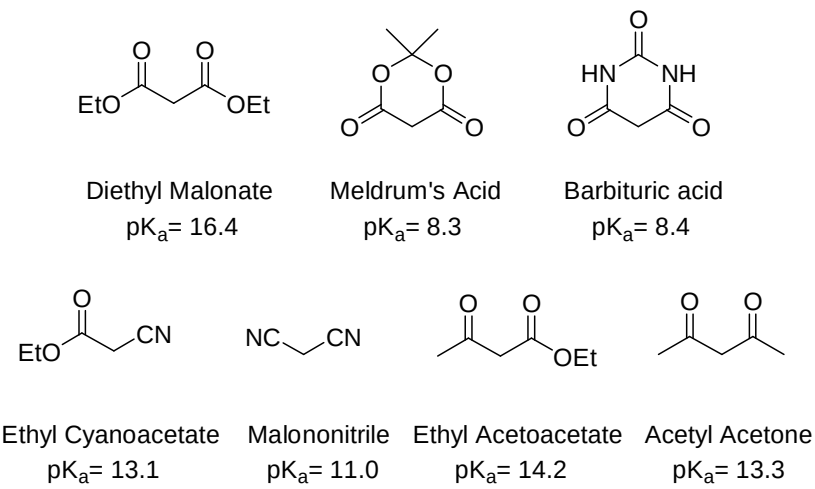
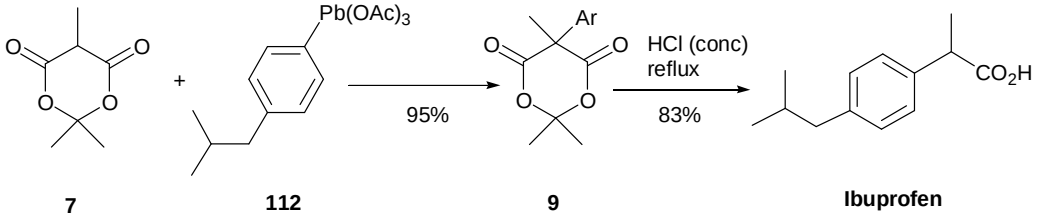


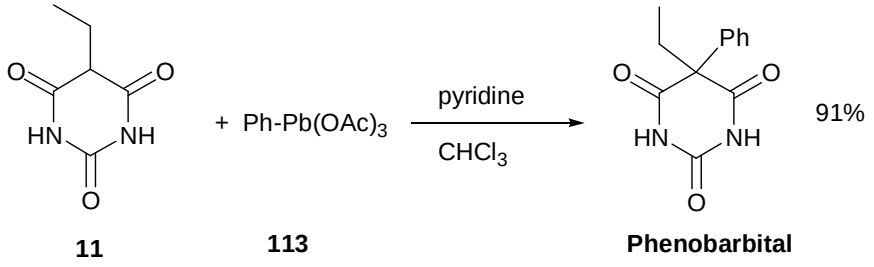
Figure 8. pK_a values of different malonate derivatives[96].

Both Meldrum's acid and barbituric acid have been arylated using aryllead reagents as developed by Pinhey[37,40]. The synthetic usefulness of this reaction was demonstrated in a short and high yielding route to the important nonsteroidal anti-inflammatory drug, ibuprofen, from 2-methyl substituted Meldrum's acid (**7**, Scheme 82) [37].



Scheme 82. Synthesis of Ibuprofen from methyl Meldrum's acid

Another synthetically useful application of this chemistry is the preparation of the anti-depressant drug, phenobarbital, by direct phenylation of 5-ethyl barbituric acid (**11**) in high yield (Scheme 83)[37].



11 **113** **Phenobarbital**

Scheme 83. Synthesis of Phenobarbital

The formation of quaternary carbon centres by arylation of a 2-substituted malonic acid derivatives is possible when using aryllead triacetates reagents and, in most cases, is a simpler reaction than that of the unsubstituted substrates. The opposite is true for palladium catalysed enolate arylations for which the formation of a quaternary carbon centre is rare, if not unprecedented, for certain types of substrates such as malonate esters.

Palladium catalysed arylation reactions of Meldrum's acid and barbituric acid were, therefore, attempted using the 2-unsubstituted substrates. Various conditions, ranging from strong bases such as NaH and NaO*t*Bu to K_2CO_3 and K_3PO_4 and amine bases as well as phosphine ligands with varying electron density and steric bulk and solvents with different polarity, were tested. Unfortunately no arylation products were detected in any of these reactions.

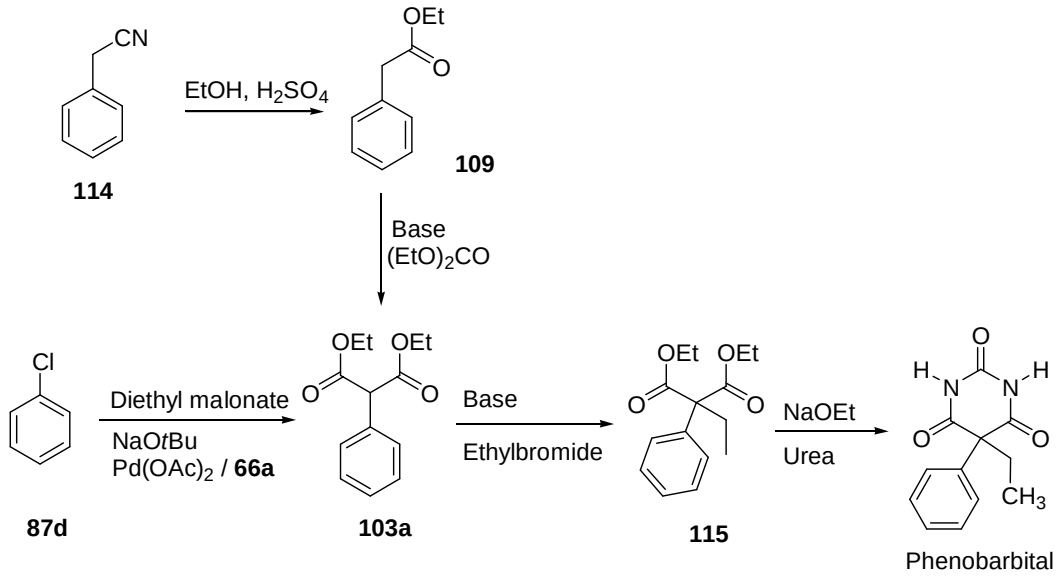
It is believed that the anions of these substrates formed stronger complexes with the catalyst as was the case for malonate esters and cyclic diketones. Buchwald also published the failure of the CuI / 2-phenylphenol conditions to arylate Meldrum's acid[60] as opposed to the successes with malonate ester arylations.

Since the aryllead arylation route to ibuprofen and phenobarbital from Meldrum's acid derivatives could not be repeated using palladium catalysis, synthetic routes to the 2-arylpropionic acid anti-inflammatory drugs and phenobarbital based on the arylation of diethyl malonate were deemed more suitable for investigation.

3.3 Application of Malonate Arylation to the Synthesis of Phenobarbital

A disconnection based synthesis of phenobarbital and the aryl propionic acids suggests that the most direct approach would be arylation of a β-dicarbonyl system. Existing syntheses do not use this approach although 2-arylated malonate esters are used as key intermediates.

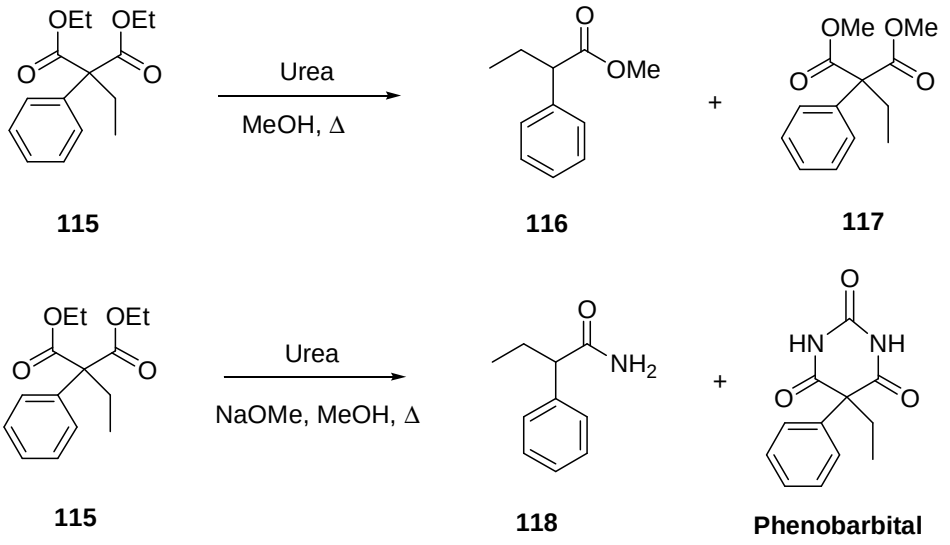
Diethyl 2-phenylmalonate **103a** is believed to be a key intermediate in the commercial route to phenobarbital. **103a** is prepared from either benzyl cyanide **114** or phenylacetic acid esters by condensation with diethyl carbonate (Scheme 84). We reasoned that **115** could be prepared from diethyl malonate by consecutive arylation with a phenyl halide followed by alkylation with bromoethane, possibly in a "one-pot" system. The arylation reaction between diethyl malonate and either bromobenzene or chlorobenzene has already been discussed in detail (see section 3.2.1).



Scheme 84. Proposed route to Phenobarbital

Ethylation of diethyl phenylmalonate **103a** was attempted using ethyl bromide and imidazole. Although the acidity of the proton on a carbon substituted by two ester groups and one phenyl group should be accessible by a mild amine base, the reaction did not proceed until formal deprotonation with an alkoxide base and heating to >100^{o}C. It is probable that alkylation of imidazole was a competitive reaction. The same base used in the arylation reaction should be used in this reaction as well (NaO*t*Bu or K_3PO_4). The arylation and alkylation reactions could then be done in one pot by addition of an extra equivalent of base and alkyl halide once the arylation reaction is complete.

Conversion of diethyl 2-ethyl-2-phenylmalonate **115** to the barbituric acid (phenobarbital) was attempted by heating with urea to liberate two molecules of ethanol. The malonate ester was heated with urea at 100^{o}C in toluene suspension but no reaction was observed. Methanol was added to improve solubility and sodium methoxide to increase the nucleophilic character of urea, but after prolonged refluxing only unreacted urea was recovered. The reaction was repeated in methanol solvent but again no phenobarbital was recovered with the major component being dimethyl 2-ethyl-2-phenylmalonate **117** (due to transesterification) and methyl 2-phenylbutyrate **116** (from decarboxylation of the starting material) (Scheme 85).



Scheme 85. Attempts at converting **115** into Phenobarbital

An Organic Syntheses[178] preparation for barbituric acid, which involves refluxing the sodium salt of diethyl malonate with urea in absolute ethanol, was repeated using sodium methoxide. Barbituric acid was formed in low yield (31% compared to the reported 72-78%). The reason for this lower yield is thought to lie with the use of sodium methoxide instead of sodium ethoxide. The higher nucleophilic character of the methoxide ion may have lead to decarboxylation of the starting material. When the Organic Syntheses procedure was repeated on diethyl 2-ethyl-2-phenylmalonate **115** two compounds formed of which the ester functionality was absent. The compounds were identified as 2-phenylbutyramide **118** (60%) and Phenobarbital (40%) by comparison of the ^{1}H and ^{13}C NMR data with that of authentic standards. This reaction was repeated using freshly prepared sodium ethoxide but although all of the starting material was consumed only 2-phenylbutyramide **118** was isolated. Decarboxylation of the product is thought to have occurred during work-up.

A patent which describes the preparation of phenobarbital from **115** and urea mentioned that low yields of phenobarbital were obtained due to malonate cleavage in the presence of a high concentration of sodium ethoxide[179]. An improved procedure was disclosed in this patent, which detailed a portion-wise addition of sodium ethoxide to a heated mixture of **115** and urea in absolute ethanol to avoid high concentrations of sodium ethoxide[179].

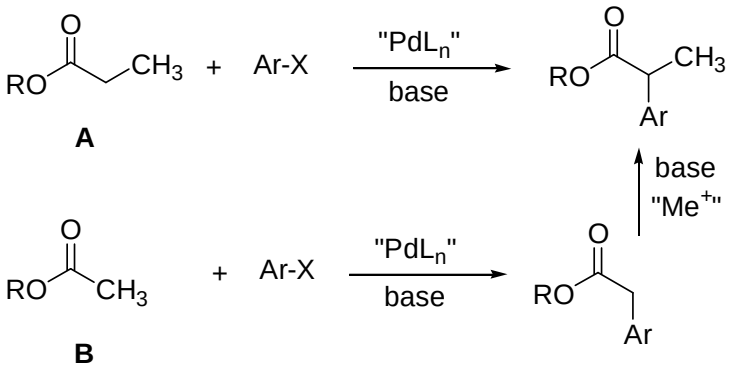
The conversion of **115** to phenobarbital was not examined further as this is a well-established conversion which is part of the existing commercial process[180]. There exists, however, a substantial possibility of making this reaction more efficient.

With a palladium loading of 0.01mol% and a palladium price of $1000/ounce (33g) the contribution of the catalyst to the raw material cost of phenobarbital production will be in the order of $3/kg. With the selling price of phenobarbital at ~$36/kg and that of the sodium salt at ~$75/kg , this technology could become an economically viable manufacturing route (diethyl malonate ±$6/kg, chlorobenzene <$2/kg) Any

improvement in turnover numbers by fine-tuning the reaction conditions or by recycling the catalyst and the use of a less expensive base such as K_3PO_4 or K_2CO_3 the will make this route more economically attractive.

3.4 Application of Malonate arylation to the Synthesis of Ketoprofen

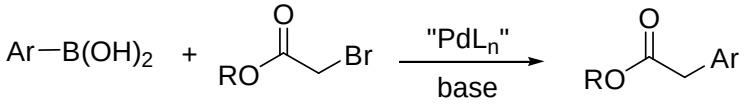
After the potential cost benefits of using enolate arylation in phenobarbital synthesis were demonstrated, we investigated the preparation of the 2-arylpropionic acid non-steriodal anti-inflammatory drugs (NSAID's) via enolate arylation as a continuation of this programme. The most direct route to introduce the aryl functionality would be the direct arylation of a propionic acid **A** derivative or, alternatively, an acetic acid derivative **B** followed by *C*-methylation (Scheme 86).



Scheme 86. Approach to aryl propionic acids by direct ester arylation

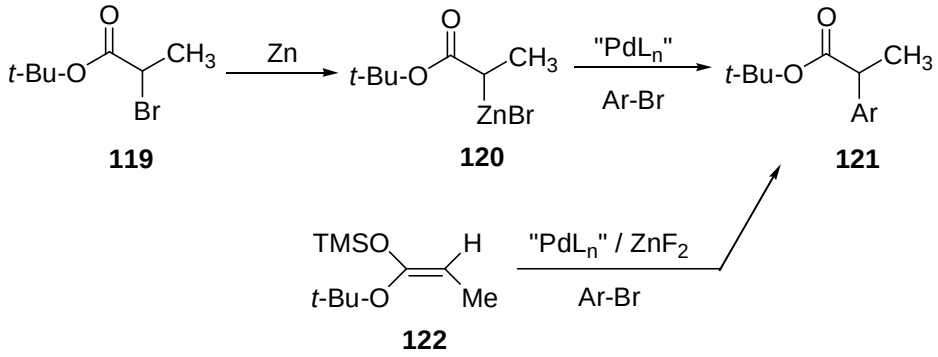
Direct arylation of acetic and propionic acid esters has been demonstrated by both Buchwald[107] and Hartwig[108,109] and we have also investigated these reactions. We found that the use of the bulky *t*-butyl esters and moisture sensitive bases coupled with the tendency of the ester enolates to take part in unwanted self-condensation reactions made this route undesirable from both a practical and economical point of view. Gooßen published another approach to arylacetic acid derivatives in a Suzuki-type coupling of arylboronic acid and ethyl bromoacetate[181] (Scheme 87). Apart from the requirement for a relative expensive aryl boronic acid and high palladium loading

(3mol%), the reaction suffered from extensive homocoupling and hydrodehalogenation.



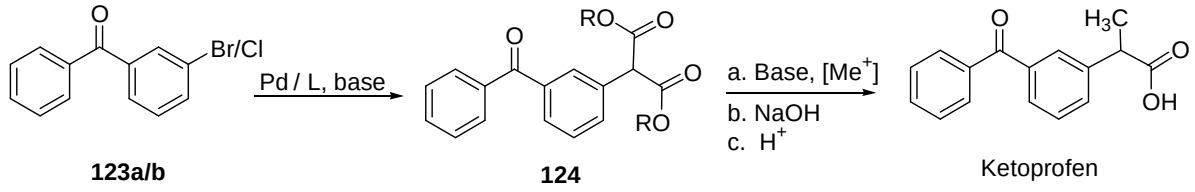
Scheme 87. Gooßen's Suzuki-type approach to arylacetic acids

Hartwig has recently published α-arylation protocols using more neutral conditions[182]. These protocols involved the use of Reformatsky reagents (**120**) which were prepared from activated zinc and α-bromo ester (**119**) and alternatively silyl ketene acetals (**122**) in the presence of 0.5 equivalents ZnF_2 (as co-catalyst)(Scheme 88). Although these protocols do not require the addition of strong bases (and hence tolerate base sensitive functional groups on the aryl halide) and diarylation does not occur, they require at least one equivalent of another metal and, again, only *t*-butyl esters can be used. Apart from being an excellent synthetic tool when dealing with sensitive substrates, this protocol offers no improvements over other arylation techniques.



Scheme 88. Ester α-arylation under more neutral conditions

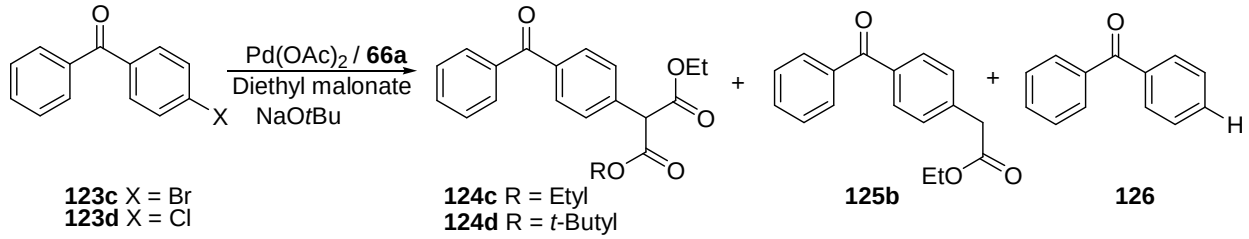
The arylation of the cheap and readily available diethyl malonate followed by methylation, hydrolysis and decarboxylation (which in principle can be performed in "one-pot") remains an attractive route to the arylpropionic acids - especially in the light of the high yields obtained with aryl chlorides using low catalyst loadings (see Section 3.2.1, Table 7).



Scheme 89. Proposed route to Ketoprofen

We investigated the preparation of ketoprofen (a generic anti-inflammatory drug which is sold as the racemate) since it contains a ketone functionality which could complicate traditional syntheses but should not be problematic in a mild malonate arylation protocol (Scheme 89).

The initial reactions were performed with 4-bromobenzophenone **123c** since it is readily available and incorporates the carbonyl function present in the required 3-bromo or chlorobenzophenone **123a/b**. The arylated malonate ester **124** was isolated in 66% yield by using 1.2 equivalents diethyl malonate, 1.3 equivalents NaO*t*Bu, 1mol% $Pd(OAc)_2$ and 2mol% 2-(di-*tert*-butylphosphino)-biphenyl (**66a**). The product was a mixture of the diethyl ester **124c** (70%) and the ethyl *t*-butyl ester **124d** (30%). Hydrodehalogenation to yield benzophenone **126** accounted for 30% of the aryl halide and ethyl 2-arylacetate **125b** was formed in 4% yield (Scheme 90).



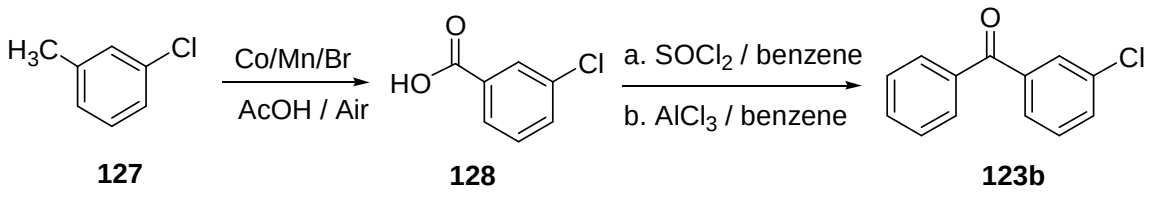
Scheme 90. Arylation of diethyl malonate with 4-halobenzophenone **123c/d**

A relationship between the extent of transesterification and hydrodehalogenation was observed, which supported our earlier proposed mechanism by which dehydrogenation of ethanol liberated by transesterification provides the hydrogen for aryl halide reduction (see Section 3.2.1, Scheme 78).

The use of 4-chlorobenzophenone **123d** under the same reaction conditions resulted in a faster (reaction completed in 1 hour compared to 4 hours with **123c**) and more selective reaction with the yield of arylated malonate being 75% (mainly **124c** with very little **124d**) while **125b** was formed in 8% yield. Benzophenone **126** was not detected by NMR analysis.

$Pd(OAc)_2$ and tri-*tert*-butylphosphine was used in the reaction between 4-bromo- and 4-chlorobenzophenone and diethyl malonate. The reaction with 4-bromobenzophenone **123c** proceeded well with full conversion of the aryl halide in 5 hours (65% **124c**/**124d** and 35% **126**). The reaction with 4-chlorobenzophenone **123c** was, however, unsuccessful with less than 5% of the desired product and 14% reduction to benzophenone after 5 hours. This result was similar to the arylation of chlorobenzene using P*t*Bu_3, once again indicating that this ligand is unsuitable for aryl chloride reactions.

Motivated by the above successes, we repeated the reactions on 3-chlorobenzophenone **123b** (see Scheme 92). This substrate was prepared from 3-chlorobenzoic acid **128** by conversion to the acid chloride with thionyl chloride in benzene followed by the addition of $AlCl_3$ to initiate Friedel-Crafts acylation between benzene and the formed acid chloride (Scheme 91). The acid chloride formation and acylation reaction was done in "one-pot" and **123b** was obtained in 95% yield.

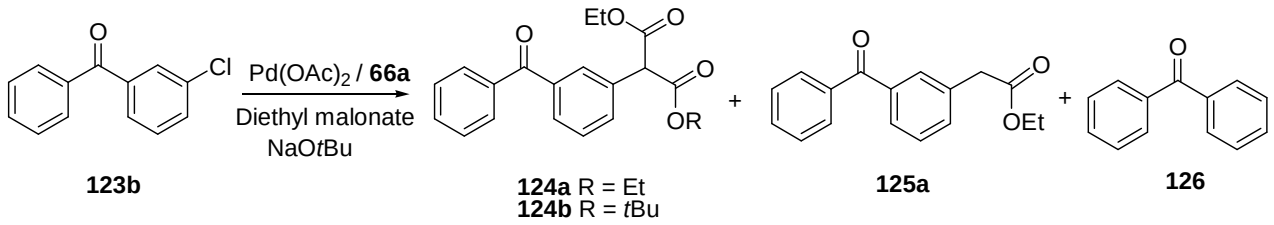


127 **128** **123b**

Scheme 91. Preparation of 3-chlorobenzophenone **123b**

The side-chain oxidation of substituted toluenes in an autoxidation reaction catalysed by cobalt and manganese salts in acetic acid /acetic anhydride solution has been extensively studied by CSIR Bio/Chemtek[183]. One of the substrates that was

successfully oxidised to the carboxylic acid, during that study, was 4-chlorotoluene **87b**. This protocol was applied to 3-chlorotoluene **127** to prepare large quantities of 3-chlorobenzoic acid **128** for the preparation of **123b** (Scheme 91). An unoptimised yield of 58% was achieved by crystallisation directly from the acetic acid reaction mixture.



123b **124a** R = Et, **124b** R = *t*Bu **125a** **126**

Scheme 92. Arylation of diethyl malonate with 3-chlorobenzophenone **123b**

The arylation reaction with 3-chlorobenzophenone (1mol% Pd) proceeded smoothly with 94% conversion of **123b** in 2 hours and 95% after 20 hours. The yield of the arylated malonate was 86% (with 70:30 split between **124a** and **124b**, Scheme 92). The extent of hydrodehalogenation was estimated at ~5% while 4% of **125a** was also formed. The same results were achieved when this reaction was repeated.

Lowering the catalyst loading by a factor of 10 (ie. 0.1mol% Pd) resulted in a slow reaction and low arylation yield (8 and 6% **124a/b** with 2 and 1.5% **126** in duplicate experiments). The addition of 0.1mol% catalyst to such a reaction after 3 hours of reaction did, however, accelerate product formation and 50% of **124a/b** was formed in 20 hours. The use of 0.25mol% of either $Pd(OAc)_2$ or $Pd(dba)_2$ with 0.5mol% of **66a** resulted in a fast reaction with full conversion of **123b** achieved in 1 hour of reaction. The yield of **124a/b** was similar than achieved using 1mol% Pd (81% **124a/b**) although the extent of hydrodehalogenation was much higher (19% **126** formed). More diethyl malonate and **123b** was added to the reaction mixture (generating an effective 0.125mol% catalyst loading,) and reacted further. Although full conversion of the additional aryl chloride was not achieved (70% conversion, turnover number (TON) of 1350) the catalyst still had significant activity.

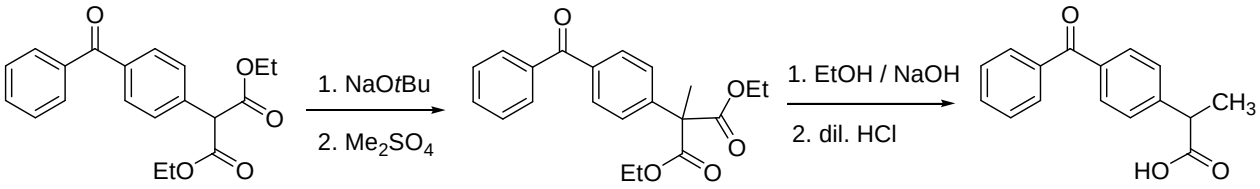
Reactions had been performed at 5mmol scale in sealed tubes and it was decided to test the reaction protocol at a larger scale. A reaction was performed at 50mmol scale in a reflux system with a 0.2mol% palladium loading. Full conversion of **123b** was achieved in 2 hours and ^{1}H NMR spectroscopy revealed 83% of the arylated product (**124a** and **b**) and 17% benzophenone **126**. The isolated yield of **124a** after purification by flash chromatography was 80% with only 5% of the isolated product being **124b**. This result was an encouraging indication that identical yields could be obtained at larger scale. Further scale-up was limited by supplies of both $Pd(OAc)_2$ and **66a**.

The reduction of the valuable aryl halide in this process was, however, still a concern. NaO*t*Bu is not the ideal base due to transesterification, but lower alkoxide bases would, however, be more problematic. The use of a milder, non-nucleophilic base such as K_2CO_3 or K_3PO_4 would be advisable. A reaction with anhydrous K_2CO_3 was performed with 4-bromobenzophenone **123c** (1.5 equivalents to diethyl malonate) as a base. The rate of reaction was much lower and most of the starting material was still present after 4 hours, only 4% of the 4-bromobenzophenone **123c** was reduced. After 20 hours and the addition of extra K_2CO_3, 40% of the desired arylated product **124c** and 30% benzophenone **126** had formed while 30% was unreacted bromobenzophenone. The formation of such a large quantity of benzophenone could have been a result of ethanol dehydrogenation which could have been liberated by hydrolysis of the ethyl esters of malonic acid. Hydrolysis could have been caused by hydroxide formed by decomposition of hydrogen carbonate.

The use of K_3PO_4 should be examined because the protonated species generated cannot decompose in the same manner as HCO_3^- to generate a nucleophile capable of initiating either transesterification or hydrolysis of the malonate.

A brief investigation into the *C*-methylation of **124c** was carried out (Scheme 93). Deprotonation of **124c** was done by using 1.5 equivalents of NaO*t*Bu in toluene followed by the addition of 1.5 equivalents of dimethyl sulphate. Heating to 90^{o}C was required to initiate a fast methylation reaction. The diethyl 2-(4-benzoylphenyl)-2-

methylmalonate **129** isolated was hydrolysed by heating in ethanolic caustic (1.5 equivalent, 60^{o}C) and subsequent acidification with dilute hydrochloric acid, resulting in the liberation of carbon dioxide gas, and crude 2-(4-benzoylphenyl)propionic acid **130** was recovered in 91% yield.



124c **129** **130**

Scheme 93. Methylation of **124c** and decarboxylation of **129**

Based on the earlier observations, this indicates that the conversion of the arylated malonate ester **124a** to ketoprofen should also be feasible.

With a palladium loading of 0.2mol% and a palladium price of $1000/ounce (33g) the contribution of the catalyst to the raw material cost of phenobarbital production will be as high as $60/kg and with the import price of ketoprofen from Indian manufacturers being $78/kg, significant improvement in the catalyst turnover numbers will need to be achieved before this procedure becomes economically attractive.

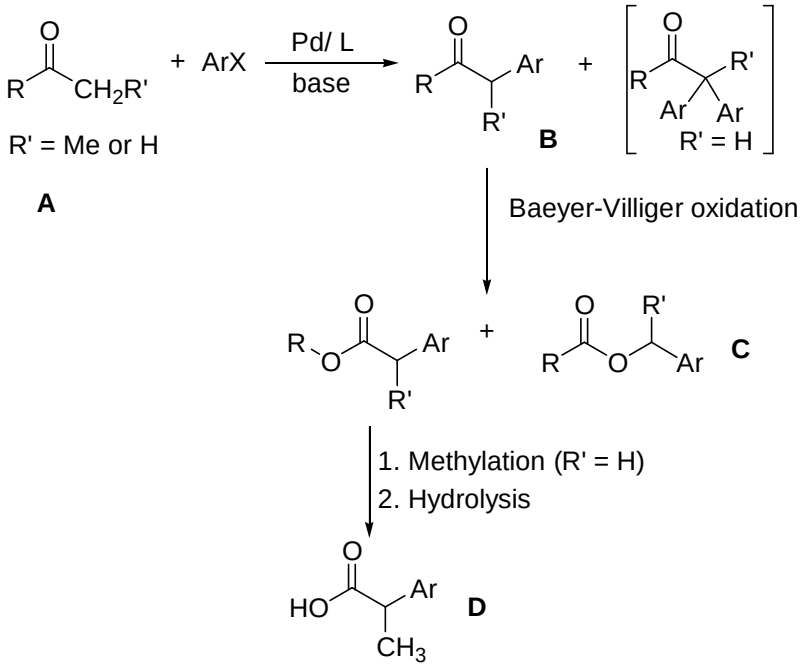
For a generic pharmaceutical of this type, a rule of thumb is that the raw material cost should not exceeed 30-50% of the selling price (the remainder being plant and labour costs and profit).

3.5 Novel Synthetic Approach to the Synthesis of Arylpropionic Acids

During our studies of the arylation reactions of various enolates we came to the conclusion that the substrates that are most readily arylated are ketones and especially a few specific ketones that can be arylated using unligated palladium[100]. It is, therefore, not surprising that the first examples of enolate arylation dealt with ketone substrates [90,91,99,100]. Hartwig first demonstrated the ease at which propiophenone **86** can be

arylated by obtaining the mono-phenylated product **88** in 98% yield with the use of 0.005mol% $Pd(OAc)_2$ and P*t*Bu_3[99]. Buchwald reduced the catalyst loading even further and proved that this reaction did not require the addition of a phosphine ligand (74% yield with 0.001mol% $Pd(OAc)_2$ only, see Scheme 69)[100].

During our quest to find more economically viable synthetic routes to the α-arylacetic and propionic acids we proposed an arylated ketone that could be converted to the acid at a later stage. The arylation of a methyl or ethyl ketone **A→B** under relatively simple conditions (using a low palladium loading and no pyrophoric phosphines) followed by an uncomplicated and selective conversion to an α-arylacetic and propionic acid **C** (or esters thereof) would constitute a viable route to the profen drugs **D** (NSAID's) (Scheme 94).

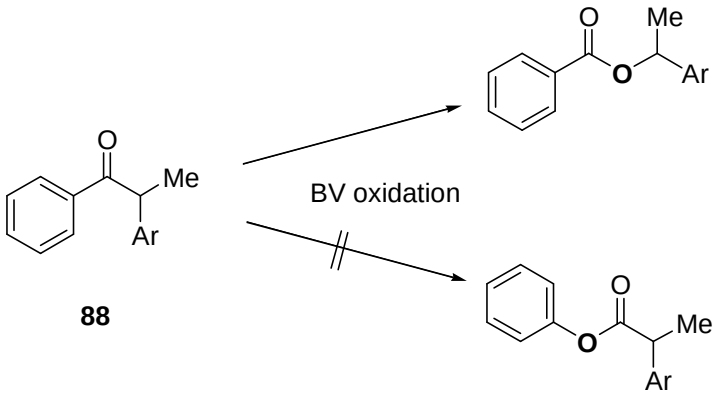


Scheme 94. Proposed synthetic route to α-arylpropionic acids via ketone arylation

Ketones can be converted into esters by the Baeyer-Villiger (BV) oxidation which involves the introduction of oxygen between the carbonyl and the highest substituted alkyl chain[184,185]. The regioselectivity of the BV reaction not only depends on the level of substitution in the alpha position but the presence of an electron donating group will also favour the direction of oxygen insertion. The benzylic position is especially

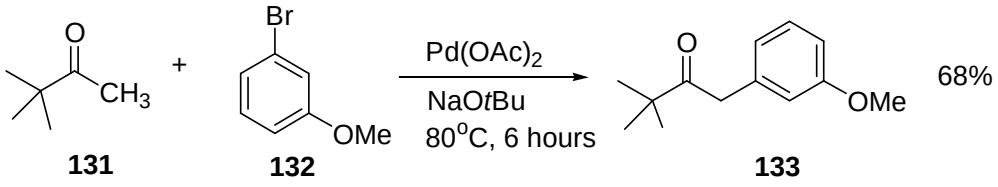
activated toward oxygen insertion. The general trend for selectivity in the BV reaction is therefore quaternary > tertiary ≥ benzylic > secondary > primary.

In order for the BV reaction to give high selectivity to an α-arylated ester, the opposing ketone substituent has to be either a highly substituted alkyl group (like *t*-butyl) or an activated benzylic group. Arylated propiophenone **88**, for example, would not be a suitable substrate as oxygen insertion will take place exclusively in the ketone-benzylic position (Scheme 95).



Scheme 95. Regioselectivity of the Baeyer-Villiger oxidation of arylated propiophenone **88**

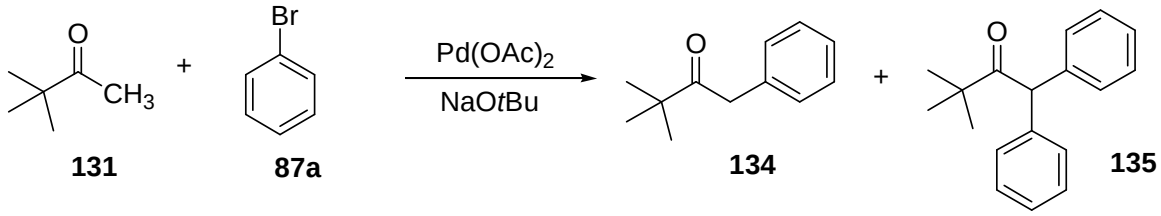
Another example of a ketone arylation that does not require the addition of a phosphine ligand is pinacolone (*tert*-butylmethylketone) **131**. Buchwald[100] reported the reaction of pinacolone **131** with 3-methoxy-bromobenzene **132** using 1mol% $Pd(OAc)_2$ (Scheme 96).



Scheme 96. Arylation of pinacolone **131** with $Pd(OAc)_2$

In order to examine the proposed synthetic route to α-arylacetic and propionic acids, phenylation of pinacolone was performed followed by BV oxidation.

The arylation of pinacolone **131** with bromobenzene **87a** was performed using NaO*t*Bu in toluene using $Pd(OAc)_2$ as well as a $Pd(OAc)_2$ / 2-(di-*tert*-butylphosphino)-biphenyl **66a** combination (Scheme 97). The reactions were performed on 5mmol scale (bromobenzene) with 1.2 equivalents (to **131**) NaO*t*Bu in toluene solvent and heating to 110°C. The reaction performed with 2mol% $Pd(OAc)_2$ and 4mol% **66a** was unselective and the ratio of mono and di-arylation was 1.2:1 with full conversion of bromobenzene. The reaction using 2mol% $Pd(OAc)_2$ with no additional ligand was more selective and a mono to di-arylation ratio of 5:1 (**134:135**) was achieved. The arylation selectivity in both reactions was high with very little hydrodehalogenation and homocoupling taking place, the selectivity on pinacolone was also high as no substrate appeared to be lost to condensation reactions.

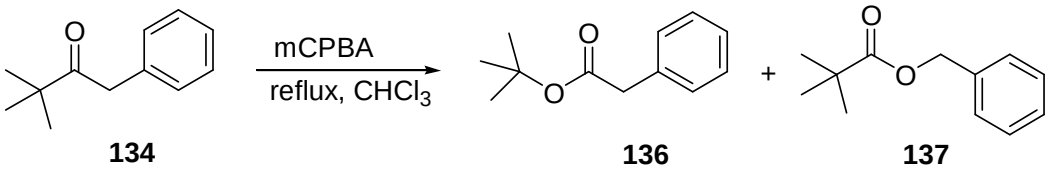


Scheme 97. Phenylation of pinacolone using $Pd(OAc)_2$ as catalyst

The phosphine free reaction was repeated on 50mmol scale (bromobenzene) using 0.2 mol% $Pd(OAc)_2$. A bromobenzene conversion of 81% was achieved with the arylation selectivity being 93%. The ratio of mono to diarylated product was 5.6:1 while the selectivity calculated based on pinacolone reacted was only 65%. The reason for the lower selectivity is thought to have originated from insufficient mixing in the reaction causing self-condensation reactions. It is believed that a selectivity similar to that achieved in the smaller reaction is attainable with sufficient mixing.

The diarylated product **135** proved to be crystalline and a large proportion was removed by filtration (after removal of solvent) to give a product containing only 7% of **135**. Vacuum distillation of the crude product, containing mainly **134**, removed the remainder of the diarylated compound **135**.

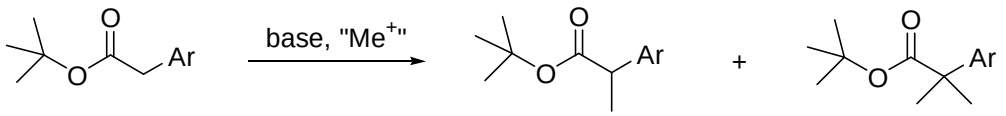
The BV oxidation was performed on this material by refluxing in chloroform with *m*-chloroperbenzoic acid (*m*CPBA) while removing water azeotropically (Scheme 98). Although the conversion of **134** was low (only 40%, due to the low activity of the *m*CPBA used) the reaction was selective towards formation of *t*-butyl 2-phenylacetate **136**. The regio-selectivity of the reaction was determined to be 7:1 (**136** to benzyl pivalate **137**).



134 **136** **137**

Scheme 98. Regioselectivity in the Baeyer-Villiger oxidation of **134**

These reactions demonstrated the concept of forming an α-arylacetic acid ester by enolate arylation of a ketone followed by a Baeyer-Villiger oxidation. Methylation of the arylacetic acid ester **136** will produce the correct 2-arylpropionic acid ester **138** as required in the profen drugs structure (Scheme 99). Care will, however, have to be taken to limit di-methylation (**139**).

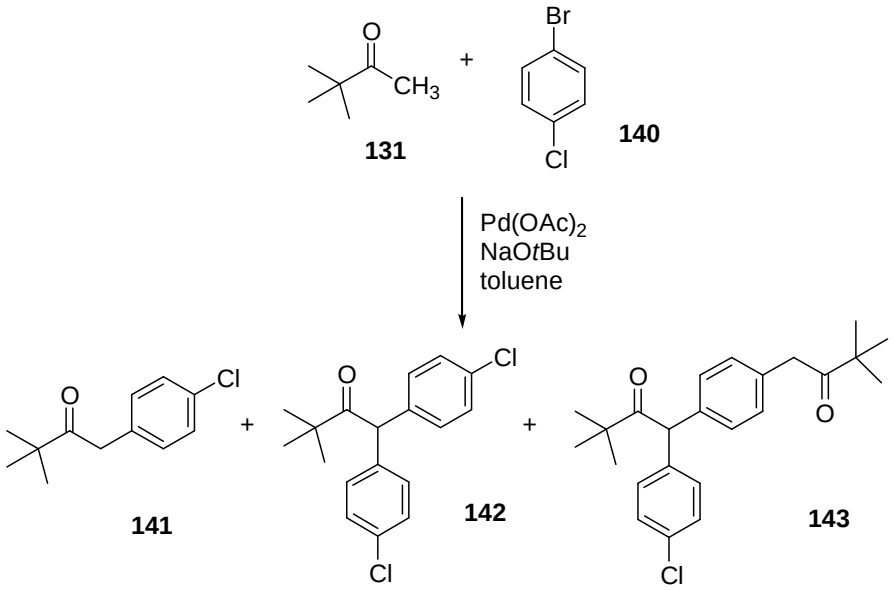


136 **138** **139**

Scheme 99. Methylation of arylacetic acid ester **136** to yield 2-arylpropionic acid ester **138**

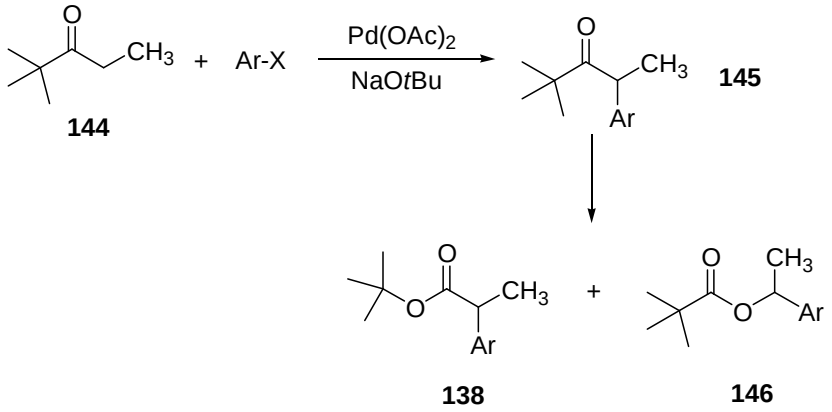
Further investigation is required to optimise the selectivities in both reactions. The wrong regio-isomer **137** formed during the BV oxidation could conceivably be removed by base hydrolysis which will hydrolyse a benzyl ester but not the more base-stable *tert*-butyl ester followed by mild base wash. Hydrogenolysis of **137** in the presence of **136** should also result in simple removal of the unwanted species.

The ligand-free palladium catalysed α-arylation of pinacolone **131** with 1-bromo-4-chlorobenzene **140** was described in a recent paper[186] (Scheme 100). The mono-selectivity (to **141**) of the arylation reaction was improved by using 2.5 equivalents of NaO*t*Bu and performing the reaction at 85°C (~18:1 from ~7:1 when 1.6 equivalents of NaO*t*Bu was used).



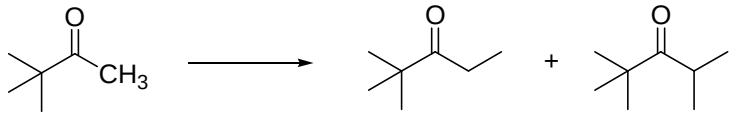
Scheme 100. Recently published arylation of pinacolone with 1-bromo-4-chlorobenzene

An alternative strategy which will reduce the problems associated with arylation selectivity, involves the use of *tert*-butyl ethyl ketone **144** (Scheme 101). This methylated pinacolone derivative is, unlike pinacolone, not commercially available and has to be prepared.



Scheme 101. Arylation of *t*-butyl ethyl ketone **144** followed by Baeyer-Villiger oxidation

Several methylation protocols (to convert pinacolone into *t*-butyl ethyl ketone **144**) were examined using different bases and dimethylsulfate. Limited success was achieved as the reaction between dimethylsulfate and the base seemed to prevail over *C*-methylation. Bases like NaOH, NaO*t*Bu and K_3PO_4 gave no *C*-methylation while the use of sodium hydride did result in the formation of the desired product **144** along with dimethylation (**147**, Scheme 102). This reaction was, however, also plagued by the fast reaction of NaH with dimethylsulfate. A conversion of approximately 70% was achieved by using two equivalents of NaH and dimethylsulfate. The ratio of mono to di-methylation was ~5:1.



131 **144** **147**

Scheme 102. Methylation of pinacolone **131**

The use of methyl iodide resulted in higher selectivity towards *C*-methylation although selectivity in terms of mono- and dimethylation was unsatisfactory. The use of one equivalent of NaH and methyl iodide resulted in a ~60% conversion of pinacolone but with equal amounts of mono and di-methylation.

Arylation of **144**, however, has not been pursued. The higher level of substitution on the projected product **145** may also prove problematic (in terms of regio-selectivity) in the Baeyer-Villiger oxidation (see Scheme 101). Attempts to lower the catalyst loading, improve mono-arylation selectivity and the regio-selectivity in the Baeyer-Villiger oxidation reaction will be the main focus of further studies. Once an optimised procedure has been established, it will be applied to the synthesis of a number of the key NSAID's such as Ibuprofen, Naproxen and Ketoprofen.

3.6 Conclusion

- Although unligated palladium can be used for the successful reaction between some ketone substrates and aryl bromides, the same reaction with an aryl chloride or deactivated aryl bromide requires the use of an electron-rich phosphine to assist with oxidative addition.
- In the arylation reaction of 1,3-diketones the choice of base is of crucial importance. It appears necessary to match the acidity of the substrate to the strength of the base employed, to avoid high concentration of the ensuing enolate. The ability of especially acyclic 1,3-diketone enolates to form stable complexes with palladium renders these substrates inactive in this type of chemistry, while cyclic 1,3-diketones can be arylated in high yield when a mild base such as K_3PO_4 together with a sterically hindered phosphine ligand is employed.
- Transesterification of both substrate and arylation product to give *tert*-butyl esters was observed during the arylation reaction of diethyl malonate when NaO*t*Bu was used. Attack of the malonate enolate by excess NaO*t*Bu followed by elimination of NaOEt is believed to be the mechanism of transesterification (see Scheme 77/78). The occurance of another side-reaction, hydrodehalogenation of the aryl halide, could be correlated to level of transesterification observed. This observation is explained by hydride transfer from a palladium hydride complex formed by β-hydrogen elimination of ethanol. Portion-wise addition of NaO*t*Bu, to match the reaction rate and to avoid the build-up of free base, should be investigated to minimise these side-reactions.
- Aryl chlorides were shown to be excellent substrates for diethyl malonate arylation when the sterically demanding "Buchwald" biphenyl phosphine ligands **66a** and **66d** were used. The observation that a recycled catalyst at low loading (0.01mol% "Pd") showed high activity, suggests that a continuous reaction with removal of products should result in high turnover numbers. The use of K_3PO_4 in the malonate arylation reaction is promising.

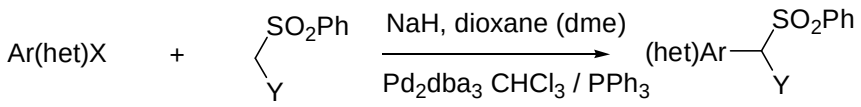
- The application of palladium catalysed malonate arylation to both phenobarbital and ketoprofen synthesis was shown in principle. At a palladium loading of 0.01mol% this procedure could become economically feasible, especially if an inexpensive base such as K_3PO_4 could replace NaO*t*Bu. A reaction on a 50mmol scale shows that reaction could be done in a reflux system and does not require rigorous inert conditions (argon atmosphere) as used in literature procedures. It was further demonstrated that solutions of $Pd(OAc)_2$ and "Buchwald" ligand **66a** in toluene were air-stable for several days, adding to the potential for industrial use.
- The use of nickel as an arylation catalyst did not show much promise and although limited activity was observed in the arylation of propiophenone, it was not active in any of the other systems investigated. The lack of activity is not thought to lie with an inability to effectively add to the aryl halide but rather with the reduction of Ni(II) to Ni(0) (which requires too high temperatures for the enolate substrates to survive) required for product elimination and the regeneration of the active catalyst. The insoluable nature of the nickel catalysts is another complicating matter.
- The combination of the relative ease of arylating pinacolone (ligand-free palladium can be used) and the ability of *tert*-butyl ketones to be converted to *tert*-butyl esters by Baeyer Villiger (BV) oxidation is a novel approach to arylpropionic acids, which avoids the more challenging malonate arylation reaction. The application of enzymatic BV procedures in this regard could be persued to produce stereochemically defined arylpropionic acids.

CHAPTER 4

PALLADIUM CATALYSED ARYLATION OF SULFONAMIDE STABILISED ANIONS

Since the early breakthroughs of 1997 [91,90,89], palladium catalysed enolate arylation has become a reliable and widely applicable reaction. The methodology has been developed in research programmes pioneered by Hartwig and Buchwald (amongst others) and now accommodates a wide variety of stabilised carbanions with a degree of rational prediction as to the base and ligand required to facilitate the reaction[120].

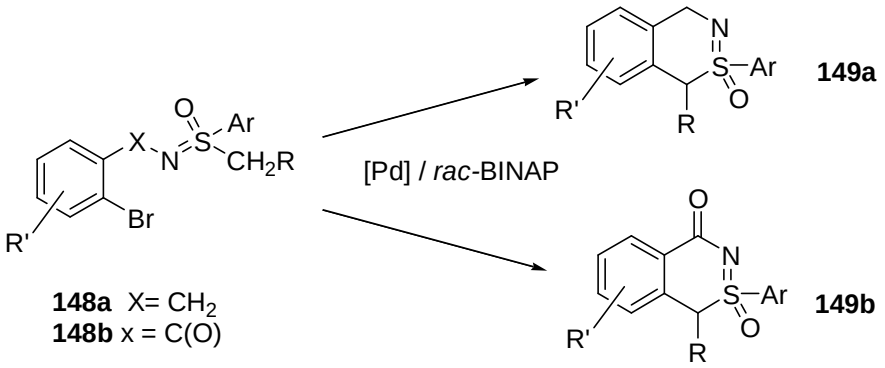
Sulfones have been demonstrated to undergo a similar type of arylation reaction. Intermolecular enolate arylation of substituted methylphenylsulfones (YCH_2SO_2Ph, Y = electron withdrawing group) with aryl iodides using CuI / NaH has been reported by Suzuki *et al.*[187] and Gorelik *et al.*[188] while the use of a palladium catalyst in this transformation was published by Kondo[189]. Ciufolini has also reported one example of an intramolecular version of this type of reaction[88]. In addition, Beletskaya and co-workers have recently published several examples of palladium catalysed intermolecular couplings of sulfone stabilised enolates with aryl bromides (as depicted in Scheme 103)[112].



Y = CO_2Et, COPh, SO_2Ph, NO_2

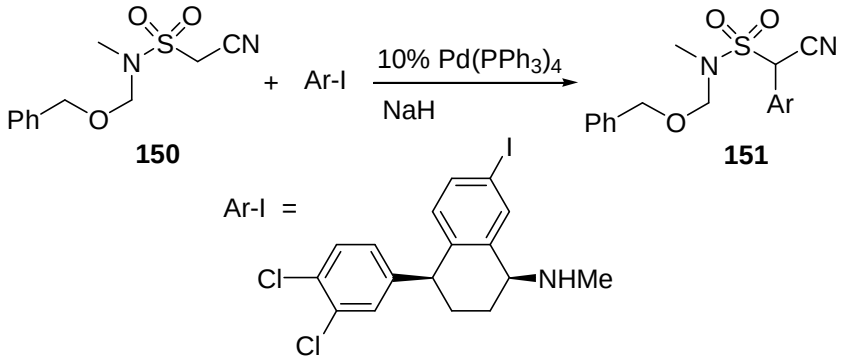
Scheme 103. Palladium catalysed arylation of sulfonyl CH-acids

N-Substituted methylphenylsulfoximes **148** have also been demonstrated) by Bolm *et al.* as suitable substrates in intramolecular versions of this coupling reaction mediated by a Pd/BINAP catalyst (Scheme 104)[113].



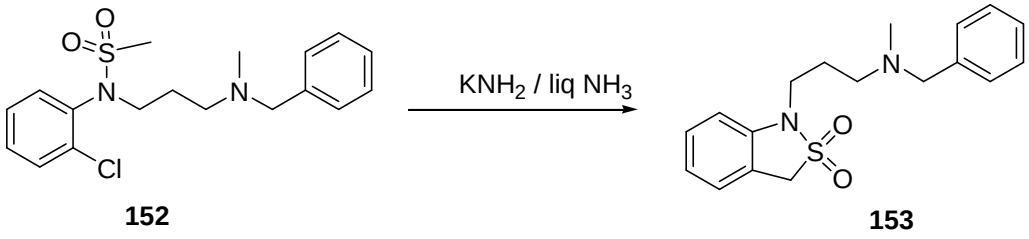
Scheme 104. Palladium catalysed intramolecular α-arylation of sulfoximines

Only one example of an arylation reaction is reported where the nucleophile is a sulfonamide[190]. However, this procedure required an enhancement of the acidity of the subject sulfonamide through the generation of a β-cyanosulfonamide. The relatively acidic 2-[*N*-(benzyloxymethyl)-*N*-methylaminosulfonyl]cyanoacetate **150** was coupled with aryl iodide **151** using tetrakis(triphenylphosphine)Pd(0) as catalyst and sodium hydride as base (Scheme 105).



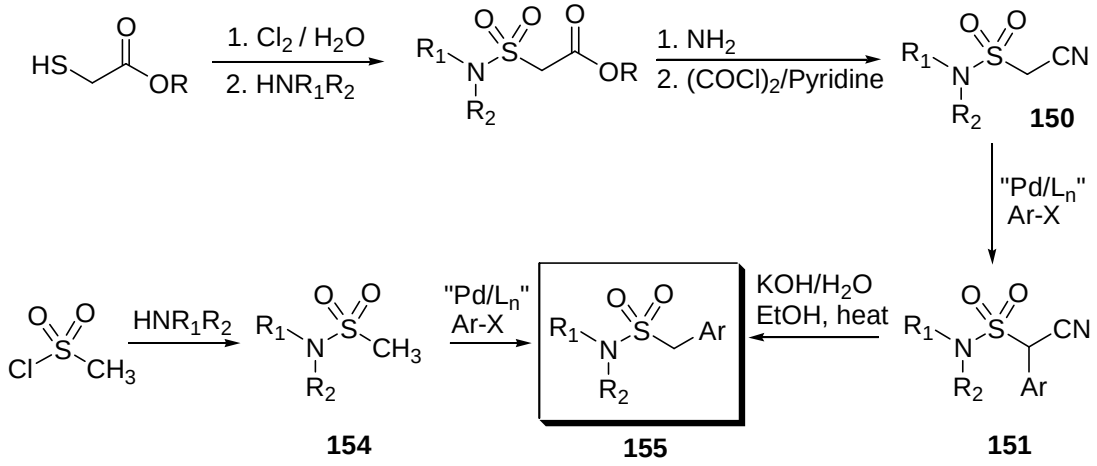
Scheme 105. Palladium catalysed arylation of a β-cyanosulfonamide

Similar reactions have previously been performed using potassium in liquid ammonia, presumably by a "benzyne type" mechanism[191] (Scheme 106).



Scheme 106. Intramolecular methanesulfonamide arylation reaction with KNH_2 / liquid ammonia

The preparation of compounds such as **150**, containing both a sulfonamide and a cyano substituent to enhance the acidity of the protons between both functional groups, is cumbersome. In cases where the α-aryl methanesulfonamide **155** is required as the target compound, such electron-withdrawing groups have to be removed after coupling of the aryl halide. The preparation of a methanesulfonamide **154**, on the other hand, is extremely simple through reaction of methanesulfonyl chloride and the appropriate amine (Scheme 107).



Scheme 107. Comparison of the preparation of **155** by arylation of a either a β-cyanosulfonamide or methanesulfonamide

It has, however, previously been reported that highly nucleophilic carbanions (stabilised by only one electron-withdrawing group) such as those derived from methylphenylsulfone and methylphenylsulfoxide are unreactive in arylation chemistry[112,192,193]. Conversely, the arylation of the closely related methylphenylsulfoximes has been demonstrated by Bolm *et al.*[113] and other systems with high pKa values such as acetamides, acetonitrile and acetic acid esters (pKa ~31-35[96]) have been used successfully in enolate arylation reactions[102,103,105,108,107].

We rationalised that the arylation of substituted methane sulfonamides with aryl halides catalysed by palladium should be feasible.

4.1 A Novel Route Towards the Synthesis of Sumatriptan

The initial investigation into methanesulfonamide arylation was focussed on the preparation of an advanced intermediate for Sumatriptan (Imitrex™, marketed by GlaxoSmithKline) a potent anti-migraine drug (see Figure 9).

A number of structurally related anti-migraine drugs are also known and are emerging as sumatriptan replacements. These substituted tryptamine compounds have, similar to serotonin (5-hydroxytryptamine; 5-HT), a vasoconstrictor action in the vascular bed by an agonistic action at the "5-HT_1-like" receptors. Sumatriptan and related drugs have a more selective affinity toward a sub-population of "5-HT_1-like" receptors making them more effective in migraine therapy while showing less undesirable and potentially dangerous side-effects[194].

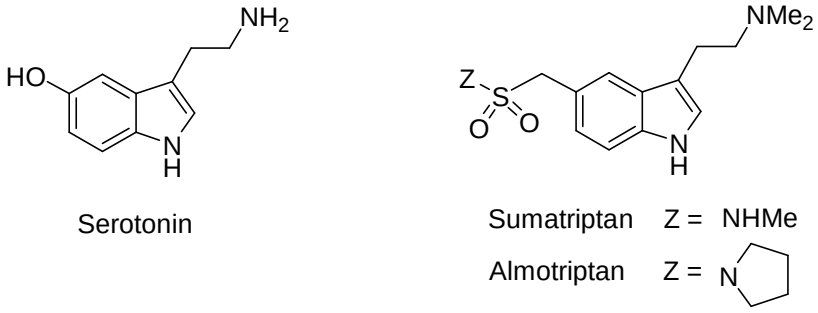
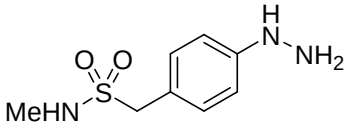


Figure 9. Tryptamine based anti-migraine agents

Sumatriptan, however, not only has an affinity for the 5-HT_{1D} receptor but also the 5-HT_{1A} receptor which can cause hypotension by a central nervous system action and other side effects[194]. It was found that by introducing a nitrogen ring in the methanesulfonyl group, greater specificity for the 5-HT_{1D} receptor is obtained and hence less side effects. One such compound is almotriptan which contains a pyrrolidine ring as part of the methanesulfonyl group (Figure 9).

Almotriptan (marketed as Axert™ by Pharmacia UpJohn) was registered for pharmaceutical use in 2001 and is on the top 100 drug list. The parent patent describing the preparation and use in medical treatment expires in 2014 [194].

Sumatriptan is generally synthesised through the intermediate hydrazinophenyl-methyl methanesulfonamide **156** (see Figure 10) or a derivative thereof, followed by acid mediated closure of the pyrrole ring to form the indole[195].

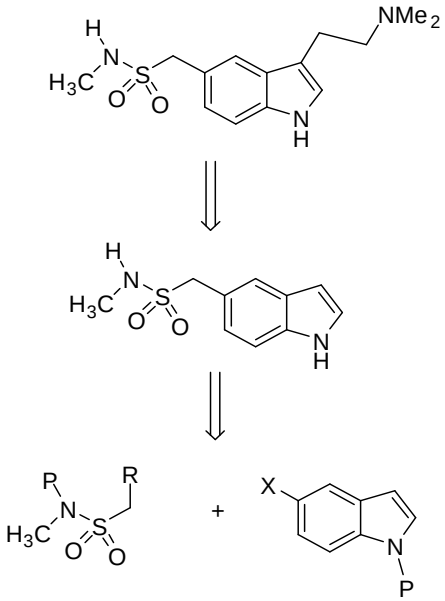


156

Figure 10. Hydrazinophenyl-methylmethanesulfonamide intermediate

The incorporation of a methanesulfonamide residue into the 5-position of a preformed indole, followed by introduction of the required substituent in the 3-position was thought to be a more direct route to sumatriptan and to be a methodology suitable for rapid generation of similar species.

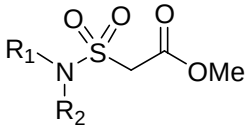
The subject of this work relates to an alternative process whereby the sulfonamide is incorporated into a preformed indole (see Scheme 108). The concept is analogous to the enolate arylations described by Hartwig and Buchwald for a variety of aryl halides and enolates[99,90,100].



Scheme 108. Proposed disconnection approach to sumatriptan

To date, however, no examples have been reported where a halogenated indole is used as the aryl-halide component for enolate arylation and sulfonamide arylation has only limited precedent[190].

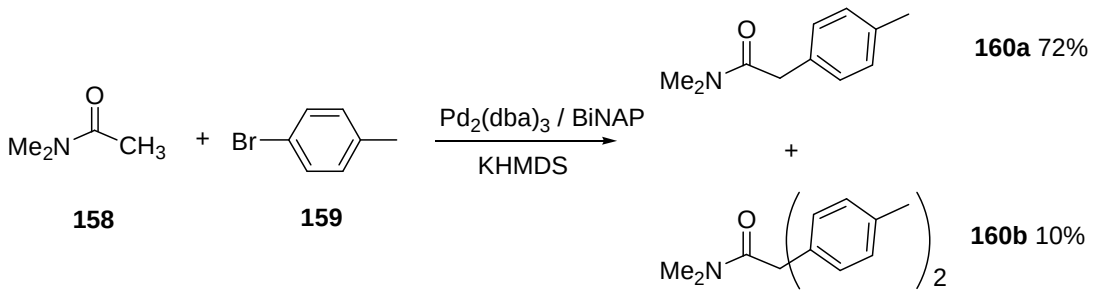
Taking the precedent set out by Middleton[190] where a sulfonamide stabilised enolate is arylated, we set out to examine the simpler methyl 2-[(methylamino)sulfonyl]acetate and other structurally related enolate precursors **157** (Figure 11).



157

Figure 11. Methyl 2-[(methylamino)sulfonyl]acetate derivatives **157**

While this has no precedent, it would appear reasonable due to structural homology of the nucleophile with malonic acid derivatives. Examples of arylation of amide enolates are limited, the leading work in the area having been carried out by the research group of Hartwig demonstrating arylation of *N*,*N*-disubstituted amides[102](Scheme 109), further suggesting the advantages of the stabilised enolate.



158 **159** **160a** 72% **160b** 10%

Scheme 109. Palladium catalysed amide enolate arylation by Hartwig

In view of the limited precendent for the work to be carried out, a proof of concept study was carried out to answer a series of questions:-

1. Was 5-bromoindole **161** (Scheme 110) a viable aryl halide for enolate arylation reactions either as the free-base or in a protected form?
2. Could the sulfonamido acetate precursor **157** be prepared in a manner suitable for commercial implementation?
3. Was the sulfonamido acetate a viable enolate in an enolate arylation protocol?
4. Was the coupling of both components feasible?

With regard to the 5-bromoindole **161** substrate, it would be reasonable to expect that the indolyl nitrogen could be a complicating factor in any reaction involving nucleophilic addition. It is noted in the bulk of heterocyclic literature that the nitrogen of the indole is a powerful nucleophile in all protocols not mediated by a magnesium metal containing base[196]. Since amination of aryl halides is well precedented under transition metal mediated conditions [197,3] (in many cases generating di-arylamines) it appeared that the addition of the indolyl nitrogen to the 5-position of another indolyl residue could constitute a complicating factor to the proposed transformation. Consequently, we felt that protection of the indolyl nitrogen would be advisable. The protecting groups of choice would appear to be *tert*-butyloxycarbonyl (BOC) or other similar carbamates or benzyl. Simple acyl protection as the amide was not considered due to the known lability of this functionality. The BOC group would also be capable of removing electron density from the indole with a possible acceleration in rate of the enolate arylation reaction. Both BOC and benzyl groups have been used extensively in indole chemistry and their removal is well precedented.

Similarly, the lability of the N-H of the sulfonamide was also a potential complicating factor. No reports of amide arylation have appeared where the amide is mono-substituted. Consequently, we felt that there may be a need for amide protection. If this was to be carried out, the goals would be to utilise a cheap protecting group that would be removed in a single step together with the indole protecting group. The most

likely species to satisfy these requirements would be a benzyl or a modified benzyl species.

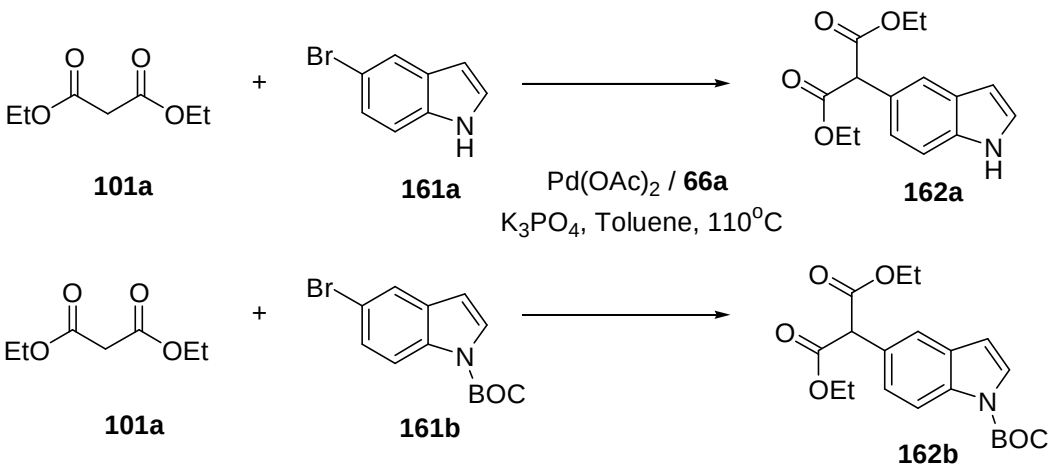
As a consequence of these factors, our approach to the problem at hand was:

1. To examine the use of 5-bromoindole **161** in both protected and free base forms in enolate arylation using diethyl malonate **101** to establish the bromo-indole as a substrate.
2. To investigate the preparation of the sulfonamido acetate **157** (or structurally related enolate precursors).
3. To test the sulfonamido acetate **157** (or structurally related enolate precursors) as an enolate with halobenzene derivatives such as bromobenzene.
4. To examine methanesulfonamide **154** derivatives as alternative substrates with halobenzenes.
5. To test both of the required substrates in tandem.
6. To refine the process according to the findings above.

4.1.1. Arylation reactions between diethyl malonate and 5-bromoindole **161**

The viability of 5-bromoindole **161** as a substrate in palladium catalysed arylation was investigated. This was carried out by comparing the reaction between diethyl malonate and both 5-bromoindole and *N*-BOC protected 5-bromoindole as well as with other aryl bromides under similar conditions. Diethyl malonate was chosen as the model substrate due to its similarity to the proposed sulfonamido acetate substrate and since its reaction with other aryl bromides has been studied by us and others[99,90,100].

The arylation of diethyl malonate **101** with 5-bromoindole **161a** (see Scheme 110) reaction was performed in toluene solution using K_3PO_4 as base and a catalyst consisting of a 1:2 mixture of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)biphenyl **66a**. After 15 hours at 110°C GC analysis revealed full consumption of 5-bromoindole while a large proportion of diethyl malonate remained. From internal standard calculations and ^{1}H-NMR spectroscopy it was determined that 15% of the anticipated diethyl indolylmalonate **162a** was produced.



Scheme 110. Arylation reaction between diethyl malonate and 5-bromoindole

The fact that all the bromoindole **161a** was consumed and a large amount of insoluble black solid was formed suggests the possibility that head-to-tail linkage of bromoindole, leading to an indole dimer/polymer **163** could have been a competing reaction (Figure 12). This type of reaction is well precedented under palladium catalysed conditions and deprotonated indole is known to be a good nucleophile[197,3].

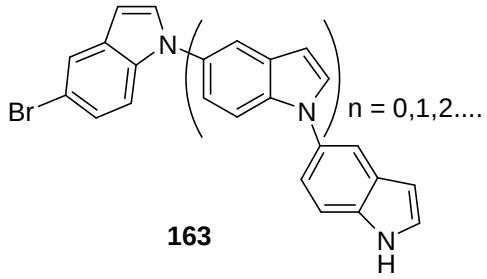


Figure 12. Proposed head-to-tail linkage of **161a**

In order to prevent aromatic amination mediated polymerisation from becoming a competitive pathway, *N*-protection of the indole was proposed. *N*-(*t*-Butyloxycarbonyl)-5-bromoindole **161b** was prepared and the arylation reaction was repeated under similar conditions. Full conversion of **161b** was observed after 15 hours at 110°C. From ^{1}H-NMR and GC analysis (internal standard) a yield of 70% for the correct product **162b** was determined. 5-Bromoindole was also recovered in about 20% yield indicating that *in situ* de-protection is a competing side reaction, suggesting that the protection strategy might require revision.

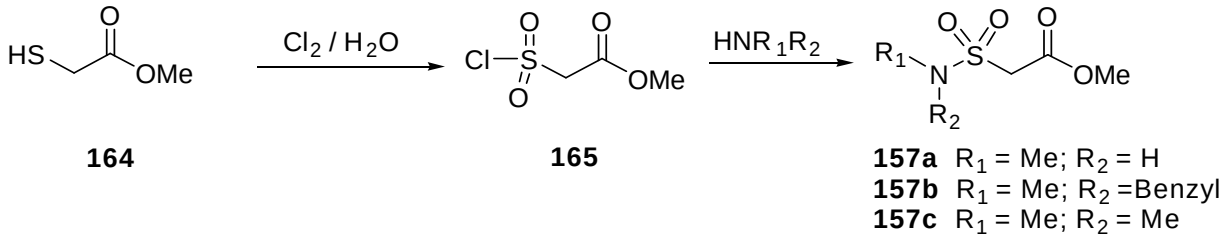
The yield of the arylation product is in good correlation to that observed by us in similar reactions involving bromobenzene **87a** and 4-bromoanisole **87h**. This suggested that *N*-Boc-5-bromoindole **161b** was a viable substrate in arylation and behaves in a manner similar to more classical aryl bromides.

4.1.2 Arylation of sulfonamide stabilised enolates

As discussed earlier, only one example of the palladium catalysed arylation of a sulfonamide enolate has been noted in the literature[190]. This involved a 2-sulfonamido acetonitrile **1** and an aryl iodide (see Scheme 103). Since the arylation of acetates[107,108,198] is known (like nitriles[97,84]), a number of α-stabilised methanesulfonamides were prepared and evaluated in arylation reactions with bromobenzene, iodobenzene and 5-bromoindole derivatives.

Methyl 2[(methylamino)sulfonyl]acetate **157a** was prepared as an acidic substrate which would generate a highly stabilised enolate, similar to diethyl malonate and the 2-sulfonamidoacetonitrile **150.** Conversion of the arylated **157a** to an α-aryl methanesulfonamide (as is required in the structure of Sumatriptan) was thought to be significantly less complicated than when a sulfonamidoacetonitrile substrate **151** would be used (see Scheme 107). Hydrolysis of the methyl ester and acid catalysed decarboxylation should yield the required product.

Methyl 2[(methylamino)sulfonyl]acetate **157a** was prepared from methyl thioglycolate **164** in two steps according to a literature procedure (Scheme 111)[190]. Chlorination of methyl thioglycolate **164** resulted in the formation of methyl 2-(chlorosulfonyl)acetate **165** which was treated with 2 equivalents of methylamine to afford **157a**.



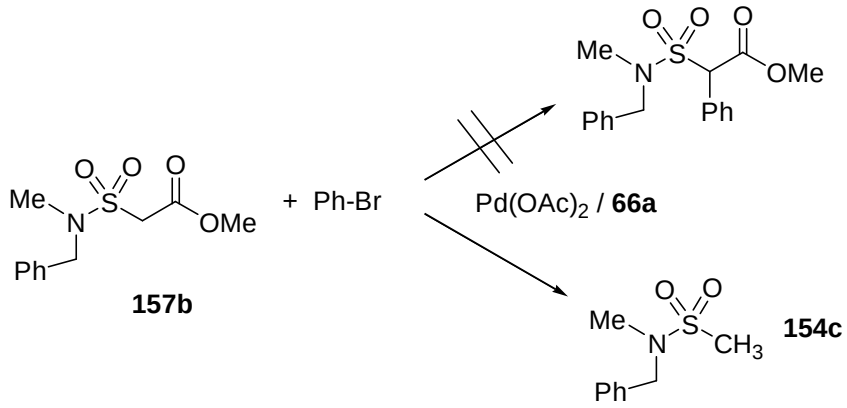
164 **165**

157a R_1 = Me; R_2 = H
157b R_1 = Me; R_2 =Benzyl
157c R_1 = Me; R_2 = Me

Scheme 111. Preparation of methyl 2-sulfamido acetates **157**

Similar reaction conditions as those applied in the arylation of diethyl malonate were used, in the reaction between **157a** and bromobenzene. Potassium phosphate was used as base since the α-proton is thought to be accessible by this base as is the case with diethyl malonate. The reaction failed to yield any of the anticipated arylation product and very little identifiable material was recovered. It is proposed that the sulfonamido acetate had decarboxylated under the conditions as none of the starting material was detected. Additionally, the free N-H of the sulfonamide **157a** might have further complicated the progress of the reaction.

In order to remove the complication associated with the free N-H, methyl 2-[(benzylmethylamino)sulfonyl]acetate **157b** was prepared as an alternative substrate in a similar manner to **157a**. Again no arylation products were detected in the reaction between **157b** and bromobenzene using the reaction conditions describe above (Scheme 110). Decarboxylation of the sulfonylacetate under the reaction conditions was confirmed when *N*-benzyl-*N*-methyl methanesulfonamide **154c** was recovered from the reaction mixture.

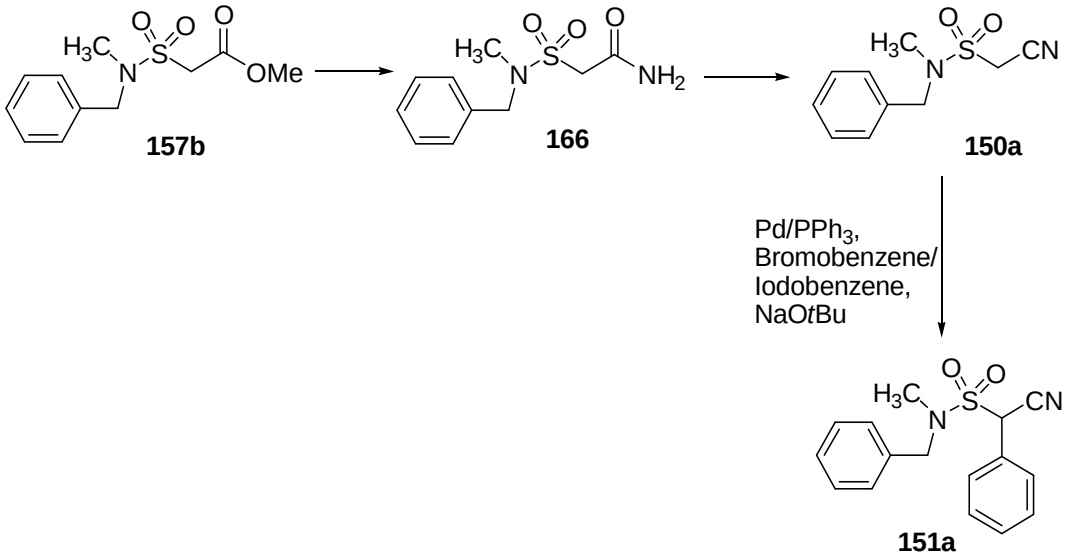


157b **154c**

Scheme 112. Attempted arylation reaction of **157b**

After the failure of the sulfonylacetate esters **157** as arylation substrates due to proposed instability under the reaction conditions, it was decided to investigate the more stable sulfamidoacetonitrile as arylation substrate. A similar compound to **150**, which has been successfully arylated employing an aryl iodide and tetrakis(triphenylphosphino) Pd(0)[190] (see Scheme 105) was prepared.

2-[(Benzylmethylamino)sulfonyl]acetonitrile **150a** was prepared from methyl 2-[(benzylmethylamino)sulfonyl]acetate **157b** in 2 steps (see Scheme 113). Firstly the ester was converted to the parent amide **166** by treatment with ammonia in THF. The amide was then dehydrated to the nitrile **150a** using thionyl chloride.



Scheme 113. Preparation and arylation of 2-[(benzylmethylamino)sulfonyl]acetonitrile **150a**

Substrate **150a** was tested under varying conditions in reactions with bromobenzene, iodobenzene, *N*-Boc-5-bromoindole **161b** and *N*-benzyl-5-bromoindole **161c**.

The reaction with iodobenzene using sodium *tert*-butoxide and palladium acetate/triphenylphosphine proved successful as heating for 2 days at 70°C gave the

desired product **151a** in 63% yield. The identity of the product was confirmed by GC-MS. Further heating at 100°C for 2 hours increased the yield slightly to 65%.

The reaction with bromobenzene was carried out under the same conditions but at higher temperature (110°C). After 15 hours at this temperature, a conversion of 77% was achieved by GC. Once again, this indicates that the reaction is more successful at higher temperature. The reaction mixture was isolated and purified to afford **151a** in 42% yield.

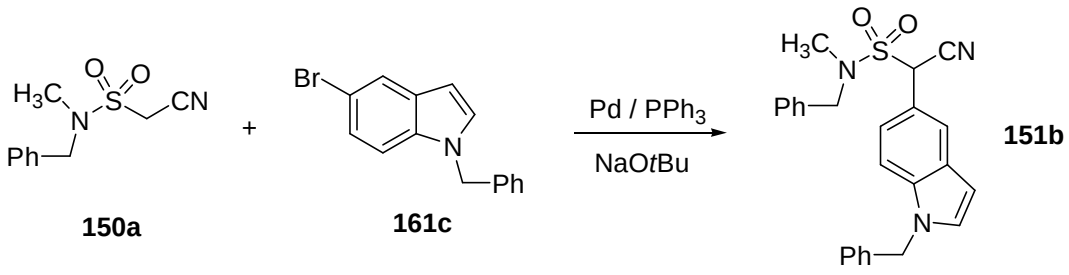
The reaction was also repeated using tri-*tert*-butylphosphine as ligand. Again the reaction proceeded smoothly to give the arylation product **151a** in 81% yield (by GC).

The arylation reaction using K_3PO_4 as base with iodobenzene was also attempted. At first no product was observed even after heating at 80°C for 15 hours. Since the K_3PO_4 reactions sometimes suffer from lack of solubility in toluene, dimethyl acetamide (DMA) was added to aid the solubility of K_3PO_4. Heating at 100°C for 3 hours did result in the formation of the correct product **151a** in 37% yield. Heating for 16 hours at 90°C increased the yield slightly to 41%.

Previously the *N*-Boc protecting group on 5-bromoindole had been shown to be unstable under NaO*t*Bu conditions. Due to the higher acidity of the α-protons on the sulfonamide acetonitrile substrate **150a**, as demonstrated by the successful arylation reaction employing the weaker and milder K_3PO_4 base, the reaction with *N*-Boc-5-bromoindole **161b** using K_3PO_4 was attempted. The reaction was performed in toluene solvent with added DMA and heated for 15 hours at 110°C. No arylation product was, however, observed by ^{1}H-NMR spectroscopy.

The nitrile substrate **150a** was also tested in a reaction with *N*-benzyl-5-bromoindole **161c** using NaO*t*Bu and Pd/PPh_3 catalysts (Scheme 114). After heating at 110°C for 15 hours the reaction was quenched and the product mixture isolated. From ^{1}H-NMR spectroscopy it appeared as if the arylation product **151b** was present in small quantity.

The coupling product **151b** was isolated by flash column chromatography albeit in very low yield. The identity of **151b** was confirmed by mass spectrometry.



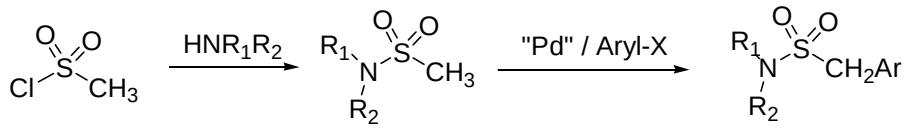
Scheme 114. Coupling reaction between **161c** and **150a**

4.1.3 Arylation of sulfonamide stabilised anions

Although the sulfonamidoacetonitrile substrate **150a** was successfully arylated using a number of aryl halides, including *N*-benzyl 5-bromoindole **161c** required in the novel Sumatriptan synthesis, a more direct arylation reaction to α-arylmethanesulfonamides was sought to make this an attractive approach. The direct arylation of a methanesulfonamide stabilised anion would make the hydrolysis and decarboxylation of the nitrile substituent redundant.

N-Methyl methanesulfonamide **154a** was prepared from methanesulfonyl chloride and two equivalents of methylamine in tetrahydrofuran (THF)(Scheme 115).

It was thought the higher pK_a (between 32 and 35)[96,102]of the methanesulfonamide stabilised anion would necessitate the use of a strong base as has been observed for substrates like aliphatic amides and esters[102,107,108] with similar pK_a values. An arylation reaction with bromobenzene was attempted using conditions similar to those described for the arylation of *t*-butyl acetate[107]. Lithium hexamethyldisilazane (LiHMDS) was used as base with a 1:1 mixture of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)biphenyl **66a** as catalyst. No arylation was observed and starting materials were recovered virtually unchanged. It was proposed that the acidity of the N-H proton of **154a** is a possible cause of this failure.



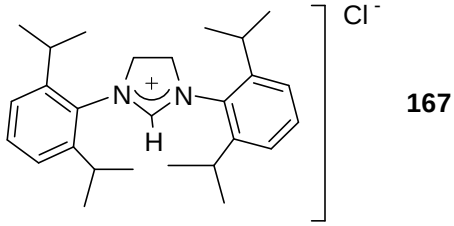
154a R_1 = Me; R_2 = H
154b R_1 = Me; R_2 =Me
154c R_1 = Me; R_2 =Benzyl

155

Scheme 115. Preparation and arylation reaction of methanesulfonamides

In order to eliminate the complications associated with the N-H acidity on the sulfonamide, the di-methylamino equivalent **154b** was prepared in a similar manner to **154a**. This compound was tested in arylation reactions using a number of different reaction conditions.

Bromobenzene was reacted with **154b** using NaHMDS as base and a 1:1 mixture of bis di-benzylidine acetone palladium(0) ($Pd(dba)_2$) and 1,3-bis-(2,6-diisopropylphenyl) imidazolinium chloride **167** (Figure 13). These conditions were used by Hartwig in the arylation of *t*-butyl acetate[108].



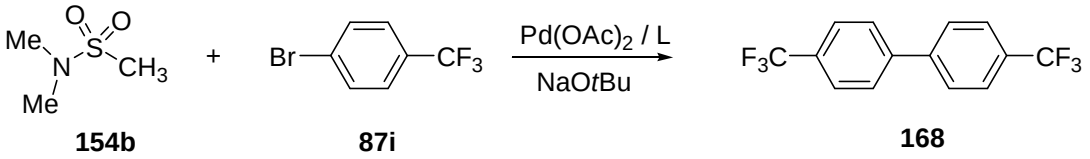
167

Figure 13. 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride **167**

Another reaction was performed using NaHMDS and a palladium/BINAP catalyst system that has been reported for amide arylation[102]. Again very little change was noted after extended reaction times.

It was decided to move away from the HMDS bases, which are highly moisture sensitive, to the more conventional/widely used NaO*t*Bu. Three catalyst systems were examined in reactions with 4-trifluoromethylbromobenzene **87i** (Scheme 116). $Pd(OAc)_2$ was used in combination with three equivalents of PPh_3, 2 equivalents of tricyclohexylphosphine and one equivalent of 2-(di-*tert*-butylphosphino)biphenyl **66a**.

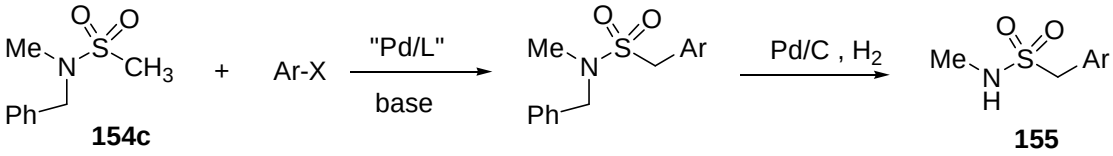
In all cases the only product that was formed was the homo-coupled arene **168** (between 10 and 25% yield).



154b **87i** **168**

Scheme 116. Reactions between **154b** and 4-trifluorobromobenzene **87i**

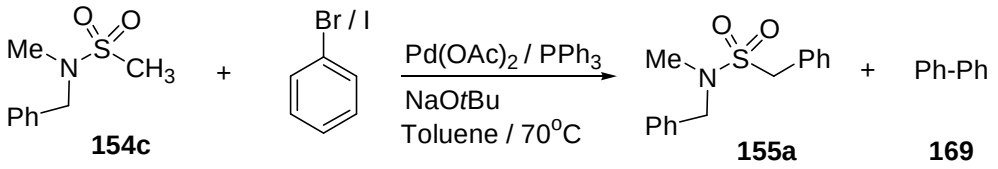
N-Benzyl-*N*-methylmethanesulfonamide **154c** was prepared by reacting methanesulfonyl chloride and two equivalents of benzylmethylamine (Scheme 115) as an alternative *N*-dialkylated sulfonamide. This was done for two reasons: firstly, the benzyl group can act as a protecting group that could be removed under hydrogenation conditions leaving the desired mono-arylated methanesulfonamide (see Scheme 117). Secondly, a starting material could be detected easily by thin layer chromatography (tlc).



154c **155**

Scheme 117. Proposed protection / deprotection strategy

In a reaction between **154c** and bromobenzene using the $Pd(OAc)_2/PPh_3$ catalyst system and NaO*t*Bu as base, a new peak was detected by GC after 15 hours of stirring the reaction mixture at 70°C. GC-MS confirmed this as the desired product **155a** (see Scheme 118). The yield of **155a** was only ~10% while ~20% of biphenyl (homo-coupling) was formed in the same reaction. A similar experiment using K_3PO_4 as base did not yield the required product.



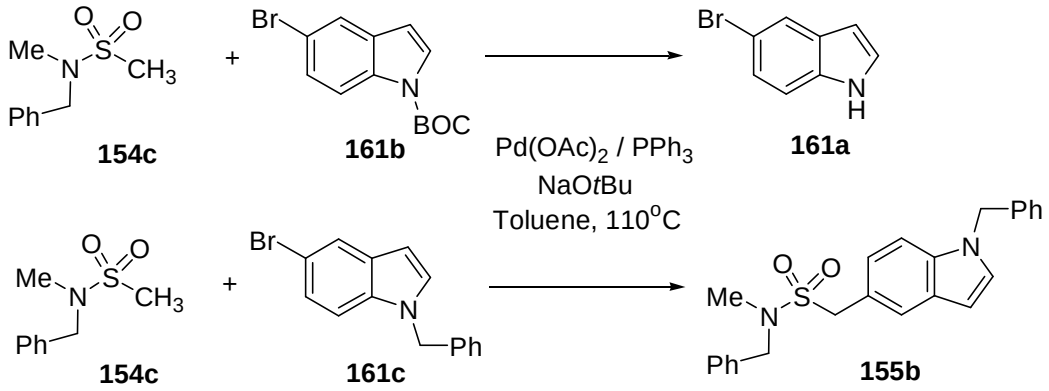
Scheme 118. Arylation of *N*-benzyl-*N*-methyl methanesulfonamide **154c**

The successful reaction was repeated on iodobenzene in order to examine what the rate limiting step might be. Approximately 50% of the arylated product **150a** was formed after ~2 days at 75°C. Approximately 15-20% of bi-phenyl **169** was also formed. The isolated product mixture was purified by means of column chromatography and the identity was verified by NMR spectroscopy.

The yield of the arylation reaction between bromobenzene and **154c** was improved to 59% in 15 hours by increasing the reaction temperature to 110°C. The yield of biphenyl was dramatically lower at ~5%. The use of tri-*tert*-butylphosphine as ligand also resulted in the formation **150a** albeit in lower yield (28%).

This reaction was then applied to *N*-boc-5-bromoindole substrate **161b** (Scheme 119). Unfortunately the starting material was unstable under the reaction conditions (NaO*t*Bu) resulting in the BOC protecting group being cleaved. No reaction between the free 5-bromoindole **161a** and the sulfonamide **154c** was observed.

An alternative protecting group for the indole appeared to be necessary – the benzyl group seemed appropriate since the sulfonamide synthon already contained such a group. Both the benzyl protecting groups may, conceivably, be removed in one hydrogenation reaction. *N*-Benzyl-5-bromoindole **161c** was prepared by treatment of 5-bromoindole with sodium hydride and benzyl bromide.



Scheme 119. Arylation reactions between **154c** and 5-bromoindole **161** derivatives

The reaction between *N*-benzyl-*N*-methylmethanesulfonamide **154c** and *N*-benzyl-5-bromoindole **161c** was performed using the conditions used for reaction with bromobenzene (see Scheme 118 and 119). The reaction mixture was heated at 90°C for 15 hours followed by 4 hours at 110°C. Very little change was observed by GC except for a decrease observed in the size of the aryl halide peak. The reaction was quenched and the crude product isolated. After purification by flash column chromatography a fraction was collected that was identified by ^{1}H-NMR and mass spectrometry to be the desired product **155b**.

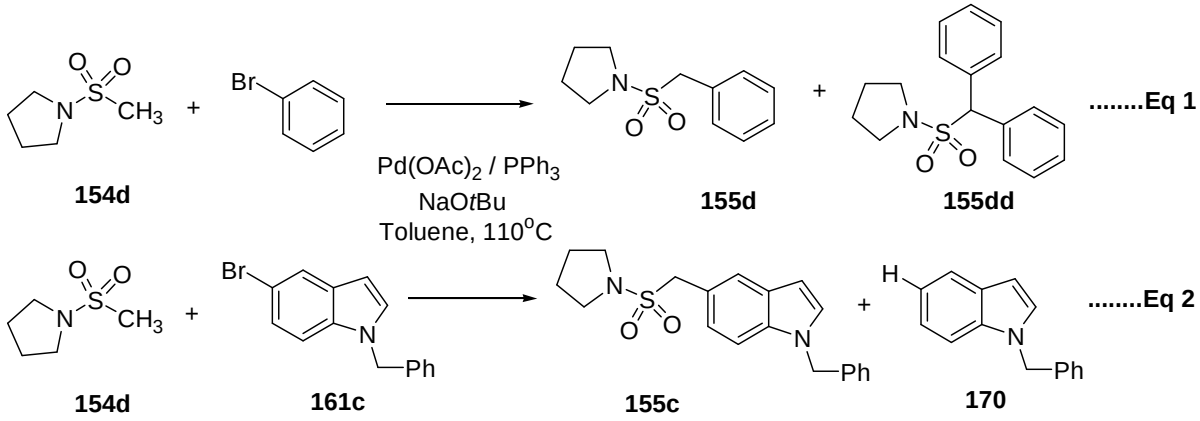
The product **155b** solidified on standing and was re-crystallised from hexane/ethyl acetate to give a light yellow solid that was shown to be greater than 90% pure by both ^{1}H and ^{13}C-NMR spectroscopy. The yield of the isolated material was 38% calculated on the indolyl bromide **161c** used. The same product was also isolated from a reaction employing tri-*tert*-butylphosphine as ligand albeit in lower yield (15%).

4.2 Application to the Synthesis of an Almotriptan Intermediate

The methanesulfonamide arylation strategy, developed for the synthesis of a sumatriptan intermediate, was applied to the synthesis of an almotriptan intermediate **155c** (see Scheme 120). This intermediate only differs from that prepared for Sumatriptan (**155b**) in the amine substituent of the sulfonamide. The appropriate

arylation substrate **154d** was prepared by reacting methanesulfonyl chloride with pyrrolidine.

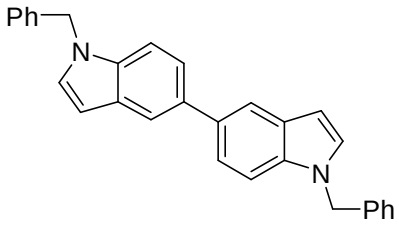
The arylation concept was first demonstrated by using bromobenzene as the aryl halide using $Pd(OAc)_2$ / PPh_3 as catalyst in toluene with NaO*t*Bu as base (Scheme 120, Equation 1). The mono and diphenylated products (**155d** and **155dd**) were formed in modest yields of 35 and 6% respectively. Homocoupling was the major side reaction with 9% of biphenyl being formed in the reaction. The yield for the arylation reaction was lower than that observed in the arylation of *N*-benzyl-*N*-methyl methanesulfonamide **154c** (59%, used for the sumatriptan intermediate **155b**).



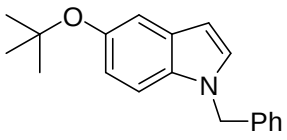
Scheme 120. Preparation of key intermediate towards Almotriptan

The reaction with *N*-benzyl-5-bromoindole **161c** was subsequently performed under the same reaction conditions (Scheme 120, Equation 2). After 20 hours of heating it was observed by GC analysis that the aryl bromide had been fully converted while 80% of the methanesulfonamide was consumed. A number of products were formed of which the desired arylation product **155c** (identified by ^{1}H-NMR spectroscopy) in only 12-15% yield. Approximately 25% *N*-benzyl-indole **170** was formed and the homocoupled product **171** (Figure 14) could not be detected by GC due to its low volatility. In a repeat experiment, lower conversion of starting materials was observed and only ~ 5% of **155c** was formed.

In an attempt to improve the arylation yield, tri *tert*-butylphosphine was used as ligand. The aryl bromide **161c** was consumed (95% conversion) and only 53% of the methanesulfonamide **154d** was consumed. Again hydrodehalogenation accounted for 25% of the aryl bromide while only approximately 7% of the desired product **155c** was formed. Another compound, which was identified as the *tert*-butyl ether of *N*-benzyl-indole **172** by GC-MS (Figure 14), was formed in 15% yield.



171



172

Figure 14. Byproducts derived from **161c**

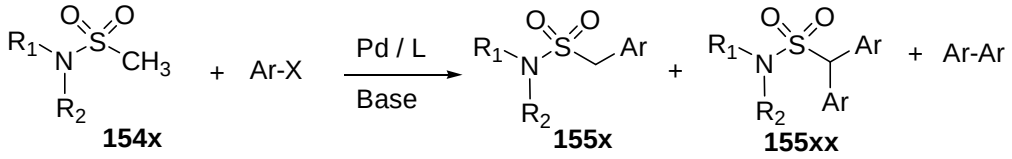
The failure of this reaction to yield significant amounts of arylated product is not understood and should be investigated further under different conditions and catalyst systems.

4.3 Arylation of Methanesulfonamides

After the successful application of the palladium catalysed methanesulfonamide arylation reaction towards a novel synthetic route of the "triptan" anti-migraine agents, sumatriptan and almotriptan, further investigation followed which was aimed at broadening the scope and improving the generality of this new and relatively successful carbanion arylation reaction. Therefore a number of methanesulfonamides and *C*-substituted methanesulfonamides were prepared and evaluated under a number of reaction conditions used for enolate arylation reactions.

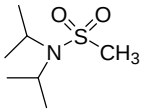
Most of the initial work was conducted using *N*,*N*-diisopropyl methanesulfonamide **154e** (Scheme 121, Table 8). Besides the formation of the desired mono-arylated product **155e** from **154e** in moderate yields (9-46% for bromobenzene) by utilising a number of phosphine ligands, diarylation to give **155ee** was also observed in varying

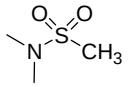
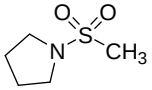
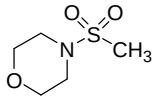
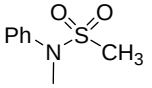
amounts. BINAP was more selective toward mono-arylation than triphenylphosphine (see entries 1 and 3). The ligands PCy_3 and P^tBu_3 behaved very differently in this transformation with PCy_3 leading preferentially to the diarylated product **155ee** while P^tBu_3 was the most selective ligand for mono-arylation (entries 5 and 6). The use of a lower palladium loading (1mol%) while maintaining a high PPh_3 loading did not lead to lower arylation activity but instead lead to the formation of similar amounts of the mono- and di-arylated products **155e** and **155ee** and suppression of biphenyl formation (entry 7).



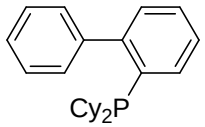
Scheme 121. *Reagents and Conditions*: 2 mmol aryl bromide, 2.2 mmol sulfonamide, 3.5 mmol NaO^tBu, 5mL toluene, $Pd(OAc)_2$, ligand, 110°C, 15 hours (see Table 1 for ligand and yields).

Table 8

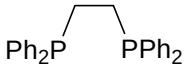
Entry	Methanesulfonamide	Ar-X	Pd mol%	Ligand (mol%)	155x yield %	155xx yield %	Biaryl yield %
1	 **154e**	Bromobenzene	8	PPh_3 (23)	**155e** 34	**155ee** 14	**169** 15
2		Bromobenzene	8	PPh_3 (23)	32[a]	10	3
3		Bromobenzene	8	$PoTol_3$ (15)	9	0	3
4		Bromobenzene	5	BINAP (8)	45	9	6
5		Bromobenzene	4	P^tBu_3 (8)	46	4	<1
6		Bromobenzene	5	PCy_3 (10)	14	25	0
7		Bromobenzene	1	PPh_3 (23)	34	29	<1
8		2-Bromotoluene	8	PPh_3 (23)	**155i** 50	**155ii** 10	n.d
9		4-Bromoanisole	8	PPh_3 (23)	**155j** 52	**155jj** 2	**173** 3
10		4-Bromoanisole	5	**108** (10)	**155j** 34	**155jj** <1	**173** 3
11		4-Bromoanisole	5	**174** (7.5)	**155j** 34	**155jj** <1	**173** 7
12		Chlorobenzene	4	P^tBu_3 (8)	**155e** 9	**155ee** 2	n.d
13			8	PPh_3 (23)	**155h** 28	**155hh** n.d	n.d

Entry	Methanesulfonamide	Ar-X	Pd mol%	Ligand (mol%)	155x yield%	155xx yield%	Biaryl yield%
14	 **154b**	Bromobenzene	8	PPh_3 (23)	**155k** 35	**155kk** 0	**169** 33
15	 **154d**	Bromobenzene	8	PPh_3 (23)	**155d** 35	**155dd** 6	**169** 9
16	 **154f**	Bromobenzene	8	PPh_3 (23)	**155f** 60	**155ff** 5	**169** 5
17	 **154g**	Bromobenzene	8	PPh_3 (23)	**155g** 34	**155gg** 4	**169** 14

a) 5.5 mmol NaO^tBu was used ; n.d = not determined



108



174

Figure 15. Cyclohexyl JohnPhos **108** and 1,2-bis(diphenylphosphino)ethane (DPPE) **174**

Using the more sterically hindered 2-bromotoluene **87j** instead of bromobenzene in the anion arylation reaction with **154e** also led to a marginal increase in selectivity of the product ratios of **155e** and **155ee**, while the unhindered and electron-rich 4-bromoanisole **87i** led to almost exclusively the mono-arylated product (entry 9) while using triphenylphosphine as ligand.

The use of either cyclohexyl JohnPhos **108** or 1,2-bis(diphenylphosphino)ethane (DPPE) **174** (see Figure 15) gave moderate activity (lower than triphenylphosphine) but with high mono-selectivity (see entries 10-11).

The problems concerning diarylation of the *N*,*N*-diisopropyl substituted sulfonamide **154e** proved to be less apparent than that observed for less sterically hindered

sulfonamides. For example, treatment of substrates **154b,d,f** and **g** under the same conditions (Table 8, entry 1) lead to ratios of the monoarylated product to the diarylated products exceeding 10:1 where the major side product was biaryl (see entries 14-17).

It would appear from these results that the initial stages of the reaction (oxidative addition and anion association to the catalyst complex) are not affected by the steric bulk of the substrates. The second part of the catalytic cycle appears to be the rate limiting step. Reductive elimination is favoured by an increase in steric bulk as it helps to destabilise the catalyst complex. During the formation of the di-arylation product, the stabilised anion forms a strong complex with the palladium catalyst and requires steric bulk to speed up reductive elimination. These results indicate that not only steric factors, but also electronic factors are important in determining the selectivity and yield of this reaction.

Chlorobenzene proved much less active than bromobenzene under these reaction conditions even when the highly electron-rich tri-*tert*-butylphosphine was used (entry 12). 1-Bromonaphthalene **87k** was arylated in moderate yield, and although di-arylation or homocoupling of the aryl bromide was not determined by GC, extensive hydrodehalogenation to naphthalene was observed (entry 13).

An interesting observation was made regarding the nature of the base used in these reactions. The reaction between *N,N*-diisopropyl methanesulfonamide **154e** and 4-bromoanisole **87i** was repeated using lithium *tert*-butoxide and potassium *tert*-butoxide, but reactions failed to give the desired product in substantial amounts while the reaction with the sodium counter-ion gave a 52% yield (entry 9). This observation is not unexpected given the preponderance of literature employing the sodium salt and the paucity of examples using the more common potassium *tert*-butoxide[91,90].

This effect can only be explained at the hand of different behaviour in solution of the three bases. Potassium *tert*-butoxide is highly hygroscopic and often (if not purified by

sublimation) contains potassium hydroxide, this could be the reason for its failure in this reaction. Lithium is a strongly coordinating metal ion and is likely to be inaccessible or forms strongly bound carbanions in non-coordinating and non-polar solvents. This could explain the failure of lithium *tert*-butoxide in toluene solution and the base should be examined in dioxane solution instead. The aggregation states of these 3 butoxide salts may differ significantly in toluene solution, explaining the different behaviour in the arylation reaction.

A reaction was performed with higher sodium *tert*-butoxide loading (2.5 molar equivalent compared to 1.5). This was done in an effort to increase the yield and selectivity to the mono-arylated product. Since the α-proton on the mono-arylated product is more acidic than that of the starting material, the formation of the product would lead to the quenching of the methanesulfonamide anion when one equivalent of base is used. This leads to incomplete conversion of the starting material, and since the mono-arylation product anion is present in higher concentration relative to the starting material anion, diarylation becomes a competitive reaction. When an excess of base is added to ensure that both the starting material and the arylation products are deprotonated, not only is full conversion of the methanesulfonamide possible, diarylation is suppressed by having a relatively high level of the more reactive methanesulfonamide anion. In practise the higher base loading did not increase the yield, but an increase in mono-selectivity was observed (compare entries 1 and 2). Biphenyl formation was also reduced, presumably due to an increased arylation reaction rate.

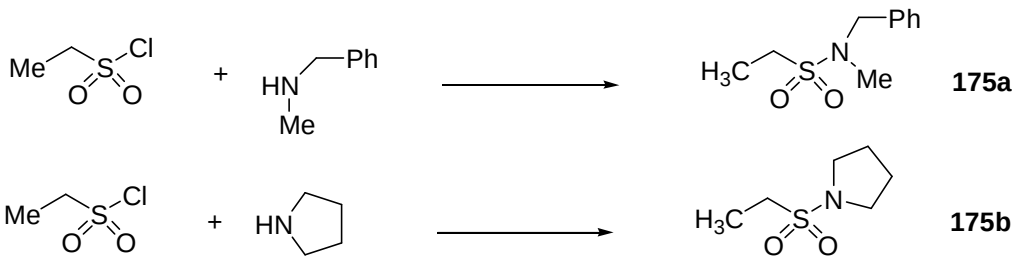
The use of potassium phosphate, which has been used successfully in the arylation of diethyl malonate, did not lead to any product formation even when using the highly polar DMF as solvent. Homocoupling was not inhibited as 18% biphenyl was detected.

From these results it does appear that sodium *tert*-butoxide is the preferred base, while the use of stronger bases like sodium hydride and hexamethyldisilazane warrants further investigation.

4.4 Arylation of *C*-substituted Methanesulfonamides

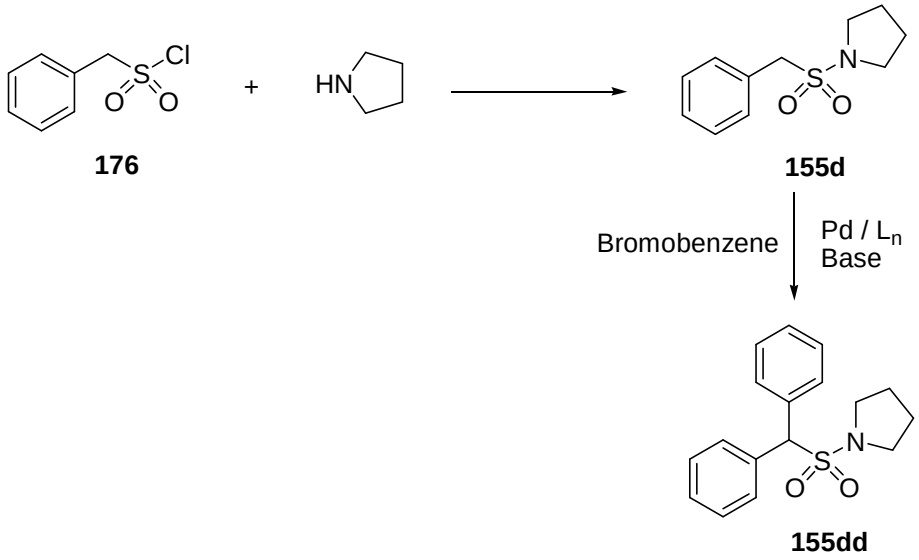
In an effort to broaden the scope of these reactions, a study was undertaken to apply the procedure to *C*-substituted methanesulfonamide anions.

Two ethanesulfonamides were prepared by reaction between ethanesulfonyl chloride and benzylmethylamine and pyrrolidine (Scheme 122). These sulfonamides, **175a** and **b**, were treated with bromobenzene under the standard palladium catalysed reaction conditions devised for methanesulfonamides (see Table 8). None of the desired arylated products were identified in any of the reactions (Table 9, entries 1-3).



Scheme 122. Preparation of Ethanesulfonamides **175**

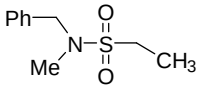
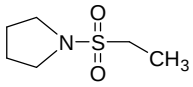
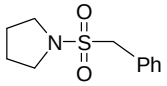
Due to the fact that diarylation of methanesulfonamides was observed in appreciable amounts, it was thought that steric hindrance by the extra alpha substituent would not be the limiting factor. This fact was further exemplified by preparing a α-toluenesulfonamide **155d** from α-toluenesulfonyl chloride **176** and pyrrolidine and using **155d** in a number of successful arylation reactions with bromobenzene (Scheme 123, Table 9, entries 5-8).



176 **155d** **155dd**

Scheme 123. Preparation of **155d** and arylation to **155dd**

Table 9. Reaction between *C*-substituted Methanesulfonamides and Bromobenzene

Entry	Sulfonamide	Ligand	Base	solvent	Yield Mono	Yield Di	Yield biphenyl
1	 **175a**	P*t*Bu$_3$	NaO*t*Bu	toluene	0	0	<1
2		PPh_3	NaO*t*Bu	toluene	0	0	8
3	 **175b**	PPh_3	NaO*t*Bu	toluene	0	0	18
4		PPh_3	NaHMDS	toluene	0	0	0
5	 **155d**	PPh_3	NaO*t*Bu	toluene	44	-	6
6		PPh_3	KO*t*Bu	dioxane	65	-	3
7		PPh_3	K_3PO_4	toluene	3	-	19
8		PPh_3	K_3PO_4	dioxane	13	-	15

Conditions: 2 mmol bromobenzene, 2.2 mmol sulfonamide, 3.5 mmol NaO^{t}Bu, 5mL solvent, 0.09mmol $Pd(OAc)_2$ and 0.18mmol P*t*Bu$_3$ or 0.16mmol $Pd(OAc)_2$ and 0.46mmol PPh_3, 110^{o}C, 15 hours.

Under the standard reaction conditions, reaction of **155d** with bromobenzene afforded the diphenylmethanesulfonamide **155dd** in 44% yield. The use of potassium *tert*-butoxide, which did not lead to product formation in methanesulfonamide reactions,

gave the arylated product **155dd** in 65% yield when using dioxane as the solvent (entry 6). Due to the extra stabilisation by the phenyl substituent, potassium phosphate was also sufficiently strong to deprotonate **155d**, especially in the more polar dioxane solution (entries 7 and 8) to yield **155dd**, although in low yield.

It is thought that due to the presence of the extra methyl, the acidity of the alpha protons could have been decreased marginally. This would reduce the concentration of deprotonated substrate available for reaction and therefore rendering the desired reaction slower than competing reactions which could have led to catalyst deactivation. The reaction was repeated using the stronger sodium hexamethyldisilasane (NaHMDS) with no result, a not unexpected observation due to failures on other substrates when using this base. A small strong base such as sodium hydride might be the key to a successful reaction (this was, however, not tested).

The facile introduction of a second aryl group when **155d** is used as the arylation substrate, indicates that diarylation is a feasible process. The introduction of the second group is further assisted by the higher acidity of the α-protons (due to the extra stabilisation imparted by the presence of an aryl functionality). This observation helps to explain the competition between mono and di-arylation observed in all the reactions of methanesulfonamides.

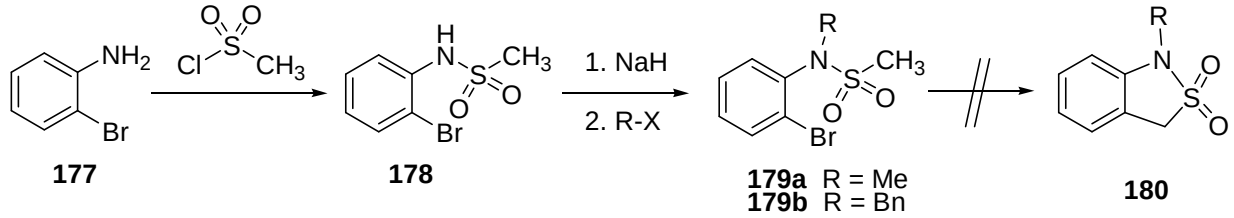
The introduction of a third aryl group (*ie* the formation of a quaternary carbon centre) was, however, not observed in any of the reactions.

The failure of the arylation protocol when using alkyl substituted methanesulfonamides was not conceived as a being a limitation since the same α-aryl alkylsulfonamide product could be prepared by consecutive arylation and alkylation reactions.

4.5 Intramolecular Reactions

Intramolecular arylation reactions have often been the forerunners of the intermolecular equivalent, due to the close proximity of both anion and aryl halide partners. A closely related example to this work is the intramolecular arylation of sulfoximines by Bolm *et al*[113] (see Scheme 104). They performed various intramolecular arylation reactions to successfully prepare six- to eight-membered heterocyclic ring systems.

In an attempt to expand the scope of our work on methanesulfonamide arylations to intramolecular reactions, we prepared a methanesulfonamide **178** with an aryl bromide as part of the amide substituent by reacting 2-bromoaniline **177** with methanesulfonyl chloride (Scheme 124). Since nitrogen bound protons have been demonstrated to be detrimental in the arylation reaction, *N*-methylation was carried out by treating a mixture of the sulfonamide and sodium hydride with iodomethane to give **179a**.

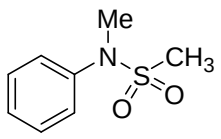


177 **178** **179a** R = Me **179b** R = Bn **180**

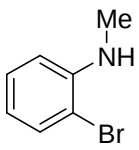
Scheme 124. Preparation of a methanesulfonamide for intramolecular arylation

This compound was subjected to the standard palladium catalysed arylation conditions using both triphenylphosphine and tri-*tert*-butylphosphine as ligands. In neither reaction was the formation of the ring-closed product **180** observed. A large percentage of the starting material was however consumed and a number of minor products were formed. Some of the products were identified by GC-MS, the major one being the hydrodehalogenated starting material **181** (Figure 16). Another product identified was *N*-methyl-2-bromoaniline **182**, by loss of the methanesulfonamide. The instability of this starting material is however puzzling as a very similar substrate **154g**

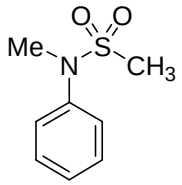
(with a phenyl substituent without the bromine) was stable and was arylated under the same conditions (Table 8, entry 17).



181



182



154g

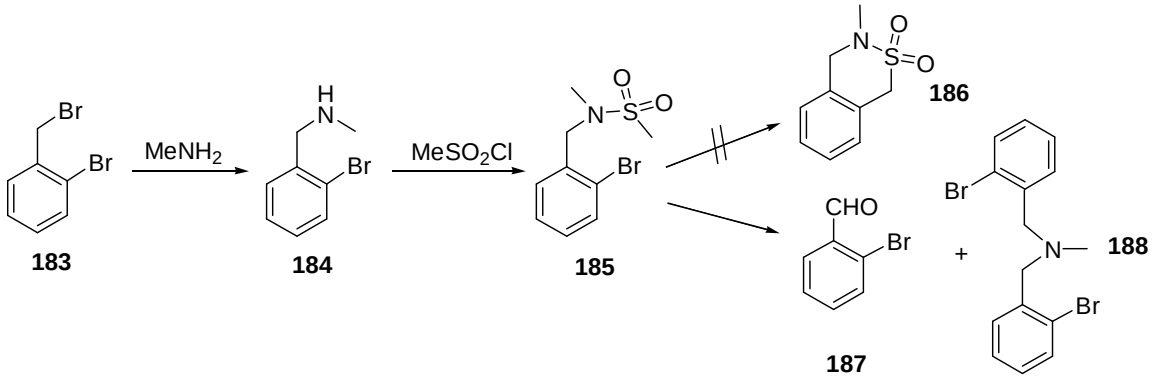
Figure 16.

A similar substrate was prepared in which the methyl was replaced by benzyl **179b** (see Scheme 124) in the hope that this would be more stable. Again none of the desired product was identified, and, although all the substrate was consumed, no major products were found by GC. This led us to believe that intermolecular arylation could have occurred leading to polymerisation of the substrate. ^{1}H-NMR spectroscopy of the isolated reaction mixture showed a large and complicated aromatic region with few peaks in the aliphatic region.

One possible explanation could be that after oxidative addition a strong interaction between the palladium and the sulfur-oxygen bond exists which would orientate the methyl group, required to undergo the reaction, away from the metal-aryl complex. Such palladium sulfonamide interactions could also account for the low turnover numbers in the intermolecular reactions.

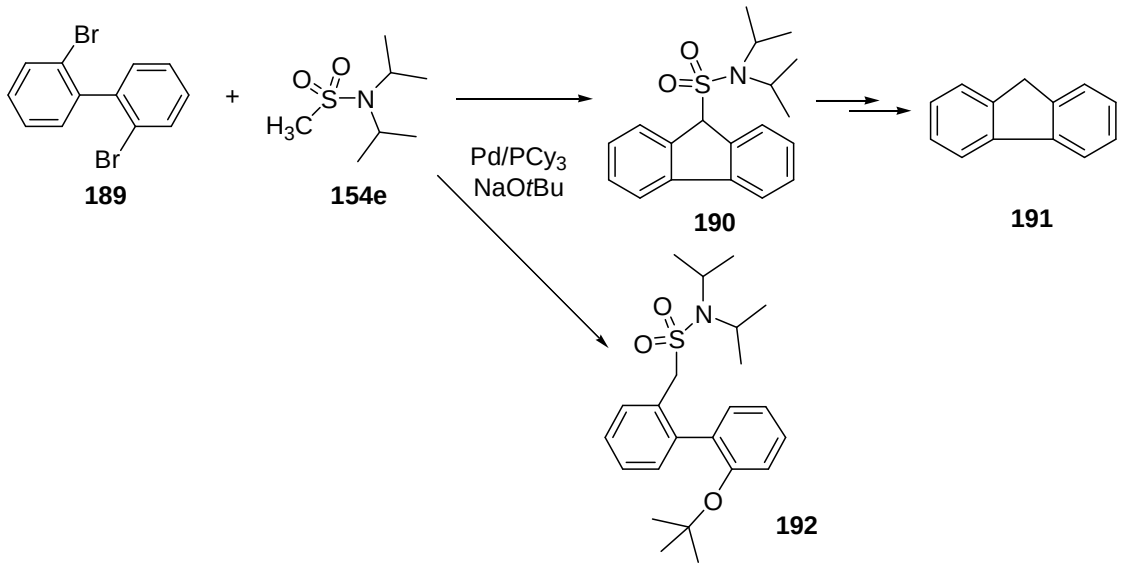
Since our efforts to prepare a 5-membered sulfonamide ring were unsuccessful, we shifted our attention to the 6-membered ring. 2-Bromobenzyl bromide **183** was reacted with methylamine to give *N*-methyl (2-bromobenzyl)amine **184** (Scheme 125). This was treated with methanesulfonyl chloride to give the corresponding sulfonamide **185**. Again no cyclised product (**186**) could be detected when **185** was reacted in the presence of $Pd(OAc)_2$, triphenylphosphine and sodium *tert*-butoxide. Most of the starting material was consumed while only minor amounts of new products were detected by GC analysis. 2-Bromobenzaldehyde **187** and di-(2-bromobenzyl)-methylamine **188** were identified by GC-MS. This substrate, **185**, is again very similar

to sulfonamides that have been successfully arylated in an intermolecular fashion before (compare with **154c**) and the conclusion was made that intermolecular arylation is responsible for substrate consumption.



Scheme 125. Preparation of **185** for 6-membered ring formation

In another attempt at performing a intramolecular arylation, 2,2'-dibromobiphenyl **189** was prepared from 1,2-dibromobenzene by treatment with *n*-butyllithium[199]. The dibromo compound **189** was reacted with *N*,*N*-diisopropyl methanesulfonamide **154e** (Scheme 126) in an attempt to perform a consecutive inter and intramolecular arylation reaction to prepare a 5-membered ring **190** which on removal of the sulfonamide group would yield fluorene **191**. Substituted fluorenes can be used as potential ligands of the cyclopentadienyl type for metallocene complexes and can be used in lanthanide based specialised polymerisation catalysts[200]. Fluorene-type componds have been incorporated into polymers to produce light-emitting polymers and have potential in the field of polymer light emitting diodes (PLEDs)[201].



Scheme 126. Attempted ring-closing intramolecular arylation using a dibromoarene

The arylation reaction between **154e** and **189** was performed using $Pd(OAc)_2$ with tricyclohexylphosphine as ligand since this ligand had shown the highest di-arylation selectivity (Table 8, entry 6) in the reaction between bromobenzene and **154e**.

After 20 hours at 110°C, GC analysis showed complete consumption of the aryl halide (**189**) while 54% of the methanesulfonamide **154e** had been converted. The major product (39% yield) was identified by means of both ^{1}H-NMR and HR-MS to be the mono-arylation product **192** in which the second bromine had been substituted with *tert*-butoxide. A small amount (~2%) of the desired ring-closed product, **190**, was also detected by GC-MS.

This result again illustrated the difficulties of intramolecular arylation using the sulfonamide substrates. The failure of the ring-closing arylation reaction might have been caused by steric congestion around both the sulfonamide anion and the palladium complex on the neighbouring ring not allowing rotation along the biphenyl axis to a sufficient degree for carbon-Pd bond assembly (see Figure 17).

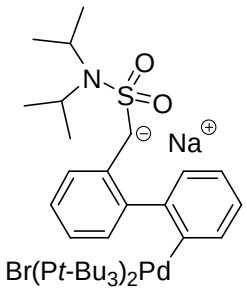
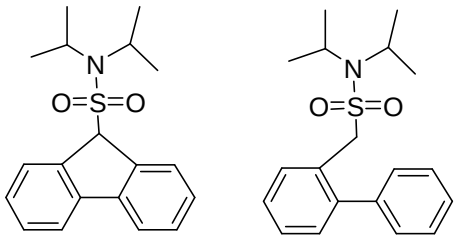


Figure 17. Proposed intermediate in the arylation reaction between **154e** and 2,2'-dibromobiphenyl **189**

The fact that the bromine was substituted during the course of the reaction indicates that oxidative addition of the Pd(0) complex did take place. The formation of *tert*-butyl aryl ethers has been studied extensively[202,6,203-205] and is known to occur under similar reaction conditions. Tricyclohexylphosphine is, however, not an active ligand in this conversion as ligands with high electron density and steric bulk (like tri *tert*-butylphosphine or di-*tert*-butylphosphinoferrocene) are required in the product forming reductive elimination step. The formation of the *tert*-butyl ether **192** does therefore suggest that ring formation (to yield **190**) is strongly disfavoured.

When the reaction between **154e** and **189** was repeated with triphenylphosphine as ligand, which is known to be inactive in the formation of *tert*-butyl aryl ethers, conversion was sluggish and only a small amount of **192** (~5%) was formed. The desired product **190** together with the mono-arylated dehalogenated product **193** (Figure 18) were, however, identified by GC-MS and ^{1}H-NMR but only in the order of 10% yield.



190 **193**

Figure 18. Products from the arylation reaction between **154e** and 2,2'-dibromobiphenyl **189**

4.6 Conclusion

This work constitutes the first example of α-arylation of methanesulfonamides under palladium catalysis conditions using phosphine ligands and NaO*t*Bu as a base. The outcome of this reaction is apparently governed by a mixture of electronic and steric effects, with the major side-reactions being homocoupling and diarylation of the substrate. Both aryl bromide and iodides are active participants in this coupling reaction.

The formation of diarylated methanesulfonamides is dependant on a number of factors and can be influenced by the choice of ligand. The ligand which expressed the highest selectivity towards mono-arylation was P*t*Bu$_3$. Mono-arylation selectivity could also be improved by using an excess of base. Diarylation was less prevalent when less sterically demanding methanesulfonamide substrates were used indicating the role of steric bulk during the product forming reductive elimination reaction.

The application of palladium catalysed sulfonamide arylation in a novel synthetic route to both sumatriptan and almotriptan synthesis was shown in principle. Improvement of the arylation yield is a prerequisite for this synthetic route to be economically feasible.

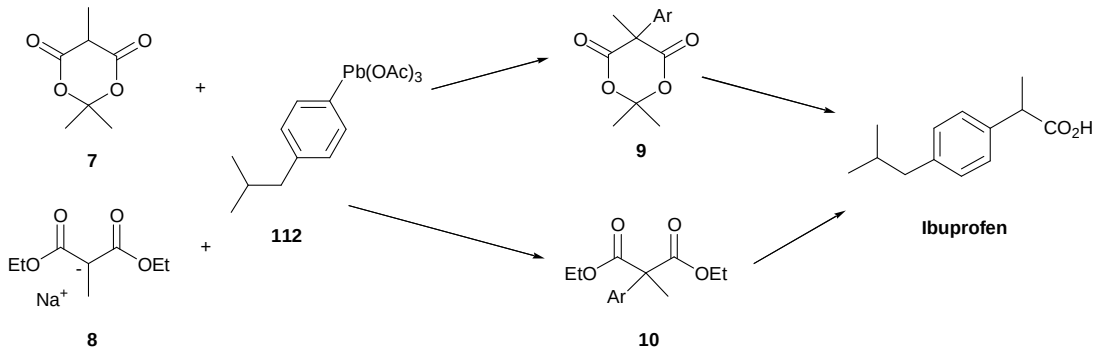
The failure of the arylation protocol when using alkyl substituted methanesulfonamide anions was not a significant limitation since the same α-aryl alkylsulfonamide product could be prepared by consecutive arylation and alkylation reactions. The use of a small and strong base such as sodium hydride should be investigated in the arylation reaction of ethanesulfonamides.

The failure of the intramolecular arylation reaction may have been caused by steric congestion around both the sulfonamide stabilised anion and the palladium complex. Interaction between palladium and the S-O bonds of the sulfonamide may also have directed the carbanion away from the aryl-palladium complex obstructing association of the carbanion and hence *C*-arylation.

CHAPTER 5

ARYLATION REACTIONS OF ACETOACETATE ESTERS

The preparation of 2-arylalkanoic acid derivatives especially arylpropionic acids has received significant attention during the past few decades since such compounds find application as non-steroidal anti-inflammatory drugs (NSAID) (Figure 19)[206]. Arylation of β-dicarbonyl carbanions has been investigated as a synthetic strategy to obtain 2-arylacetic or arylpropionic acids. For example, the preparation of ibuprofen by way of arylation of methylmalonic acid esters using an aryllead triacetate was established many years ago[37] (Scheme 127).



Scheme 127. Preparation of Ibuprofen using aryllead chemistry

More recently the copper-catalysed arylation of ethyl cyanoacetate and diethyl malonate has also been demonstrated, using aryl iodides[58,176,177]. However, the palladium-catalysed enolate arylation reaction for the preparation of 2-arylalkanoic acid derivatives has probably received the most attention. This chemistry has been mainly developed by the groups of Hartwig and Buchwald[99,100,97,60,107,108,181,109,182].

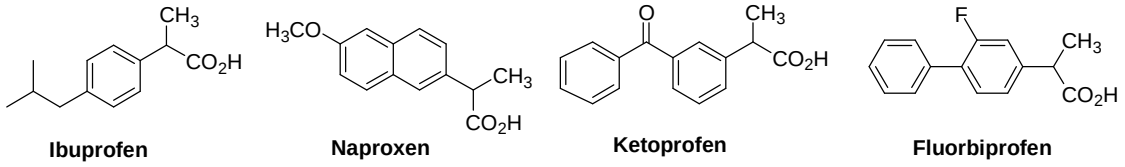
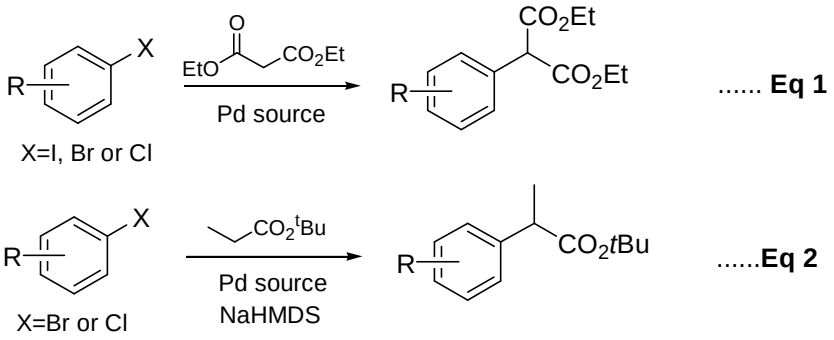


Figure 19. Examples of non-steroidal anti-inflammatory drugs

Two strategies to aryl propionic acids were recently published: a) transition metal catalysed arylation of diethyl malonate followed by methylation[97,60,57] and b) direct arylation of propionic or acetic acid esters[107-109,182]. The arylation of malonate esters requires electron-rich and bulky phosphine ligands (Scheme 128, Eq. 1). Aryl iodides

and aryl bromides are the substrates of choice and, with some speciality ligands, aryl chlorides can be also be used. The arylated malonate ester is methylated, either *in situ* or in a separate reaction, hydrolysed under alkaline conditions and decarboxylated by acidification leading to the arylpropionic acid[57].



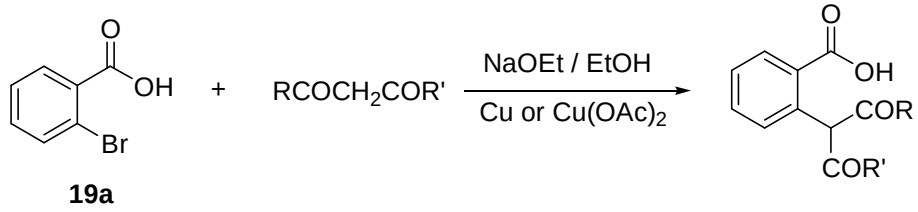
Scheme 128. Synthesis of arylpropionic acids using palladium catalysed enolate arylation

The ester arylation protocol (Scheme 128, Eq. 2), which is an even more direct route to arylpropionic acids, was developed simultaneously by Buchwald[107] and Hartwig[108]. Typically the *tert*-butyl ester of propionic acid is treated with an aryl halide (bromide or chloride) in the presence of a strong base and palladium and a bulky phosphine ligand or a bulky imidazolinium carbene. A disadvantage of this procedure is that very specific bases have to be used, sodium hexamethyldisilazane (NaHMDS) (for propionate esters) and LiHMDS (for acetate esters). These bases are expensive and moisture sensitive resulting in a requirement for pre-treatment of solvents and for the work to be carried out under inert atmosphere. The high energy ester enolate is highly reactive and self-condensation is a major side reaction which can be overcome by the use of the bulky *tert*-butyl esters [108,107]. Ethyl esters can also be used but side-reactions cause lower selectivity to the mono-arylated ester. Di-arylation can be limited by the choice of metal counter ion, ligand and the use of excess ester and base.

Although a large number of enolates have been utilised in palladium catalysed arylation chemistry[120], 1,3-dicarbonyl compounds like acetoacetate esters and acetylacetones, have not been successfully arylated as yet. The explanation presented

for the lack of success with these substrates is linked to the ability of the enolates of these compounds to form stable complexes with metals[99,60]. It is believed that when these enolates are present, the metal is deactivated during the latter stages of the catalytic cycle – preventing reductive elimination from occuring by formation of a strong complex between the product enolate and the metal (see Figure 6, Chapter 3). Pd(0) is not released to continue the catalytic cycle. With diethyl malonate this problem can be overcome by increasing steric demands late in the transition state by using very bulky ligands.

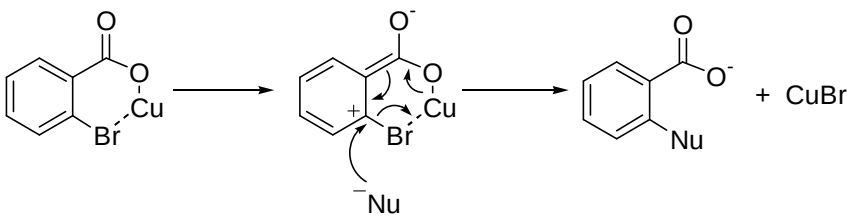
The arylation of β-dicarbonyl carbanions with a 2-halobenzoic acid **19** was demonstrated as far back as 1929 by Hurtley[49] (as depicted in Scheme 129). The conditions which consisted of sodium ethoxide in ethanol solution with copper powder or $Cu(OAc)_2$, were later refined by McKillop *et al*[51,207].



19a

Scheme 129. Hurtley reaction

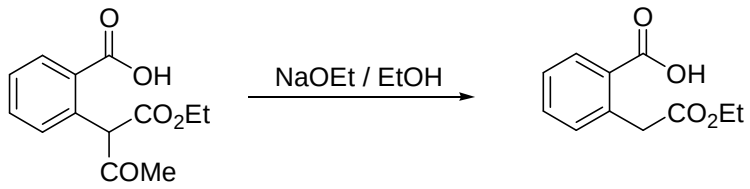
Employing sodium hydride and 6mol% CuI in ethyl acetoacetate **21** solution led to high yields of ethyl β-(2-carboxyphenyl)acetoacetate **22** from ethyl acetoacetate and 2-bromo or 2-chlorobenzoic acid **19**. α-Substituted β-keto esters also reacted under the same conditions although yields were lower. This protocol is, however, limited to aryl halide bearing a carboxylate group in the *ortho*-position or close proximity which can form a copper chelate. The halide is activated towards nucleophilic displacement by polarisation of the C-Br bond by the copper chelate, reinforced by electron withdrawal by the carboxylate group, and therefore making it a chelation assisted S_NAr mechanism (Scheme 130). Acetoacetate esters have also been arylated with aryllead triacetates[36].



Scheme 130. Copper chelate assisted S_NAr mechanism of the Hurtley reaction

5.1 Palladium Catalysed Arylation Reactions of Acetoacetate Esters

When we attempted the arylation of *tert*-butyl acetoacetate **21a** with bromobenzene using mild reaction conditions (K_3PO_4, "Pd(*t*-$Bu_3P)_2$", toluene, 90°C) we did not find any of the desired arylated acetoacetate ester but we identified a substantial amount of *tert*-butyl phenylacetate **194a** (see Scheme 132). We assumed that during the reaction *tert*-butyl acetoacetate was arylated in the 2 position which was then de-acylated by "base-cleavage" to give the phenylacetate ester and potassium acetate. McKillop has described a similar de-acylation during the copper catalysed arylation of acetoacetate with 2-bromobenzoic acid **19a** [51,207] (Scheme 131). This reaction was described as a retro-Claisen condensation as sodium ethoxide in ethanol was used, but could also be effected by treating the 2-arylacetoacetate **22** with 2N NaOH (acetoacetate esters are known to be de-acylated under strong alkaline conditions)[208,209].



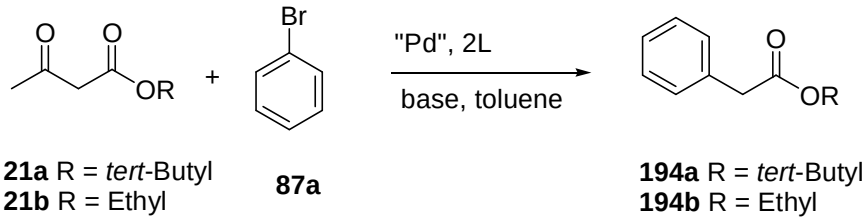
22 **23**

Scheme 131. Retro-Claisen condensation

Apart from *tert*-butyl phenylacetate **194a**, biphenyl **169** was also formed in small amounts. The yield of *tert*-butyl phenyl acetate was determined by GC (internal standard) to be 55% (Table 10, entry 1). The product mixture did not contain any residual acetoacetate ester although a substantial amount of bromobenzene was

present. No 2-phenylacetoacetate *tert*-butyl ester **195** (see Figure 21) could be detected by GC-MS and ^{1}H-NMR analysis.

This reaction was further investigated using ethyl acetoacetate and different bases, ligands and palladium sources (Scheme 132, results are presented in Table 10).



21a R = *tert*-Butyl
21b R = Ethyl

87a

194a R = *tert*-Butyl
194b R = Ethyl

Scheme 132. Palladium catalysed arylation of acetoacetate esters

Table 10.

Entry	Acetoacetate ester	Catalyst (mol%)	Base	Conv of 87a	Yield of 194 *
1	**21a**	$PdDBA_2$(1)/P*t*Bu_3 (2)	K_3PO_4	67%	55%
2	**21b**	$PdDBA_2$(1)/P*t*Bu_3 (2)	K_3PO_4	100%	45%
3	**21b**	$Pd(OAc)_2$ (1)/ P*t*Bu_3 (2)	K_3PO_4	97%	48%
4	**21b**	$Pd(OAc)_2$ (5)/PPh_3 (20)	K_3PO_4	n.d.	0%
5	**21b**	$PdDBA_2$(1)/ PCy_3 (2)	K_3PO_4	n.d.	0%

Conditions: 4 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11mmol K_3PO_4, 5ml toluene, 0.04 mmol $Pd(dba)_2$ or $Pd(OAc)_2$, 0.08 mmol ligand, 90^{o}C / 16h.

* yield determined by GC with internal standard; n.d. not determined

A similar reaction was observed when ethyl acetoacetate was used under the same conditions (entry 2). Ethyl phenylacetate was formed in 45% yield with full consumption of both starting materials.

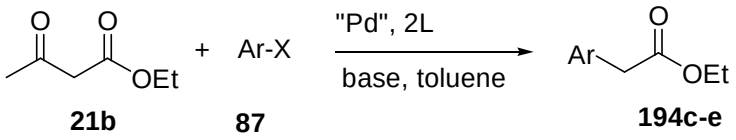
Reactions were also performed with triphenylphosphine and tricyclohexylphosphine (entries 4-5). Triphenylphosphine was entirely inactive in this reaction, even at a 5% palladium and 20% phosphine loading. Tricyclohexylphosphine, to our surprise, also showed no activity. The failure of ligands that do not possess the bulk associated with

tert-butyl substituents suggests an absolute requirement for bulk in the transition state and we propose that reductive elimination could be the rate limiting step.

The nature of the palladium source was also investigated briefly. Initially, palladium bis-dibenzylideneacetone ($Pd(dba)_2$) was used as the catalyst precursor but $Pd(OAc)_2$ was found to be as effective (48% yield, entry 3).

The use of other aryl halides was investigated (Scheme 133, Table 11). 4-Bromoanisole **87i** resulted in the formation of ethyl (4-methoxyphenyl)acetate **194c** albeit in lower yield than ethyl phenylacetate **194b** (Table 10, entry 3 and Table 11, entry 1). 4-Chloroacetophenone **87g** (an activated aryl chloride) also gave the desired arylacetic acid ester **194d** but again in lower yield (entry 2). The reaction between ethyl acetoacetate and 1-bromonaphthalene **87k** gave ethyl (1-napththyl)acetate **194e** in only 15.3%. Almost 60% of the aryl bromide was reduced to naphthalene indicating that although oxidative insertion into the aryl halide bond does occur, formation of the required intermediate is restricted due to too much bulk generated by Peri interaction.

In all the above reactions the aryl halide was fully consumed. Hydrodehalogenation of the aryl halide was found to be a major side reaction which contributed to aryl halide consumption. The extent of hydrodehalogenation increased with decreasing arylacetate yield.



21b **87** **194c-e**

Scheme 133. Arylation of ethyl acetoacetate with various aryl halides

Table 11.

Entry	Aryl halide	Product	Yield (%)
1	4-Bromoanisole **87i**	Ethyl 4-methoxy-phenylacetate **194c**	39%[a]
2	4-Chloroacetophenone **87g**	Ethyl 4-aceto-phenylacetate **194d**	30%[b]
3	1-Bromonaphthalene **87k**	Ethyl 1-naphthylacetate **194e**	15%[c]

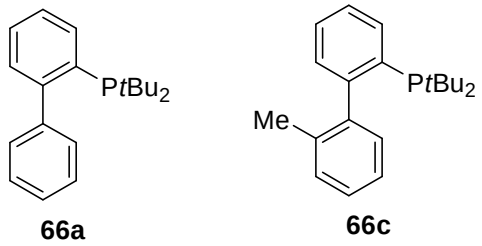
Conditions: 4mmol Aryl halide, 4.4mmol acetoacetate ester, 11mmol K_3PO_4, 5ml toluene, 0.04mmol $Pd(OAc)_2$, 0.08 mmol P*t*Bu_3·HBF_4, 90°C, 16h.

(a) 72h, isolated yield, 35% hydrodehalogenation

(b) 72h, isolated yield, 40% hydrodehalogenation

(c) 72h, isolated yield, 58% hydrodehalogenation

In an effort to improve the arylacetate yield, 2-(di-*tert*-butylphosphino)-biphenyl **66a** (from the Buchwald biphenyl ligands series[100] see Figure 20) was evaluated (see Scheme 134, Table 12). The use of **66a** led to a selective reaction to ethyl phenylacetate **21b** in 56% yield with 95% conversion of bromobenzene (Table 12, entry 1). Full conversion of bromobenzene and a yield of 70% was achieved when using 2 equivalents of ethyl acetoacetate (entry 2).



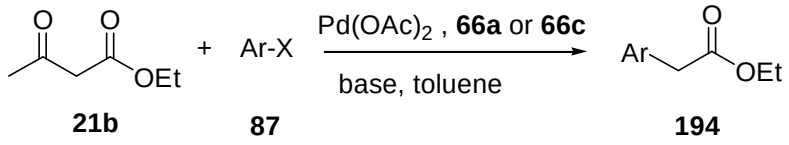
66a **66c**

Figure 20. Biphenyl phosphine ligands **66a** and **66c**

This prompted us to examine the biphenyl ligand with an extra methyl substituent on the second phenyl ring, **66c**. This ligand has been shown to be especially active in malonate ester arylation[100]. Again a highly selective reaction resulted with 89% yield of ethyl phenylacetate when 1 equivalent of ethyl acetoacetate was used and 93% with 2 equivalents of ethyl acetoacetate (entries 3 and 4).

The use of more than one equivalent of ethyl acetoacetate is thought to lead to improved yields on the aryl halide. Ethyl acetoacetate is the limiting reagent when a single equivalent is used as it is consumed faster than the aryl halide – presumably through a decarboxylation or retro-Claisen process. An increase in ethyl phenylacetate yield was also observed when tri-*tert*-butylphosphine was used using 2 equivalents of ethyl acetoacetate (58% vs 48%, Table 10, entry 3).

Since these biphenyl ligands are also known to be active with aryl chlorides in other arylation type reactions, chlorobenzene was examined in a reaction employing the standard reaction conditions using ligand **66c**. Ethyl phenylacetate **194b** was produced in 93% yield (by GC, 88% isolated yield, entry 5).



21b **87** **194**

Scheme 134. Arylation of ethyl acetoacetate with various aryl halides

Table 12.

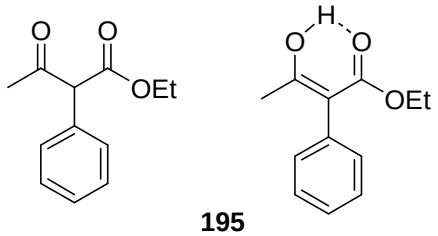
Entry	Aryl Halide	Catalyst (mol%)	Conversion of Ph-Br	Yield
1	Bromobenzene **87a**	$Pd(OAc)_2$ (1)/ **66a** (2)	95%	56% **194b** [a]
2	Bromobenzene **87a**	$Pd(OAc)_2$ (2)/ **66a** (4)	100%	68% **194b** [b]
3	Bromobenzene **87a**	$Pd(OAc)_2$ (1)/ **66c** (2)	100%	89% **194b** [a]
4	Bromobenzene **87a**	$Pd(OAc)_2$ (2)/ **66c** (4)	100%	93% **194b** [b]
5	Chlorobenzene **87b**	$Pd(OAc)_2$ (2)/ **66c** (4)	100	93% **194b** [b]
6	Chlorobenzene **87b**	$Pd(OAc)_2$ (0.2)/ **66c** (0.4)	63	49% **194b** [b]
7	4-Chloroanisole **87e**	$Pd(OAc)_2$ (0.5)/ **66c** (1)	100%	75% **194c** [b,c]

Conditions: a) 4 mmol aryl halide, 4.4 mmol acetoacetate ester, 11mmol K_3PO_4, 5ml toluene, 90°C / 16h
b) 2 mmol aryl halide, 4 mmol acetoacetate ester, 11mmol K_3PO_4, 5ml toluene, 90°C / 16h
c) Isolated yield

When the catalyst loading was lowered to 0.2 mol % palladium and 0.4% of **66c** a slower reaction was observed. The reaction was selective in that product formation followed chlorobenzene consumption. After 16 hours at 90°C, 42% chlorobenzene had been consumed while 34% product was formed. After a total of 70 hours of reaction the product yield was 49% with a 63% chlorobenzene conversion (entry 6). It is believed that a higher yield (on the aryl halide) could have been achieved if even more acetoacetate had been used as it appeared to have been the limiting reagent.

A reaction was performed with a de-activated aryl chloride. The reaction between 4-chloroanisole **87e** and ethyl acetoacetate proceeded smoothly and gave ethyl 4-methoxyphenylacetate **194c** in a 75% isolated yield after 40 hours at 90°C, using 0.5% $Pd(OAc)_2$ and 1% of **66c**.

During a reaction between bromobenzene and ethyl acetoacetate where potassium carbonate was the base, it was observed that besides 20-25% of the anticipated product (**194b**) a similar amount of another product had formed (in addition to a number of minor by-products). The same impurities were detected in all other reactions but to much smaller extent. The same effect was observed in reactions in which a lower K_3PO_4 loading was used. In a typical reaction, with the molar ratio of K_3PO_4 to ethyl acetoacetate being 2.4:1, the amount of this side-product is between 1 and 5%. When the base to substrate ratio was changed to 2:1, between 10 and 15% of this side-product was detected while the ethyl phenylacetate yield dropped by a similar amount. This effect was further demonstrated by lowering the base loading by a factor of 4 to 0.6 equivalents K_3PO_4 to ethyl acetoacetate. Only 15% of the desired product was formed and 55% of the side-product. This side-product was isolated and purified by distillation. Ethyl 2-phenylacetoacetate **195** was identified by ^1H and ^{13}C NMR as a ~2:1 mixture of the keto-enol tautomers with the enol form showing a strong intramolecular hydrogen bonding effect as is known for ethyl acetoacetate[210] (Figure 21).



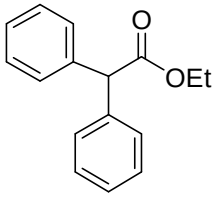
195

Figure 21. Keto and enol tautomers of **195**

From this observation it was clear that ethyl acetoacetate is arylated in the 2-position during the reaction. The formation of ethyl phenylacetate then occurs when this intermediate undergoes base mediated cleavage. This second step is clearly dependant

on base concentration and strength. To validate this postulate, reactions were carried out with a lower base content to form a large amount of the intermediate, followed by addition of extra K_3PO_4 and further heating. It was observed during such experiments that the intermediate was depleted entirely after heating for 5 hours with an increase in ethyl phenylacetate yield equal to the intermediate depleted. From the fact that potassium carbonate, even at a ratio of 2.4:1, did not deplete all of the intermediate even after extended reaction time points to the fact that potassium carbonate is less efficient in mediating the de-acylation reaction. This fact may be explained by the higher nucleophilic character of phosphate (PO_4^{3-}) compared to carbonate (CO_3^{2-}).

The choice of base has been demonstrated to be essential to the outcome of many different arylation reactions[99,100,97,60,107-109,120,102,110,211]. When sodium *tert*-butoxide (a strong soluble base) was used, the starting materials were consumed while only a small amount of product was formed. It seems that not only the strength of the base but also its availability must be tempered to match the rate of enolate formation with the rate of the arylation reaction. The same observation has been made by Buchwald in amidation of aryl halides[211]. Both K_3PO_4 and K_2CO_3 are thought to be thermodynamically strong bases in aprotic solvents but their low solubility in toluene results in a slow formation of enolate. From the fact that no arylation of ethyl phenylacetate was observed under identical reaction conditions, while the use of sodium *tert*-butoxide yielded ethyl diphenylacetate **196** (58%, Figure 22), it is concluded that K_3PO_4 is not strong enough to deprotonate a phenylacetate ester.

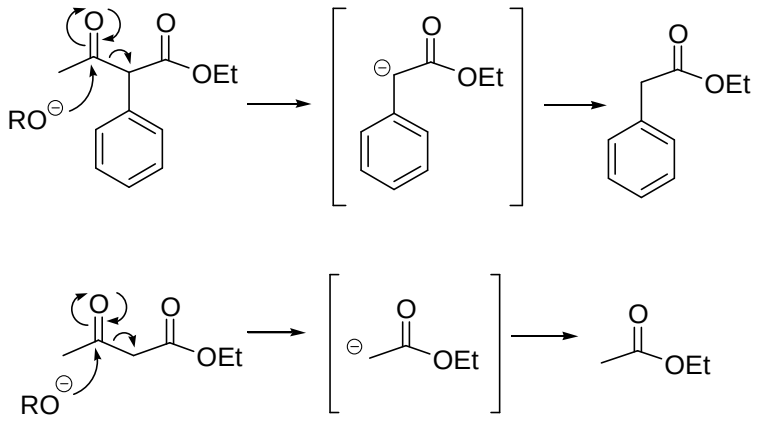


196

Figure 22. Ethyl diphenylacetate **196**

The low selectivity of the reaction when based on ethyl acetoacetate may be attributed to parallel de-acylation of ethyl acetoacetate as demonstrated by the requirement for use of ethyl acetoacetate in excess to get full conversion of the aryl halide to the

required product. It is proposed that the arylated acetoacetate ester is more susceptible to base catalysed decarbonylation as the carbanion formed is stabilised by the adjacent aromatic group (see Scheme 135). Although the de-acylation of ethyl acetoacetate is thought to be promoted by elevated temperature, ethyl acetoacetate consumption was also observed in reactions at lower temperature (60°C) albeit at slower rate, showing the instability of ethyl acetoacetate under the reaction conditions.



Scheme 135. Stabilisation of intermediates during acetoacetate decarbonylation

5.2 Copper Catalysed Reactions of Ethyl Acetoacetate

The arylation of acetoacetate esters using copper catalysis is known, albeit through a chelation assisted S_NAr mechanism. The only other examples of a truly catalytic copper arylation of active methylene compounds are that of ethyl cyanoacetate, malononitrile and acetyl acetone by the group of Miura[58] and that of diethyl malonate by the group of Buchwald[60]. Miura's reactions required the harsh conditions of dimethylsulfoxide (DMSO) and 120°C which would lead to decomposition of less stable substrates like diethyl malonate and ethyl acetoacetate. Buchwald discovered that phenols, especially 2-phenylphenol, acted as efficient ligands for copper in the arylation of diethyl malonate and recorded high yields of diethyl 2-arylmalonate using 5mol% CuI under milder conditions (dioxane, 70°C).

The cost implications of using a base metal such as copper rather than a precious metal such as palladium would have a significant impact on any process developed. The

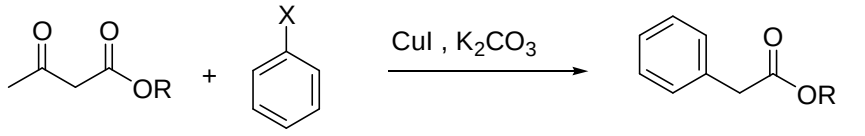
copper catalysed arylation reaction of ethyl acetoacetate was investigated following the procedures used by both Miura and Buchwald in an attempt to repeat the successes achieved in the palladium catalysed reactions.

When ethyl acetoacetate **21b** was reacted with iodobenzene in dimethylsulfoxide (DMSO) solution using 20mol% CuI with potassium carbonate as base (Scheme 136), ethyl phenylacetate **194b** was formed in 53% yield after heating at 80°C for 20 hours (Table 13, entry 1). The reaction was highly selective when based on iodobenzene conversion (52%) while ethyl acetoacetate was fully converted presumably due to decomposition catalysed by heat and base.

The experiment was repeated in both *N*-methylpyrrolidinone (NMP) and dimethylformamide (DMF). Both conversion and yield were lower in these reactions while the high selectivity on iodobenzene was maintained (entries 2,3).

When this reaction was repeated using 2-phenylphenol as a co-catalyst the reaction was slower with only 33% product formed after 6 hours. A maximum of 41% was achieved upon extended reaction time. This co-catalyst/ligand has been used to great effect by Buchwald in the copper catalysed arylation of diethyl malonate[60]. We did not observe any advantage using this additive, instead the catalyst activity seemed diminished and product formation was inhibited.

The same reactions were repeated in dioxane solution (entries 4,5). Low conversion of iodobenzene and even lower ethyl phenylacetate **194b** yield was observed. This would indicate that the copper catalyst required a strong solvent donor ligand to function properly.



21a R = *tert*-Butyl
21b R = Ethyl

87

194a R = *tert*-Butyl
194b R = Ethyl

Scheme 136. Copper-catalysed arylation of acetoacetate esters

Table 13.

Entry	Catalyst (mol %)	Solvent	Time (h)	Conversion Ph-X / (acetoacetate ester)	Yield of 194 (%)
1	CuI (20)	DMSO	20	52 (100)	53
2	CuI (20)	NMP	20	n.d. (91)	42
3	CuI (20)	DMF	20	42 (89)	43
4	CuI (20)	Dioxane	20	20 (62)	12
5	CuI(20)/phenyl-phenol (40)	Dioxane	16 72	5 (67) 5 (100)	5 6
6	CuI(20)/phenyl-phenol (40)	DMSO	16 72	38 (n.d) 70 (93)	33 41
7	CuBr (28)	DMSO	16 72	65 (48) 73 (57)	37[a] 46
8	CuBr (28)	DMSO	20	75 (63)	56[b]
9	CuI (20)	DMSO	16	100 (100)	n.d.[c]
10	CuI (20)	DMSO	16 72	38 (100) 75 (100)	33[d] 50
11	CuI (20)	DMSO	16 72	17 (n.d) 30 (n.d)	13[e] 13
12	CuI (20)	DMSO	20	13 (n.d)	2[f]
13	CuI (20)	DMSO	20	100 (98)	86[g]

Reaction conditions: 80°C, K_2CO_3 (8mmol, 4eq) Ph-I (2mmol, 1eq) ethyl acetoacetate (4mmol, 2eq)

a) Sigma-Aldrich CuBr (green powder)

b) CuBr freshly prepared (white powder)

c) K_3PO_4 (8mmol) used instead of K_2CO_3

d) 2-8eq of H_2O added

e) *t*-Butyl acetoacetate **21a**

f) Bromobenzene used.

g) 5 equivalents ethyl acetoacetate

Yields and conversion determined by GC / internal standard (2-methoxynaphthalene) / n.d. not detected

The use of CuBr in DMSO gave similar results to those obtained using CuI (entry 7). The yields were lower by ~10% and this may be attributable to halide exchange

resulting in the formation of the less active bromobenzene. When repeated using purified CuBr (white powder prepared in-house as compared to green powder purchased from Aldrich) an improved yield of 56% was obtained (entry 8).

Potassium phosphate was found to be an inefficient base as no product was formed (Table 13, entry 9). This result again demonstrates the importance of the correct choice of base since K_3PO_4 was found to be the most efficient base in the palladium catalysed version of this reaction.

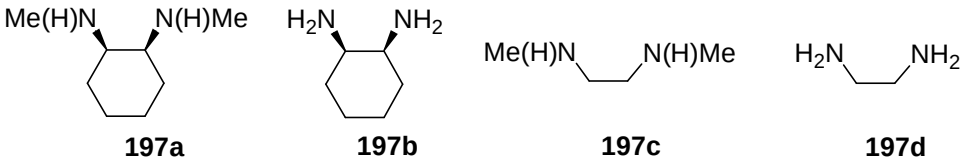
The use of the *tert*-butyl ester also led to a much lower arylation yield (entry 11) in contrast to the palladium catalysed reaction where the yield for *tert*-butyl acetoacetate **21a** arylation was comparable if not better than obtained for the ethyl ester (Table 10, entry 1).

The base case reaction in DMSO with CuI and K_2CO_3 was repeated using bromobenzene instead of iodobenzene. Although 13% conversion of bromobenzene was measured only ~2% ethyl phenylacetate **194b** was formed (entry 12).

Since ethyl acetoacetate seems to be the limiting reagent due to background decomposition, a reaction was performed with 5 equivalents of ethyl acetoacetate (entry 13). Complete conversion of both starting materials led to an 86% yield of ethyl phenylacetate **194b**. This high product yield shows the high selectivity of the aryl halide reaction. This is contrary to many of the palladium catalysed reactions in which homo-coupling and hydrodehalogenation account for significant aryl halide losses.

Recently Buchwald *et al* published a number of papers describing a revival of both the Ullmann reaction (copper-catalysed *N*-arylation of amines) and the Goldberg reaction (copper-catalysed *N*-arylation of amides) using a ligated copper species in a true catalytic sense (0.2-10mol% CuI)[212,211]. The conditions required for these reactions are, typically, toluene at 100^{o}C with potassium carbonate or potassium phosphate as base. Initially 1,10-phenanthroline was used as ligand[213] and then 2,6-lutidine[214] but it

was discovered that some alkyl-1,2-diamines were more active ligands (see Figure 23). Although *N*,*N*-dimethyl-*trans*-1,2-cyclohexanediamine **197a** and *N*,*N*-dimethyl-1,2-ethanediamine **197c** are the most active and preferred ligands, ethylenediamine **197d** has shown excellent activity in especially the *N*-arylation of indoles[215].



197a **197b** **197c** **197d**

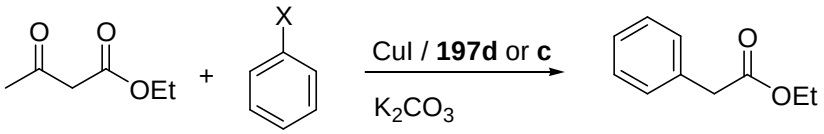
Figure 23. Diamine ligands used by Buchwald for the *N*-arylation of amines and amides

These reactions were thought to be similar to the copper catalysed enolate arylation reaction with regard to conditions used and in terms of the need for high copper loading and highly polar solvents. The use of ethylenediamine **197d** (EDA) was, therefore, examined in the reaction between ethyl acetoacetate **21b** and iodobenzene (see Scheme 137, Table 14).

The previously unsuccessful reactions in dioxane (Table 13, entry 4,5) were repeated in the presence of EDA **197d** (2-3 equivalents to CuI). The yield of ethyl phenylacetate was 48% with 64% conversion of iodobenzene and 94% of ethyl acetoacetate (Table 14, entry 1). The addition of this ligand clearly eliminated the need for a highly polar solvent.

The addition of **197d** to the reaction in DMSO had a detrimental effect on the yield as only 19% ethyl phenylacetate **194b** was formed in comparison to 53% without **197d** (Table 14, entry 2 and Table 13, entry 1).

The use of **13** also led to successful reaction in toluene solution (entry 3) albeit in lower yield than the DMSO reaction.



21b **87** **194b**

Scheme 137. Diamine assisted copper-catalysed arylation of ethyl acetoacetate

Table 14.

Entry	Catalyst	Base	Solvent	Conv. of Ph-X (Ethyl acetoacetate)	Yield of Ethyl phenylacetate 194b
1	CuI/ **197d**	K_2CO_3	Dioxane	64 (84)	48
2	CuI/ **197d**	K_2CO_3	DMSO	86 (100)	29
3	CuI/ **197d**	K_2CO_3	Toluene	45 (80)	38
4	CuI/ **197d**	K_3PO_4	Toluene	64 (85)[a]	34
5	CuI/ **197c**	K_2CO_3	Toluene	50 (61)	23
6	CuI/ **197d**	K_2CO_3	NMP	16 (100)[b]	7

Reaction conditions: 80°C, K_2CO_3 (8mmol, 4eq), Ph-I (2mmol, 1eq), ethyl acetoacetate (4mmol, 2eq)

a) K_3PO_4 (8 mmol) was used.

b) Bromobenzene was used.

Another reaction with K_3PO_4 as base was attempted in toluene medium using the EDA ligated catalyst. This time the reaction using K_3PO_4 gave a modest yield of ethyl phenylacetate (33%) although still slightly lower than with K_2CO_3 (entries 3 and 4)

A reaction was performed was performed using *N,N'*-dimethyl-ethylenediamine **197c**. The reaction in toluene with K_2CO_3 gave only 23% yield of ethyl phenylacetate **21b** as compared to 38% with EDA (**197d**). This is in contrast to the amination and amidation reactions in which EDA (**197d**) gave inferior results to **197c** [215].

In an effort to apply the copper catalysed reaction to aryl bromides, a reaction with bromobenzene using CuI and EDA was performed in NMP medium. Again, reactivity was low with 16% conversion of bromobenzene and 7% product yield. CuI / EDA is known to catalyse halogen exchange in aryl bromides[155] and could account for the formation of product via the formation and reaction of iodobenzene. The extent of

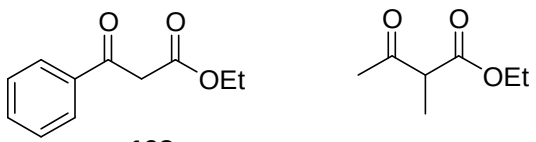
iodobenzene formation could, however, not be measured due to co-elution with NMP in the GC analysis. This reaction should be repeated in a medium such as toluene or dioxane to validate this postulate.

Since aryl iodides are expensive and the preparation of functionalised aryl iodides is difficult, the main focus of the copper catalysed reactions is to replace iodides with the less expensive bromides or chlorides. The inter-conversion of bromobenzene and iodobenzene is known under copper catalysed conditions[155] and has been observed by us during reactions involving bromobenzene (which was converted to iodobenzene by CuI) and CuBr resulting in conversion of iodobenzene to bromobenzene. From this it would appear that the conversion of aryl bromides could be possible in the presence of a catalytic amount of an iodide salt under the correct conditions.

The high yield obtained using 5 equivalents of ethyl acetoacetate (Table 13, entry 13) is an encouraging result and should be examined further. Addition of ethyl acetoacetate with time may improve the selectivity based on this reagent. The use of a ligated copper species in a environmentally benign solvent and lower catalyst loading (1-5mol%) should be assessed to make this reaction feasible from both an environmental and economic point of view.

5.3 Arylation Reactions of other Acetoacetate Substrates

In order to determine whether other β-keto esters could be arylated under the same conditions and whether the reaction products would undergo the same decarbonylation to yield an arylacetic ester, ethyl benzoylacetate **198** and ethyl 2-methylacetoacetate **199** (Figure 24) were reacted with bromobenzene using the standard reaction conditions

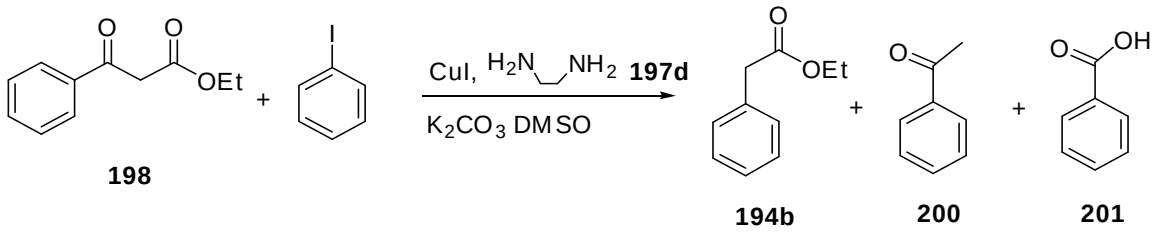


198 **199**

Figure 24.

Unlike the reactions involving ethyl acetoacetate, a thick white emulsion was formed with ethyl benzoylacetate **198** (indicating the formation of a large amount of insoluble potassium enolate). Dioxane was added to the emulsion to allow stirring. No arylation products were detected by GC analysis and it was observed that all bromobenzene was unconverted while a significant amount of **198** was converted. The only product formed was acetophenone, presumably formed by decarboxylation of the starting material. The same result was obtained in a parallel experiment involving 4-bromoanisole **87i**.

A reaction between iodobenzene and ethyl benzoylacetate **198** was performed using CuI and ethylenediamine **197d**. The reaction was performed in DMSO with potassium carbonate as base (Scheme 138). After 20 hours at 80°C, GC analysis revealed a 68% conversion of iodobenzene and 54% conversion of ethyl benzoylacetate **198**. Ethyl phenylacetate **194b** was detected in 12% yield while 16% acetophenone and 9% benzoic acid were also formed. When repeated in toluene less conversion of both starting materials took place while 13% ethyl phenylacetate was formed with less acetophenone and benzoic acid.

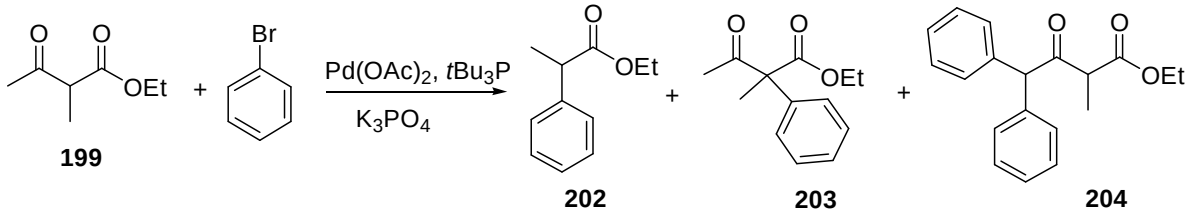


198 **194b** **200** **201**

Scheme 138. Reaction between ethyl benzoylacetate **198** and iodobenzene

The reaction between ethyl 2-methylacetoacetate **199** and bromobenzene was performed using $Pd(OAc)_2$ and P*t*Bu_3 with potassium phosphate in toluene solution (Scheme 139). After heating for 16 hours at 95°C all acetoacetate was consumed while 86% of bromobenzene had been converted. A number of products were formed and were identified by GS-MS and ^{1}H-NMR. The anticipated product, ethyl 2-phenylpropionate **202**, was formed in 4% yield. Ethyl 2-methyl-2-phenylacetoacetate

203 was the major product (12%) while a third product was tentatively identified (by GC-MS spectroscopy) as ethyl 2-methyl-4,4-diphenylacetoacetate **204** in approximately 3% yield.



Scheme 139. Arylation reaction of ethyl 2-methylacetoacetate **199**

A similar reaction using CuI in DMSO solution with iodobenzene gave small amounts of ethyl 2-phenylpropionate **202** and biphenyl as the only identified products.

The failure of the arylation reaction of ethyl benzoylacetate **198** using palladium catalysis may be caused by the formation of a more stable enolate (due to the extra stabilisation imparted by the phenyl group) resulting in a complex with palladium. The copper catalysed reaction did, however, give some of desired phenylacetate although again in a more sluggish reaction than observed for ethyl acetoacetate.

The low arylation yield observed for ethyl 2-methylacetoacetate **199** is probably due to steric hindrance but does demonstrate that the tertiary enolate can be arylated. The decarbonylation reaction was clearly less facile in the presence of a methyl substituent, possibly by either destabilising the product carbanion (see Scheme 135) or by steric hinderance.

5.4 Conclusion

In conclusion, this work constituted the first example of a palladium-catalysed intermolecular arylation of an acetoacetate ester. We have demonstrated the formation of the arylated acetoacetate ester (e.g., **195**) and its *in situ* base catalysed de-acylation to an arylacetic acid ester (e.g., **194b**). A variety of mono-arylated acetic acid esters

can be prepared in this manner and the reaction is applicable to both aryl bromides and chlorides[216]. The palladium catalysed reactions could be repeated with iodobenzene using 20mol% CuI or CuBr although yields were generally lower (40-50%). The requirement for a highly polar reaction medium such as DMSO or NMP was overcome by employing ethylenediamine as ligand for copper, giving comparable results in dioxane solvent while reactions conducted in toluene gave slightly inferior results. Bromobenzene was, however, not active in the copper catalysed reactions, the low yields obtained were ascribed to the formation of small amounts of iodobenzene by halogen exchange with CuI.

CHAPTER 6

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 200MHz Gemini 2000 spectrometer. Coupling constants (*J* values) are measured in Hz. Gas liquid chromatograghy (GC) was performed on a HP 5890 instrument and gas chromatography – mass spectrometry (GC-MS) was performed on a Finnagan TSQ700 instrument. High resolution mass spectra were recorded on a VG70-SEQ mass spectrometer. Melting points were determined on a Reichert hot-stage.

Merck Silica gel 60 (70-230 mesh) was used for preparative flash chromatography. Thin layer chromatography was carried out on aluminium backed Merck Silica gel 60 F_{254} plates precoated with 0.2mm silica gel 60. THF, toluene, 1.4-dioxane were distilled from sodium/benzophenone while DMF and NMP were distilled from calcium hydride.

6.1 Experimental Procedures Relating to Chapter 2

General procedure for Heck reaction of 2-ethylhexyl acrylate using a homogenous catalyst under phase transfer conditions:

4-Bromoanisole (1 molar equivalent), 2-ethylhexyl acrylate (1.1 molar equivalent) and sodium carbonate (0.5 molar equivalent) were mixed together. Methyl tri-n-octylammonium chloride (aliquat 336) was added (1 mass percent of the total reaction mixture). $Pd(OAc)_2$ was added together with triphenylphosphine (PPh_3) in a 1:10 to 1:40 ratio. The reaction mixture was heated at 150-160^{o}C for 20 hours. Conversion and selectivity were calculated after analysis by gas chromatography of a sample partitioned between water and ethyl acetate.

General procedure for Heck reaction of acrylic acid:

Sodium carbonate (1.5 molar equivalents) was suspended in a solvent consisting of either NMP, xylene (with 1% aliquat 336) or the relevant aryl bromide (and 1% aliquat 336). Acrylic acid (2 molar equivalents) was added carefully to this suspension,

resulting in rapid evolution of carbon dioxide. The aryl bromide was added to the resultant thick white suspension, followed by addition of the catalyst. The catalyst was comprised of a 1:40 mixture of $Pd(OAc)_2$ and PPh_3 or palladium on carbon. The reaction mixture was heated to 150^{o}C and the reaction progress monitored by GC. Samples were made up by addition of ethyl acetate and sodium hydrogen carbonate solution. Conversion of the aryl bromide was calculated by comparison with an internal standard. The yield of cinnamic acid (or substituted cinnamic acid) was determined by extracting the entire reaction mixture with ethyl acetate and sodium hydrogen carbonate and re-extracting the aqueous layer after acidification.

General procedure for Heck reaction of 2-ethylhexyl acrylate using a heterogenous catalyst:

Equimolar amounts of 4-bromoanisole (or other aryl bromide) (1 molar equivalent) and 2-ethylhexyl acrylate were mixed with 1.5 molar equivalents of sodium carbonate in 1-methyl-2-pyrrolidinone (NMP) (~30% of organic reagents in solution). Palladium on a carbon support (10% palladium on carbon with ~60% moisture, PMC 1940C) was added. In some instances a known amount of an inert reference was added as an internal standard for GC analysis. The resulting black slurry was heated to 185^{o}C in a sealed tube or Parr reactor depending on the scale of reaction. The reaction was monitored by GC analysis and the reaction mixture cooled once full conversion was achieved or the reaction ceased.

In instances where water was added as co-solvent, the reaction was performed in a pressure reactor since the autogenous pressure was 6-7 bar.

2-Ethylhexyl *trans*-4-methoxycinnamate (OMC) 56a: NMR data in agreement with literature values[217] δ_H (200MHz; $CDCl_3$) 0.92 (6H, m, 2×CH_3), 1.34 (4H, m, 2×CH_2), 1.41 (2H, m, CH_2), 1.64 (2H, m, CH), 3.81 (3H, s, CH_3), 4.11 (2H, m, CH_2), 6.32 (1H, d, *J* 16.0, olefinic CH), 6.89 (2H, d, *J* 6.8, Ar-H), 7.47 (2H, d, *J* 6.8, Ar-H), 7.63 (1H, d, *J* 16.0, olefinic CH).

Methyl 4-methoxycinnamate 56b [218]: NMR data in agreement with literature values[219] δ_H (200MHz; $CDCl_3$) 3.68 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.45 (1H, d, *J* 15.8, olefinic CH), 7.02 (2H, d, *J* 8.7, Ar-H), 7.54 (1H, d, *J*15.8 , olefinic CH), 7.66 (2H, d, *J* 8.7, Ar-H).

2-Ethylhexyl 3-(2-ethylhexyloxy)-propionate 57 [220]: δ_H (200MHz; $CDCl_3$) 0.94 (12H, t, 4×CH_3), 1.23-1.42 (16H, m, 8×CH_2), 1.54-1.63 (2H, m, 2×CH), 2.58 (2H, t, *J* 6.2, CH_2), 3.31 (2H, d, *J* 5.8, OCH_2), 3.68 (2H, t, *J* 6.2, OCH_2), 4.00 (2H, d, *J* 5.8, OCH_2);

3-(4-Methoxyphenyl)-propenoic acid / 4-methoxycinnamic acid 59a: NMR data in agreement with literature values[221]: δ_H (200MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 6.41 (1H, d, *J* 16.0, olefinic CH), 6.98 (2H, d, *J* 8.8 , Ar-H), 7.58 (1H, d, *J* 16.0, olefinic CH), 7.65 (2H, d, *J* 8.8, Ar-H), 12.0 (1H, br, COOH).

3-Phenylpropenoic acid / cinnamic acid 59b: NMR data in agreement with literature values[222]: δ_H (200MHz; $CDCl_3$) 6.47 (1H, d, *J* 16.1, olefinic CH), 7.40 (2H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.56 (2H, m, Ar-H), 7.81 (1H, d, *J* 16.1, olefinic CH), 11.0 (1H, br,COOH).

2-Ethylhexyl 3-(4-methoxyphenyl)-propionate 60 [223]: δ_H (200MHz; $CDCl_3$) 0.92 (6H, m, 2×CH_3), 1.34 (4H, m, 2×CH_2), 1.41 (2H, m, CH_2), 1.64 (2H, m, CH), 2.64 (2H, m, CH_2CO_2R), 2.88 (2H, m, CH_2Ar), 3.81 (3H, s, CH_3), 4.11 (2H, m, CH_2), 6.89 (2H, d, *J* 6.8, Ar-H), 7.47 (2H, d, *J* 6.8, Ar-H).

Tris-(2-*t*-butyl-4-methoxyphenyl)-phosphite **62**:

To an ice-bath cooled solution of PCl_3 (1.3ml, 14.5 mmol) in toluene (20ml) was added 3-BHA (3-*t*-butyl-4-hydroxyanisole) (8.64g, 48 mmol) in toluene (30ml). Triethyl amine (4.85g, 48 mmol) was added dropwise which initiated an exothermic reaction and the formation of a white precipitate. The resulting viscous slurry was heated to reflux for 2h, cooled and filtered. The filtrate was evaporated *in vacuo* to a viscous

light yellow syrup (8.2g, 99%). Pure **62** (1.0g) was obtained by column chromatography (10% ethyl acetate in hexane) as a colourless oil.

δ_H (200MHz; $CDCl_3$) 1.40 (27H, s, CH_3), 3.79 (9H, s, OCH_3), 6.64 (3H, dd, *J* 8.8 and 3.0 , Ar-H), 6.96 (3H, d, *J* 3.0, Ar-H), 7.31 (3H, dd, *J* 8.8 and 2.0, Ar-H); δ_C (50 MHz; $CDCl_3$) 29.8, 34.9, 55.8, 110.8, 114.3, 117.0, 137.8, 148.8, 153.5; δ_P (81MHz; $CDCl_3$) 148.74; Exact mass calculated for $C_{33}H_{45}O_6P$ $[M]^+$: 568.2954. Found: 568.2964.

(2,2'-Di-*tert*-butyl-4,4'-dimethoxy-6,6'-biphenoxy)-phenylphosphine **64**:

Dichlorophenylphosphine (1.79g, 1.35ml, 10 mmol) in toluene (2ml) was added to a suspension of 3-BHA dimer (2,2'-di-*tert*-butyl-4,4'-dimethoxy-6,6'-biphenol) **63** [224] (3.58g, 10 mmol) in toluene (20ml). Dropwise addition of triethylamine (2.5g, 25 mmol) initiated an exothermic reaction and the formation of white cloudiness and later a white precipitate. The resulting viscous slurry was heated to reflux for 2h, cooled and filtered. The filtrate was diluted with ethyl acetate (50ml), washed with saturated sodium hydrogencarbonate solution (3x50ml), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to a viscous oil (4.5g).

(2,2'-Di-*tert*-butyl-4,4'-dimethoxy-6,6'-biphenoxy)-phenylphosphine 64: δ_H (200MHz; $CDCl_3$) 1.22 (18H, s, *t*-Butyl), 3.88 (6H, s, OCH_3), 6.81 (2H, m, Ar-H), 6.98 (2H, m, Ar-H), 7.20-7.64 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 29.8, 35.4, 56.0, 112.1, 115.5, 123.5, 128.8, 129.0, 130.8, 137.4, 139.2, 146.1, 153.5; δ_P (81MHz; $CDCl_3$) 181.41; Exact mass calculated for $C_{28}H_{33}O_4P$ $[M]^+$: 464.2122. Found: 464.2117.

Phenylphosphine **68**:

A solution of phenylphosphonic dichloride **67** (9.8g, 50 mmol) in diethyl ether (30ml) was added dropwise to a stirred and cooled (ice-bath) suspension of $LiAlH_4$ (1.9g, 50 mmol) in diethyl ether (30ml). The resulting mixture was refluxed under a nitrogen atmosphere for 2.5h before cooling to room temperature. The reaction mixture was diluted with wet diethyl ether (20ml) and water (4ml) was carefully added. After stirring for 16h the mixture was filtered through celite under a nitrogen atmosphere. The crude product was obtained as a colourless cloudy oil (2.6g, 47%) which was

identified by ^{1}H and ^{31}P NMR spectroscopy as phenylphosphine **68** contaminated with ~10% diethyl ether. NMR data in agreement with literature values[225].

Preparation of phenyl phosphabicyclononanes **70a** and **70b**:

Cyclooctadiene **69** (1.2g, 11 mmol) and AIBN (20mg) was added to heated (95-100^{o}C) phenylphosphine (2.4g, 22 mmol). A further 30mg AIBN was added as a solution in toluene (3ml) over 30min. After 2h of heating the mixture was cooled to room temperature and allowed to stir for 3days. ^{1}H and ^{31}P NMR spectroscopy suggested that a large proportion of **69** had been consumed although **68** was still the major phosphorus containing compound (amongst several others). The reaction mixture was distilled under reduced pressure and a fraction was collected (0.7g, 170^{o}C, 0.5mbar) which was a 2:1 mixture of 2 tertiary phosphines **70a/b**.

9-phenyl-9-phospha-bicyclo[4.2.1]nonane 70b [226]: δ_H (200MHz; $CDCl_3$) 1.5-1.8 (8H, m, CH_2), 2.0-2.2 (4H, m, CH_2), 2.80-2.90 (2H, m, CH), 7.20-7.43 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 26.1 (*J* 7.6), 34.3 (*J* 6.1), 35.2 (*J* 17.6), 40.8 (*J* 13.0), 126.3, 128.2, 130.3, 140.2 (*J* 18.5); δ_P (81MHz; $CDCl_3$) 9.29, After treatment with *t*BuOOH: δ_P (81MHz; $CDCl_3$) 66.53; Exact mass calculated for $C_{14}H_{19}P$ $[M]^+$: 218.1224. Found: 218.1247.

9-phenyl-9-phosphabicyclo[3.3.1]nonane 70a [227] δ_H (200MHz; $CDCl_3$) 1.5-1.8 (8H, m, CH_2), 2.0-2.2 (4H, m, CH_2), 2.35-2.40 (2H, m, CH), 7.20-7.43 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 25.0 (*J* 11.5), 25.4 (*J* 4.6), 31.9 (*J* 13.7), 126.1, 128.4, 130.4, 140.2 (*J* 18.5); δ_P (81MHz; $CDCl_3$) –21.73. After treatment with *t*BuOOH: δ_P (81MHz; $CDCl_3$) 41.03; Exact mass calculated for $C_{14}H_{19}P$ $[M]^+$: 218.1224. Found: 218.1247.

2-(Dichlorophosphino)-biphenyl **72**:

Bromobenzene (9.42g, 40 mmol) was added to a slurry of magnesium turnings (1.8g, 76 mmol) in THF (70ml). A grey solution was formed by heating in a 60^{o}C oil-bath followed by stirring the exothermic reaction at 60^{o}C for 30min. 2-Bromo chlorobenzene **71** (9.6g, 50 mmol) was added to the hot mixture over 20min followed by heating for 1h. The mixture was cooled to 30^{o}C and filtered through Celite under a nitrogen atmosphere. The yellow/orange filtrate was added dropwise to a cold (-10^{o}C)

suspension of PCl_3 (10.8g, 6.9ml, 78 mmol) in THF (30ml). The resulting viscous slurry was allowed to warm to room temperature and stirred for 16h. The slurry was filtered under a nitrogen atmosphere, diluted with diethyl ether and filtered again. The orange filtrate was evaporated to dryness *in vacuo* to an orange coloured oil (6.8g), which was used without further treatment in the preparation of 2-phosphino-biphenyl (**73**). δ_P (81MHz; $CDCl_3$) 158.2.

2-Phosphino-biphenyl **73**:

A solution of 2-(dichlorophosphino)-biphenyl **72** (6.8g, ~20mmol) in diethyl ether (20ml) was added dropwise to a suspension of $LiAlH_4$ (0.38g, 10 mmol) in diethyl ether (10ml). THF (5ml) was added to aid solubility. Hydrogen gas evolution was observed and a further 10 mmol $LiAlH_4$ was added and the mixture was heated to reflux for a total of 4h. The reaction mixture was cooled to room temperature and quenched by the careful addition of water (2ml). The resulting slurry was filtered through Celite, the Celite was rinsed with diethyl ether (20ml) and the yellow filtrate was evaporated to dryness to yield a yellow oil (1.6g).

2-Phosphino-biphenyl 73: NMR data in agreement with literature values[228]; δ_P (81MHz; $CDCl_3$) –122.09 (*J*(PH) 216).

6.2 Procedures Relating to Chapter 3

General procedure for the arylation of propiophenone 86: [99,100]

Into a screw capped pyrex tube (50ml) was weighed NaO^tBu (0.63g, 6.5 mmol), propiophenone (0.80g, 6 mmol) and the appropriate aryl halide (5 mmol) as well as 6ml toluene (distilled from sodium). $Pd(OAc)_2$, the appropriate phosphine ligand (if required) and an accurately weighed amount of 2-methoxynaphthalene (internal standard) were dissolved in toluene (2ml) and added to the reaction mixture. The tube was flushed with nitrogen and sealed and heated at 110°C in a Robosynthon multireactor for 15 hours. The amount of aryl halide, propiophenone and arylation product present were determined by GC analysis based on internal standard calculation. Isolation was done by addition of water and dilute hydrochloric acid to

acidify the mixture followed by extraction into diethyl ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was analysed by NMR and the spectrum compared to either that of an authentic standard or reference data. In cases where the isolated yield was determined the crude product was purified by flash column chromatography (20% ethyl acetate in hexane).

1,2-Diphenyl-1-propanone 88 [99] was prepared in 94% with 0.2% $Pd(OAc)_2$ and 93% when NaH instead of NaO^tBu was used as base with 0.3mol% $Pd(OAc)_2$.
88: δ_H (200MHz; $CDCl_3$) 1.61 (3H, d, *J* 7.3, CH_3), 4.70 (1H, q, *J* 7.3, CH), 7.22-7.50 (8H, m, Ar-H), 8.05 (2H, d, *J* 7.2, Ar-H); δ_C (50 MHz; $CDCl_3$) 19.7, 47.9, 127.0, 127.8, 128.5, 128.8, 129.0, 132.8, 136.5, 141.5, 200.3.

2-(4-Methylphenyl)-propiophenone 89 [100] was prepared from 4-chlorotoluene **87b** in 3% after 16hours with 1mol% $Pd(OAc)_2$ and in 91.5% yield in 30min with 1mol% $Pd(OAc)_2$ and 2mol% **66a**.
89: δ_H (200MHz; $CDCl_3$) 1.58 (3H, d, *J* 7.8, CH_3), 2.32 (3H, s, Ar-CH_3), 4.70 (1H, q, *J* 7.8, CH), 7.12 (2H, d, *J* 7.7, Ar-H), 7.23 (2H, d, *J* 7.7, Ar-H), 7.38-7.52 (3H, m, Ar-H), 8.05 (2H, d, *J* 8.1, Ar-H); δ_C (50 MHz; $CDCl_3$) 19.7, 21.5, 47.9, 127.8, 128.5, 128.8, 129.8, 132.8, 136.5, 136.6, 138.1, 200.3.

Preparation of 2-(di-*tert*-butylphosphino)-phenylethane **90**:
A mixture of phenethylbromide (2.78g, 15 mmol) and magnesium turnings (0.40g, 16.5 mmol) and THF (5ml) was warmed carefully until the reaction became exothermic. THF (15ml) was added to dilute the exothermic reaction and the reaction temperature was maintained at 60°C. Freshly recrystallised CuCl (from dilute hydrochloric acid)(0.69g, 10 mmol) was added followed by di-*tert*-butylphosphine chloride (0.90g, 0.95ml, 5 mmol). After heating for 3h the resulting black reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with a mixture of ethyl acetate (25ml), hexane (25ml) and aqueous ammonium hydroxide solution (50ml, 25% m/V). The organic layer was washed with water until

colourless, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to a yellow/green oil (1.45g) which solidified on standing. Crystalline product was obtained by filtration and washing with hexane.

2-(di-*tert*-butylphosphino)-phenylethane 90: δ_H (200MHz; $CDCl_3$) 1.45 (18H, d, *J* 10.4, *t*-Butyl), 2.14 (2H, m, CH_2), 3.10 (2H, m, CH_2), 7.20-7.35 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 24.2 (*J* 5.7), 30.4 (*J* 5.3), 33.7 (*J* 7.1), 34.7 (*J* 8.0), 126.4, 128.4, 128.8, 138.5; δ_P (81MHz; $CDCl_3$) 29.31; Exact mass calculated for $C_{16}H_{27}P$ $[M]^+$: 250.1850. Found: 250.1860; mp 119-121^{o}C.

Nickel catalysed arylation of propiophenone **86**:

The general procedure for the palladium catalysed aylation of propiophenone was followed using bromobenzene (1.0g, 6.4 mmol) and propiophenone (0.67g, 5 mmol) (with the exception that $Ni(OAc)_2$ (17.7mg, 0.10 mmol), 2-(di-*tert*-butylphosphino)-biphenyl **66a** (60mg, 0.20 mmol) and zinc metal powder (19.5, 0.30 mmol) were used as the catalyst). The yield of 1,2-diphenyl-1-propanone (**88**) was determined by ^{1}H-NMR to be 34%.

Reaction between cyclohexanone **91** and bromobenzene: [99]

Into a screw capped pyrex tube (50ml) was weighed K_3PO_4 (5.3g, 25 mmol), cyclohexanone (1.5g, 15 mmol) and bromobenzene (1.57g, 10 mmol) as well as 15ml 1,4-dioxane (distilled from CaH_2). $Pd(OAc)_2$ (22.4mg, 0.1 mmol, 1mol%) and P*t*Bu_3 (20.2mg, 0.1mmol, 1mol%) in 1,4-dioxane (1ml) were added and the tube flushed with nitrogen, sealed and heated at 100^{o}C in a Robosynthon multireactor. The conversion of bromobenzene and cyclohexanone and the formation of the arylation products were followed by GC analysis. After 2 hours of heating the reaction was quenched by addition of dilute hydrochloric acid as most bromobenzene had been consumed. The crude product was isolated by extraction into diethyl ether, drying over anhydrous $MgSO_4$ and evaporation of the volatile components under reduced pressure. Compounds **92**, **93** and **94** were identified by GC-MS analysis of the crude product. The crude product was purified by flash chromatography (10% ethyl acetate in hexane) to yield 1.1g of **5** (64% yield) as a clear colourless oil.

2-phenylcyclohexanone 92: NMR data in agreement with literature values[99] δ_H (200MHz; $CDCl_3$) 1.8-2.6 (8H, m, CH_2), 3.64 (1H, dd, *J* 12.3, 5.4, CH), 7.15-7.20 (2H, m, Ar-H), 7.28-7.42 (3H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 25.3, 28.0, 35.1, 42.2, 57.4, 127.0, 128.3, 128.6, 138.9, 210.4

2,6-diphenylcyclohexanone 93: NMR data in agreement with literature values[229] δ_H (200MHz; $CDCl_3$) 1.8-2.6 (6H, m, CH_2), 3.85 (2H, dd, *J* 12.3, 5.4, CH), 7.15-7.42 (10H, m, Ar-H).

2-cyclohexylidenecyclohexanone 94: NMR data in agreement with literature values[230] δ_H (200MHz; $CDCl_3$) 1.48 (6H, m, CH_2), 1.64 (2H, m), 1.78 (2H, m), 2.10 (2H, m), 2.31 (4H,m), 2.40 (2H, m).

General procedure for the arylation of cyclic 1,3-diketones: [100]

Into a screw capped pyrex tube (50ml) was weighed K_3PO_4 (2.44g, 11.5 mmol), indandione **95** or dimedone **97** (6 mmol) and bromobenzene (0.79g, 5 mmol) as well as 15ml 1,4-dioxane (distilled from CaH_2). $Pd(OAc)_2$ (11.2mg, 0.05 mmol, 1mol%) and 2-(di-*tert*-butylphosphino)-biphenyl ligand **66a** (29.8mg, 0.1mmol, 2mol%) in 1,4-dioxane (1ml) were added and the tube flushed with nitrogen, sealed and heated at 80^{o}C in a Robosynthon multireactor for 16 hours. The conversion of bromobenzene and diketone and the formation of the arylation products were followed by GC analysis. The reaction mixture was quenched by addition of dilute hydrochloric acid and the crude product was isolated by extraction into ethyl acetate, drying over anhydrous $MgSO_4$ and evaporation of the volatile components under reduced pressure.

2-Phenyl-indan-1,3-dione 96 [231] was isolated from the reaction between indandione **8** and bromobenzene as a sticky purple solid 1.03g (92.6%) which was recrystallised from diethyl ether to afford a brown powder (**96**).

2-Phenyl-indan-1,3-dione 96: NMR data in agreement with literature values[231] δ_H (200MHz; $CDCl_3$) 4.26 (1H, s, CH), 7.10-7.26 (2H, m, Ar-H), 7.30-7.40 (3H, m, Ar-H), 7.88-7.95 (2H, m, Ar-H), 8.02-8.14 (2H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 59.5, 123.4, 127.5, 128.4, 128.6, 132.8, 135.6, 142.3, 197.8; mp 130-135^oC (Lit. 140-141^oC [232]).

2-Phenyl-dimedone / 5,5-dimethyl-2-phenyl-cycloxan-1,3-dione 98 [233] was isolated from the reaction between dimedone and bromobenzene as a yellow oil (0.98g, 90%).
98: NMR [233] δ_H (200MHz; $CDCl_3$) 1.22 (6H, s, CH_3), 2.63 (2H, s, CH_2), 3.07 (2H, s, CH_2), 7.43-7.52 (3H, m, Ar-H), 7.43-7.68 (1H, br, OH), 7.97-8.01 (2H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 28.4, 32.9, 44.7, 47.6, 128.9, 130.4, 132.0, 133.9, 134.6, 178.2, 202.5.

General procedure for malonate ester arylation: [97,99,100]

Into a screw capped pyrex tube (50ml) was weighed NaO^tBu (0.63g, 6.5 mmol), diethyl malonate (0.80g, 5 mmol) and the appropriate aryl halide (6 mmol) as well as toluene (6ml, distilled from sodium). $Pd(OAc)_2$, the appropriate phosphine ligand and an accurately weighed amount of naphthalene (internal standard) were dissolved in toluene (2ml), heated for 2 minutes at ~60^oC and added to the reaction mixture. The tube was flushed with nitrogen and sealed and heated at 110^oC in a Robosynthon multireactor for 15 hours. The amount of aryl halide, diethyl malonate and arylation product present was determined by GC analysis based on internal standard calculation. Isolation was done by addition of water and dilute hydrochloric acid to acidify the mixture followed by extraction into diethyl ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was analysed by NMR and the spectrum compared to either that of an authentic standard or reference data. In cases where the isolated yield was determined the crude product was purified by flash column chromatography (10-20% ethyl acetate in hexane).

The following compounds were prepared using the above general procedure:

Diethyl 2-phenylmalonate 103a [99] was prepared from **87a** and **87d**:
103a: NMR data in agreement with literature values [97] δ_H (200MHz; $CDCl_3$) 1.28 (6H, t, *J* 7.2, CH_3), 4.23 (4H, q, *J* 7.2, CH_2), 4.63 (1H, s, CH), 7.36-7.45 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 13.9, 58.2, 61.9, 128.2, 128.6, 129.4, 133.4, 168.3

Diethyl 2-(4-methylphenyl)-malonate 103d [234,170] was prepared from 4-chlorotoluene **87b** in 72% yield using 2-(di-*tert*-butylphosphino)-biphenyl (**66a**) and 86% yield with K_3PO_4 as base in 1,4-dioxane solvent.
103d: NMR data in agreement with literature values[234,170] δ_H (200MHz; $CDCl_3$) 1.27 (6H, t, *J* 7.2, CH_3), 2.36 (3H, s, Ar-CH_3), 4.12-4.31 (4H, m, CH_2), 4.58 (1H, s, CH), 7.16 (2H, d, *J* 9.6, Ar-H), 7.32 (2H, d, *J* 9.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 13.9, 21.1, 57.2, 61.9, 129.7, 129.9, 132.4, 136.4, 168.5.

Diethyl 2-(4-methoxyphenyl)-malonate 103e [97] was prepared from 4-chloroanisole **87e** in 82% yield using ligand **66a**.
103e: NMR data in agreement with literature values[97] δ_H (200MHz; $CDCl_3$) 1.27 (6H, t, *J* 7.2, CH_3), 3.81 (3H, s, OCH_3), 4.15-4.30 (4H, m, CH_2), 4.56 (1H, s, CH), 6.90 (2H, d, *J* 7.6, Ar-H), 7.33 (2H, d, *J* 7.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 14.0, 55.3, 57.1, 61.7, 114.0, 124.8,130.3, 159.4, 168.5.

Diethyl 2-(4-ethoxycarbonylphenyl)malonate 103f [97] was prepared from ethyl 4-chlorobenzoate **87f** in 85% yield using ligand **66a**.
103f: NMR data in agreement with literature values[97] δ_H (200MHz; $CDCl_3$) 1.11 (6H, t, *J* 7.2, CH_3), 1.25 (3H, t, *J* 7.2, CH_3), 4.01-4.12 (2H, m, CH_2), 4.23 (4H, q, *J* 7.2, CH_2), 4.57 (1H, s, CH), 7.33 (2H, d, *J* 9.3, Ar-H), 7.88 (2H, d, *J* 9.3, Ar-H); δ_C (50 MHz; $CDCl_3$) 14.0, 15.3, 56.3, 57.9, 62.1, 129.4, 129.8, 130.0, 137.6, 166.7, 167.5

Diethyl 2-(4-acetylphenyl)-malonate 103g [97] was prepared from 4-chloroacetophenone **87g** in 76% yield using K_3PO_4 (2.4g, 11.5 mmol) in 1,4-dioxane solvent.

103g: NMR data in agreement with literature values[97] δ_H (200MHz; $CDCl_3$) 1.27 (6H, t, *J* 7.2, CH_3), 2.61 (3H, s, CH_3), 4.16-4.30 (4H, m, CH_2), 4.68 (1H, s, CH), 7.49-7.54 (2H, m, Ar-H), 7.94-7.98 (2H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 14.0, 26.7, 57.8, 62.1, 128.6, 129.6,136.8, 137.8, 167.5, 197.7.

Ethyl phenylacetate **109**:

109 was detected in the reaction of diethyl malonate and chlorobenzene catalysed by $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)-biphenyl (**66a**).

Ethyl phenylacetate 109: NMR data in agreement with literature values[62] δ_H (200MHz; $CDCl_3$) 1.28 (3H, d, *J* 7.2, CH_3), 3.64 (2H, q, *J* 7.2, CH_2Ph), 4.18 (2H, s, OCH_2), 7.24-7.42 (5H, m, PhH); δ_C (50 MHz; $CDCl_3$) 14.2, 41.4, 60.7, 127.1, 128.5, 129.3, 134.2, 171.5.

General procedure for the copper catalysed malonate arylation to prepare diethyl 2-phenylmalonate 103a: [60,58]

Into a screw capped pyrex tube (50ml) was weighed K_3PO_4 (0.64g, 3 mmol), diethyl malonate (0.64g, 4 mmol) and iodobenzene (0.41g, 2 mmol) and solvent (5ml). CuI (80mg, 0.4 mmol, 20mol%) and 2-phenylphenol (136mg, 0.8mmol, 40mol%) and an accurately weighed amount (~20mg) of 2-methoxynaphthalene (internal standard) in 1ml solvent were added and the tube flushed with nitrogen, sealed and heated to the appropriate temperature. Soon after heating was started the colour of the reaction mixture became orange/brown which became progressively darker with time. The conversion of iodobenzene and diethyl malonate and the formation of diethyl phenylmalonate **103a** were followed by GC analysis. Once product formation became slow or stopped, the reaction mixture was quenched by addition of dilute hydrochloric acid and the crude product was isolated by extraction into diethyl ether, drying over anhydrous $MgSO_4$ and evaporation of the volatile components under reduced pressure.

i. The yield of **103a** was 16% when THF (distilled from sodium/benzophenone) was used (70^{o}C for 24hours)
ii. The yield of **103a** was 27% when 1,4-dioxane (distilled from CaH/$LiAlH_4$) was used (100^{o}C for 24hours)
iii. The yield of **103a** was 46% when DMSO (stored over CaH) was used (100^{o}C for 20hours)

Phenobarbital from diethyl phenylmalonate **103a**:

Diethyl phenylmalonate **103a** (0.5g, 2.1 mmol, as prepared by the general palladium catalysed malonate arylation procedure) was dissolved in toluene (10ml) and NaO*t*Bu (0.24g, 2.5 mmol) was added. After stirring for 30min ethyl bromide (0.28g, 2.6 mmol) was added dropwise to the reaction mixture. After determining by GC analysis that no alkylation was taking place the mixture was heated to reflux. After 1 hour of reflux the reaction mixture was cooled and quenched by the addition of ethyl acetate and dilute hydrochloric acid. After drying the organic layer over anhydrous $MgSO_4$ the volatiles were removed under reduced pressure to yield **115** as a light yellow oil (0.48g, 87% yield).

Diethyl 2-ethyl-2-phenylmalonate 115: NMR data in agreement with literature values[235] δ_H (200MHz; $CDCl_3$) 0.92 (3H, t, *J* 7.4, CH_2CH_3), 1.27 (6H, t, *J* 7.1, OCH_2CH_3), 2.39 (2H, q, *J* 7.4, CH_2CH_3), 4.25 (4H, q, *J* 7.1, OCH_2CH_3), 7.28-7.50 (5H, m, Ar-H); δ_C (50MHz; $CDCl_3$) 9.2, 13.8, 28.7, 61.2, 63.0, 127.2, 127.9, 128.0, 136.8, 170.6.

To a solution of urea (60mg, 1 mmol) and NaOMe (54mg, 1 mmol) in methanol (2ml) was added a solution of **115** (264mg, 1 mmol) in methanol (1ml) and the resulting mixture was heated to reflux. More urea (300mg, 5 mmol) and NaOMe (110mg, 2 mmol) was added and the mixture was refluxed for 14 hours to yield a white suspension. Methanol was removed at room temperature under reduced pressure followed by the addition of water and 10% hydrochloric acid. A white sticky paste formed which could not be crystallised. ^{1}H-NMR revealed 2 compounds of which the minor component (40%) corresponded to spectral data for Phenobarbital.

5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione (Phenobarbital): NMR data in agreement with literature values[236] δ_H (200MHz; $CDCl_3$) 0.99 (3H, t, *J* 7.3, CH_2CH3), 2.49 (2H, q, *J* 7.3, CH_2CH_3), 7.36 (5H, m, Ar-H), 8.79 (2H, s, N-H); δ_C (50 MHz; $CDCl_3$) 10.3, 30.0, 61.3, 125.8, 128.4, 129.5, 136.9, 148.9, 170.3.

Methyl 2-phenylbutyrate 116: NMR data in agreement with literature values[237] δ_H (200MHz; $CDCl_3$) 0.89 (3H, t, *J* 7.3, CH_2CH_3), 1.78-2.12 (2H, m, CH_2CH_3), 3.39 (1H, t, *J* 7.6, CHCOOH), 3.67 (3H, s, OCH_3), 7.25-7.32 (5H, m, Ar-H).

2-Phenylbutyramide 118: NMR data in agreement with literature values[238] δ_H (200MHz; $CDCl_3$) 0.88 (3H, t, *J* 7.4, CH_2CH_3), 1.80 (1H, m, CH_2CH_3), 2.20 (1H, m, CH_2CH_3), 3.28 (1H, dd, *J* 8.1 and 7.0, CH), 5.44 and 5.50 (each 1H, br, 2×N-H), 7.23-7.37 (5H, m, Ar-H).

Preparation of ketoprofen intermediates:

Preparation of 4-chlorobenzophenone **123d**:

4-Chlorobenzoic acid **128** (10 g, 63.9 mmol) was heated with thionyl chloride (20 m*l*, 4.3 molar equivalents) under reflux for 2 hours. The excess thionyl chloride was removed under vacuum and the thick residue was diluted with benzene and evaporated to dryness to remove traces of thionyl chloride. The residue was dissolved in benzene (50ml) and slowly added (over 10 min) to a cold (ice-bath, care was taken not to let benzene freeze) suspension of aluminum trichloride (11.5 g, 1.35 molar equivalents) in

benzene (50ml). The mixture was allowed to warm to room temperature whereafter it was heated to reflux. Gas evolution started at ~60°C and ceased after 30 minutes of reflux. The mixture was allowed to cool and was poured onto crushed ice (200g) and hydrochloric acid (32%, 30ml). The greasy suspension was diluted with diethyl ether (100ml). The aqueous layer was washed with diethyl ether (3×100ml). The combined ether layers were washed once with 5% sodium hydroxide solution and twice with water. The ether layer was dried over anhydrous magnesium sulphate and evaporated to give 12.0g (87%) of an off-white solid.

4-Chlorobenzophenone 123d: NMR data in agreement with literature values[239] δ_H (200MHz; $CDCl_3$) 7.38-7.84 (9H, m, Ar-*H*); δ_C (50 MHz; $CDCl_3$) 128.3, 128.6, 129.9, 131.2, 132.5, 136.0, 137.3, 138.9, 195.1; mp 73-74°C (Lit. 75°C[240]).

Diethyl 2-(4-benzoylphenyl)malonate **124c**:

124c was prepared from both 4-bromobenzophenone (**123c**) and 4-chlorobenzophenone (**123d**) following to the general malonate palladium catalysed arylation procedure (see earlier). $Pd(OAc)_2$ (1 mol%) and 2-(di-*tert*-butylphosphino)-biphenyl (**66a**, 2 mol%) was used.

When **123c** was used, **124c** was formed together with ethyl *tert*-butyl 2-(4-benzoylphenyl)malonate (**124d**), ethyl 2-(4-benzoylphenyl)acetate (**125b**) and benzophenone (**126**). Silica gel flash chromatography afforded **124c** as a colourless oil (46% yield). **124d** and **125b** were not separated and accounted for 33% with **124d** being the major component. **126** was isolated in 30% yield.

Diethyl 2-(4-benzoylphenyl)malonate 124c: NMR data in agreement with literature values[97] δ_H (200MHz; $CDCl_3$) 1.28 (6H, t, *J* 7.2, CH_3), 4.24 (4H, m, OCH_2), 4.71 (1H, s, CH), 7.46-7.83 (9H, m, Ar-H); δ_C (50MHz; $CDCl_3$) 14.0, 57.8, 62.2, 128.4, 129.4, 130.0, 130.4, 132.5, 137.0, 137.3, 137.5, 167.6, 196.2.

Ethyl *tert*-butyl 2-(4-benzoylphenyl)malonate 124d: δ_H (200MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.2, CH_3), 1.47 (9H, s, *t*-Bu), 4.23 (2H, m, OCH_2), 4.64 (1H, s, CH), 7.46-7.83 (9H, m, Ar-H); Exact mass calculated for $C_{20}H_{20}O_5$ ($C_{22}H_{24}O_5$-C_2H_4) $[M]^+$: 340.1311. Found: 340.1292.

Ethyl 2-(4-benzoylphenyl)acetate 125b [241]: δ_H (200MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.2, CH_3), 3.72 (2H, s, CH_2Ar), 4.22 (2H, q, *J* 7.2, OCH_2), 7.46-7.83 (9H, m, Ar-H); Exact mass calculated for $C_{17}H_{16}O_3$ $[M]^+$: 268.1099. Found: 268.1114.

Preparation of 3-chlorobenzophenone **123b**:

To a solution 3-chlorotoluene **127** (21.49g, 0.17mol) in glacial acetic acid (100g) was added cobalt(II) acetate (0.86g, 2mol%), manganese(II) acetate (0.70g, 2mol%) and 48% hydrobromic acid (1.28g, 4mol%). The resulting blue solution was heated to reflux and oxygen was bubbled through the solution at such a rate that a condenser at 5°C was able to condense all the refluxing acetic acid. The reaction was followed by GC and after 6.5 hours of oxygen bubbling, 94% of 3-chlorotoluene had been converted. 3-Chlorobenzoic acid (**128**) was the major product (77%) with a number of unidentified intermediates/by-products also formed. The dark purple solution was allowed to cool to room temperature upon which white crystals formed. The crystals were filtered off, washed with dilute acetic acid and dried to afford 15.4g (58%) off-white solids (**128**, mp 154.5°C, literature 158°C[242]). ^1H and ^{13}C NMR spectral data was in accordance with literature values[243].

3-Chlorobenzoic acid (**128,** 10g, 63.9mmol) was heated with thionyl chloride (20ml, 4.3 molar equivalents) under reflux for 2 hours. The excess thionyl chloride was removed under vacuum and the thick residue was diluted with benzene and evaporated to dryness to remove traces of thionyl chloride. The residue was dissolved in benzene (50ml) and slowly added (over 10min) to a cold (ice-bath, care was taken not to let benzene freeze) suspension of aluminum trichloride (11.5g, 1.35 molar equivalents) in benzene (50ml). The mixture was allowed to warm to room temperature whereafter it was heated to reflux. Gas evolution started at ~60°C and ceased after 30 minutes of

reflux. The mixture was allowed to cool and was poured onto crushed ice (200g) and hydrochloric acid (32%, 30ml). The greasy suspension was diluted with diethyl ether (100ml). The aqueous layer was washed with diethyl ether (3×100ml). The combined ether layers were washed once with 5% sodium hydroxide solution and twice with water. The ether layer was dried over anhydrous magnesium sulphate and evaporated to give 13.5g (95%) of an off-white solid.

3-Chlorobenzophenone 123b [244]: δ_H (200MHz; $CDCl_3$) 7.38-7.84 (9H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 128.2, 128.4, 129.6, 129.7, 130.0, 132.2, 132.8, 134.5, 137.0, 139.2, 195.2; mp 83.6°C (Lit. 82-83°C[245,240]).

Diethyl 2-(3-benzoylphenyl)malonate **124a**:

124a/b were prepared from **123b** in 86% yield while **125a** was formed in 4% and **126** in 5% (as determined by ^{1}H-NMR spectrometry).

Diethyl 2-(3-benzoylphenyl)malonate 124a [246]: δ_H (200MHz; $CDCl_3$) 1.26 (6H, t, *J* 7.2, CH_3), 4.23 (4H, q, *J* 7.2, OCH_2), 4.72 (1H, s, CH), 7.42-7.83 (9H, m, Ar-H).

Ethyl *t*-butyl 2-(3-benzoylphenyl)malonate 124b: δ_H (200MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.2, CH_3), 1.48 (9H, s, *t*-Bu), 4.23 (2H, q, *J* 7.2, OCH_2), 4.61 (1H, s, CH), 7.42-7.83 (9H, m, Ar-H); ν_{max}(neat)/cm^{-1} 1741 (ketone C=O), 1665 (ester C=O), 1284 ($CHCO_2R$), 1180 and 1151 (C-O); HRMS (EI): Exact mass calculated for $C_{20}H_{20}O_5$ ($C_{22}H_{24}O_5$-C_2H_4) $[M]^+$: 340.1311. Found: 340.1274.

Ethyl 2-(3-benzoylphenyl)acetate 125a [246]: δ_H (200MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.2, CH_3), 3.71 (2H, s, CH_2Ar), 4.23 (2H, q, *J* 7.2, OCH_2), 7.42-7.83 (9H, m, Ar-H); HRMS (EI): Exact mass calculated for $C_{17}H_{16}O_3$ $[M]^+$: 268.1099. Found: 268.1095.

50Mmol arylation reaction of 3-chlorobenzophenone (123b) to prepare diethyl 2-(3-benzoylphenyl)malonate (124a):

To a 250ml round bottomed flask was charged 6.24g (65mmol, 1.3 molar equivalents) sodium *tert*-butoxide and toluene (50ml, distilled from sodium/benzophenone). A solution of diethyl malonate (9.6g, 60 mmol) in toluene (50ml) was added under a nitrogen atmosphere. This addition was exothermic and a thick waxy slurry was formed. Naphthalene (0.128g) in toluene (20ml) was added as an internal GC standard. The catalyst solution, prepared by dissolving $Pd(OAc)_2$ (22.4mg, 0.1mol%) and 2-(di-*tert*-butylphosphino)-biphenyl **66a** (59mg, 0.2 mol%) in 50ml hot (~60^{o}C) toluene, was added. 3-Chlorobenzophenone (**123b**, 10.8g, 50mmol) was added together with a further 20ml toluene. This reaction mixture was heated to reflux under nitrogen for 3 hours.

The progress of the reaction was followed by GC based on the disappearance of diethyl malonate compared to the internal standard. After 0.5 hour at reflux temperature 50% of the malonate had been converted and after 1 hour this was 83%. Very little change was observed during the second hour. The disappearance of 3-chlorobenzophenone was also measured with 38% of the 3-chlorobenzophenone being converted in the first 0.5 hour, of which 7.5% was by reduction to benzophenone. After 1 hour 88% was converted (9.9% by reduction) and after 2 hours the starting material was virtually all converted. After 3 hours the mixture was cooled to room temperature and water (100ml) and diethyl ether (100ml) was added. The aqueous layer was acidified by addition of dilute hydrochloric acid and the layers were separated.

The organic layer was dried over anhydrous magnesium sulphate and evaporated to dryness to give 17.1g of thick syrup. ^{1}H-NMR spectroscopy revealed a 91:9 mixture of **124a** and diethyl malonate, contaminated with small amounts of **124b** and **126**. The crude reaction mixture was purified by flash chromatography using 20% ethyl acetate in hexane to afford **124a** in >95% purity (13.6g, 80% yield).

Preparation of 2-(4-benzoylphenyl)propionic acid **129**:

Diethyl 2-(4-benzoylphenyl)malonate **124c** (0.5g, 1.5 mmol) was dissolved in 3ml toluene and NaO*t*Bu (0.21g, 2.2 mmol, 1.5eq) was added which caused an orange to red colour. The mixture was heated to 60^{o}C followed by the addition of dimethyl sulfate (0.28g, 2.2 mmol, 1.5eq). After heating the mixture at 90^{o}C for 15min the orange colour disappeared and became light yellow. Crude diethyl 2-(4-benzoylphenyl)-2-methylmalonate **129** was isolated after addition of water, extraction into diethyl ether and evaporation of the solvent. The unpurified product was used as is in the next reaction.

Diethyl 2-(4-benzoylphenyl)-2-methylmalonate 129: δ_H (200MHz; $CDCl_3$) 1.28 (6H, t, *J* 7.5, CH_3), 1.93 (3H, s, CH_3), 4.26 (4H, t, *J* 7.5, OCH_2), 7.42-7.85 (9H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) 14.1, 22.8, 59.1, 61.9, 127.8, 128.4, 129.1, 131.9, 132.2, 136.7, 137.7, 142.6, 171.0, 196.4; HRMS (EI): Exact mass calculated for $C_{21}H_{22}O_5$ $[M]^+$: 354.1467. Found: 354.1486.

Crude diethyl 2-(4-benzoylphenyl)-2-methylmalonate (**129**, ~1.5mmol) was dissolved in ethanol (4ml) and dilute NaOH (4ml, 80mg, 2 mmol) was added. After 10min of heating at 60^{o}C the hydrolysis was deemed complete (by tlc). The slow addition of dilute hydrochloric acid (10%) initiated gas evolution (final pH was 3). The resulting mixture was concentrated under reduced pressure (to remove ethanol) and was extracted with chloroform. Crude 2-(4-benzoylphenyl)propionic acid (**130**) was isolated as a light yellow oil (0.34g, 91% overall from **124b**).

2-(4-Benzoylphenyl)propionic acid 130: δ_H (200MHz; $CDCl_3$) 1.59 (3H, d, *J* 7.4, CH_3), 3.88 (1H, q, *J* 7.4, CH), 7.45-7.86 (9H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) 18.2, 45.6, 127.8, 129.2, 129.8, 132.3, 132.8, 136.7, 137.7, 141.6, 179.7, 196.4; ν_{max}(nujol)/cm^{-1} 2853 (COOH), 1696 (Ketone C=O), 1660 (Acid C=O), 1463 (Ar-C), 1274 and 1186 (C-C=O), 698 ($ArCH_2$); HRMS (EI): Exact mass calculated for $C_{16}H_{14}O_3$ $[M]^+$: 254.0943. Found: 254.0931; mp 98-99^{o}C.

Preparation of 3,3-dimethyl-1-phenyl-butan-2-one / benzyl *tert*-butyl ketone (**134**) by $Pd(OAc)_2$ catalysed arylation of pinacolone (**131**):

A screw capped pyrex tube (50ml) was charged with sodium *tert*-butoxide (0.63g, 6.5mmol), dry toluene (10ml, distilled from sodium), pinacolone **131** (0.6g, 6.0mmol), and bromobenzene (0.79g, 5 mmol). $Pd(OAc)_2$ (22.4mg, 0.1mmol, 2mol%) and 2-methoxynaphthalene (40mg, internal standard for GC analysis) was added and the tube was flushed with nitrogen. The mixture was heated to 110°C in a Robosynthon multireactor for 15 hours. The reaction was cooled and quenched by the addition of water and dilute hydrochloric acid and was diluted using diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and evaporated to a light-yellow oil (0.9g). The crude product was purified by flash column chromatography (10% ethyl acetate in hexane) to yield **134** as a pale yellow oil (0.64g, 73%) and **135** as white crystals(0.17g, 13%).

3,3-Dimethyl-1-phenyl-butan-2-one / benzyl *tert*-butyl ketone 134: NMR data in agreement with literature values[247] δ_H (200MHz; $CDCl_3$) 1.27 (9H, s, *t*-Bu), 3.86 (2H, s, CH_2Ph), 7.20-7.36 (5H, m, Ph-H).

3,3-Dimethyl-1,1-diphenyl-butan-2-one / diphenylmethyl *tert*-butyl ketone 135: NMR data in agreement with literature values[248] δ_H (200MHz; $CDCl_3$) 1.23 (9H, s, *t*-Bu), 5.65 (1H, s, $CHPh_2$), 7.20-7.36 (10H, m, Ph-H); mp 127.7°C (Lit. 123-126°C [249]).

Baeyer-Villiger oxidation of benzyl *tert*-butyl ketone 134:

Benzyl *tert*-butyl ketone (**134**) (1.7g, 10mmol) was dissolved in of chloroform (50ml). 3-Chloroperoxybenzoic acid (3.5g, ~50%, 10mmol) was added and the mixture heated to reflux using a Dean Stark apparatus (designed for return of solvents heavier than water) to collect water. Conversion of **134** was determined by GC analysis to be ~10%. More 3-chloroperoxybenzoic acid (2g, ~6mmol) was added and heating was continued for 16 hours. Conversion of **134** was 40% with the formation of *tert*-butyl phenylacetate (**136**) and benzyl 2,2-dimethylpropionate (**137**) in a 7:1 ratio. The reaction mixture was isolated by washing with saturated aqueous sodium hydrogen

carbonate and evaporation of the solvent. The crude product was determined to consist of 60% **134**, 35% **136** and 5% **137** by ^{1}H- NMR spectroscopy.

***tert*-Butyl phenylacetate 136**: NMR data in agreement with literature values[62] δ_H (200MHz; $CDCl_3$) 1.48 (9H, s, *t*-Bu), 3.56 (2H, s, CH_2Ph), 7.27-7.39 (5H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 28.2, 43.1, 81.4, 127.5, 128.6, 129.7, 135.2, 171.6.

Benzyl 2,2-dimethylpropionate 137: NMR data in agreement with literature values[250] δ_H (200MHz; $CDCl_3$) 1.29 (9H, s, *t*-Bu), 5.14 (2H, s, OCH_2Ph), 7.20-7.39 (5H, m, Ph-H); δ_C (50MHz; $CDCl_3$) 27.2, 38.8, 66.0, 127.6, 128.4×2, 136.4, 178.2.

6.3 Procedures Relating to Chapter 4

Palladium catalysed arylation of diethyl malonate to prepare diethyl (5-indolyl)-malonate (162a) and diethyl 2-[(*N*-*t*-butylcarboxy)-5-indolyl]malonate (162b):

Diethyl (5-indolyl)-malonate **162a**:

Into a screw capped pyrex tube (50ml) was weighed K_3PO_4 (2.44g, 11.5 mmol), diethyl malonate (0.96g, 6 mmol) and **161a** (0.92g, 5 mmol) as well as toluene (6ml, distilled from sodium). $Pd(OAc)_2$ (11.2mmg, 0.05 mmol, 1mol%) and **66a** (30mg, 0.1 mmol, 2mol%) and an accurately weighed amount of 2-methoxynaphthalene (internal standard) were dissolved in toluene (3ml), heated for 2 minutes at ~60^{o}C and added to the reaction mixture. The tube was flushed with nitrogen and sealed and heated at 110^{o}C in a Robosynthon multireactor for 15 hours. The amount of aryl halide, diethyl malonate and arylation product present was determined by GC analysis based on internal standard calculation. Isolation was done by addition of water and dilute hydrochloric acid to acidify the mixture followed by extraction into ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give 1.28g of a mixture brown oil and solids. The crude product was determined to contain **162a** (200mg), diethyl malonate (500mg) and indole (20mg) through analysis by GC (internal standard calculations) and ^{1}H-NMR spectroscopy.

Diethyl 2-(5-indolyl)malonate 162a: δ_H (200MHz; $CDCl_3$) 1.27 (6H, t, *J* 7.0, CH_3), 4.22 (4H, m, OCH_2), 4.74 (1H, s, CH), 6.54 (1H, m, Ar-H), 7.01 (1H, m, Ar-H), 7.21 (1H, m, Ar-H), 7.41 (1H, m, Ar-H), 7.61 (1H, m, Ar-H), 8.30 (1H, br, N-H); δ_C (50 MHz; $CDCl_3$) 14.3, 58.1, 61.9, 104.5, 115.5, 120.1, 123.4, 125.7, 126.7, 127.5, 135.1, 168.7; HRMS (EI): Exact mass calculated for $C_{15}H_{17}O_4N$ $[M]^+$: 265.1158. Found: 265.1154.

Preparation of *N*-*t*-butylcarboxy-5-bromoindole **161b**:

To a solution of 5-bromoindole **161a** (1.96g 10mmol) and di-*t*-butyl pyrocarbonate (2.6g, 12mmol) in dichloromethane (50ml) was added triethylamine (1.2g, 12mmol) and was stirred at room temperature for 1 hour. When the reaction was complete by tlc (20% ethyl acetate in hexane) the reaction mixture was treated with water (50ml) and acidified using dilute hydrochloric acid. The organic layer was washed with water (50ml) and evaporated to dryness to yield 3.0g of a brown oil which solidified on standing which was used further without purification.

***N*-*t*-butylcarboxy-5-bromoindole 161b**: δ_H (200MHz; $CDCl_3$) 1.71 (9H, s, *t*-Bu), 6.521 (1H, d, *J* 3.6, Ar-H), 7.40 (1H, dd, *J* 8.8 and 1.6, Ar-H), 7.59 (1H, d, *J* 3.6, Ar-H), 7.69 (1H, d, *J* 1.6, Ar-H), 8.03 (1H, d, *J* 8.8, Ar-H); δ_C (50 MHz; $CDCl_3$) 28.4, 84.3, 106.7, 116.2, 116.8, 123.7, 127.2, 132.5, 134.2, 149.6; Exact mass calculated for $C_{13}H_{14}O_2NBr$ $[M]^+$: 295.0208. Found: 295.0207; mp 55.6^oC

Diethyl 2-[(*N*-*t*-butylcarboxy)-5-indolyl]malonate **162b**:

162b was prepared using the same reaction conditions as described above by using **161b** (1.5g, 5 mmol). The crude product was a light brown oil which solidified on standing and was determined to contain **162b** (1.31g), diethyl malonate (280mg) and 5-bromoindole **161a** (330mg) through analysis by GC (internal standard calculations) and ^{1}H-NMR spectroscopy.

Diethyl 2-[(*N*-*t*-butylcarboxy)-5-indolyl]malonate 162b: δ_H (200MHz; $CDCl_3$) 1.27 (6H, t, *J* 7.0, CH_3), 1.68 (9H, s, *t*-Bu), 4.22 (4H, m, OCH_2), 4.71 (1H, s, CH), 6.56 (1H, m, Ar-H), 7.36 (1H, m, Ar-H), 7.61 (1H, m, Ar-H), 7.62 (1H, m, Ar-H), 8.13 (1H, d, *J* 8.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 14.3, 28.4, 58.1, 61.9, 84.0, 107.5, 115.5, 122.0,

125.5, 126.7, 127.5, 131.0, 135.1, 149.8, 168.7; ν_{max}(nujol)/cm^{-1} 1746 and 1720 (C=O), 1340 (IndoleC-NH-C), 1255 ($CHCO_2Et$), 1163, 1082 and 1034 (C-O), 765 (Ar-CH); HRMS (EI): Exact mass calculated for $C_{20}H_{25}O_2N$ $[M]^+$: 365.1682. Found: 375.1680; mp 76-78^oC.

Preparation of methyl-2-[(methylamino)sulfonyl]acetate **157a**:

To a solution of methylthioglycolate **164** (10g, 94mmol) in dichloromethane (57ml) was added ice (34.6g). Chlorine gas (380mmol generated by slow addition of 32% hydrochloric acid to potassium permangenate) was slowly bubbled through the stirred solution that was kept below 5°C by external cooling. The chlorine bubbling was continued for 2 hours until the solution had a persistent yellow/green colour. The aqueous layer was removed and the organic layer was purged with nitrogen to remove dissolved chlorine. The organic layer was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give methyl 2-(chlorosulfonyl)acetate (**165**) as an oily, yellow liquid (13.9g, 80% yield), NMR data is agreement with literature values[190].

To a solution of methyl 2-(chlorosulfonyl)acetate **165** (2,4g, 14mmol), in tetrahydrofuran (15ml) at 5°C was added, a solution of methylamine in tetrahydrofuran (14ml of a 2M solution) over 30 min maintaining the temperature between 5 and 10°C. The resulting white suspension was stirred for 30min at room temperature before addition of water (25ml) and ethyl acetate (25ml). The aqueous layer was washed with ethyl acetate and the combined organic layers dried over anhydrous magnesium sulfate and evaporated to give methyl 2-[(methylamino)sulfonyl]acetate (**157a**) as an orange oily liquid (1.2g, 51% yield).

Methyl 2-[(methylamino)sulfonyl]acetate 157a: ^{1}H-NMR data in agreement with literature values[190] δ_H (200MHz; $CDCl_3$) 2.87 (3H, s, N-CH_3), 3.81 (3H, s, OCH_3), 4.01 (2H, s, CH_2), 4.68 (1H, br, NH).

Preparation of methyl 2-[(benzylmethylamino)sulfonyl]acetate **157b**:

A solution of methyl 2-(chlorosulfonyl)acetate **165** (2,1g, 12mmol) in THF (10ml) was cooled in an ice-bath. A solution of benzylmethylamine (2.95g, 24mmol) in THF was added over 20min maintaining the temperature below 10°C. The mixture was stirred at room temperature for 30min. Brine and ether were added and the organic layer dried over anhydrous magnesium sulfate and evaporated to 2.7g of a yellow oil. The product was contaminated with benzylmethylamine that was removed by leaving under strong vacuum. The product was a yellow syrup (2.35g, 76% yield).

Methyl 2-[(benzylmethylamino)sulfonyl]acetate 157b: ^{1}H-NMR data in agreement with literature values[251] δ_H (200MHz; $CDCl_3$) 2.87 (3H, s, N-CH_3), 3.83 (3H, s, OCH_3), 4.03 (2H, s, CH_2), 4.40 (2H, s, CH_2Ph), 7.32-7.43 (5H, m, Ar-H).

Preparation of 2-[(Benzylmethylamino)sulfonyl]acetonitrile **150a** from **157b**:

To a solution of methyl 2-[(benzylmethylamino)sulfonyl]acetate (**157b**, 10.0g, 39mmol) in THF (10ml) was added aqueous ammonia solution (25%m/V, 30ml) at ambient temperature. After stirring for 18 hours a white solid had precipitated. Concentration of reaction mixture under reduced pressure led to precipitation of more white solids. The solids were filtered off and dried under vacuum (7.0g) and was used without further purification in the next step.

To a cold (5^{o}C) solution of DMF (1.7ml) in THF (35ml) was added thionyl chloride (2.5g, 1.5ml, 20.7mmol). A solution of the above product (5g, 20.6mmol) in THF (20ml) was added and the mixture heated to reflux (66^{o}C) for 30min. Analysis by tlc still showed the presence of starting material. More thionyl chloride (0.5g) was added and the mixture was stirred overnight at ambient temperature. Analysis by tlc confirmed the absence of starting material. Pyridine (3.1g, 39.5mmol) was added followed by water (50ml). The mixture was extracted with ethyl acetate (3×50ml) and the combined organic extracts were evaporated to an oily product which crystallized upon cooling (5.3g, 61% yield).

2-[(Benzylmethylamino)sulfonyl]acetonitrile 150a: δ_H (200MHz; $CDCl_3$) 2.99 (3H, s, N-CH_3), 3.97 (2H, s, CH_2), 4.54 (2H, s, CH_2Ph), 7.36-7.44 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 35.6, 39.9, 55.1, 111.6, 128.2, 128.7, 129.6, 134.7; ν_{max}(nujol)/cm^{-1} 2266 (C≡N), 1340 (SO_2N), 1152 (CH_2SO_2), 982 and 916 (CNCH_2S), 789, 750, 728 and 702 (Ar-CH_2); HRMS (EI): Exact mass calculated for $C_{10}H_{12}O_2N_2S$ $[M]^+$: 224.0620. Found: 224.0606; mp 73-74^{o}C.

General procedure for the palladium catalysed arylation reaction of 2-[(benzylmethylamino)sulfonyl]acetonitrile (150a):

A screw capped pyrex tube (50ml) was charged with sodium *tert*-butoxide (0.34g, 3.5 mmol), aryl halide (2.0mmol), **150a** (0.54g, 2.4 mmol) and dry toluene (10ml, distilled from sodium). The tube was flushed with nitrogen and a warmed suspension (60°C, 1min) of $Pd(OAc)_2$ (36mg, 0.16mmol, 8mol%) and triphenylphosphine (120mg, 0.46mmol, 23mol%) and an accurately weighed amount of 2-methoxynaphthalene (internal standard) and toluene (3ml) was added. The tube was again flushed with nitrogen and sealed. The mixture was heated to 110°C in a Robosynthon multireactor for 15-20 hours. Conversion of starting materials and formation of products were measured based on internal standard calculations. The reaction was quenched by the addition of water and was diluted using ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford the crude product. The crude product was purified using column chromatography (10-20% ethyl acetate, 80-90% hexane).

1-Cyano-1-phenyl-*N*-benzyl-*N*-methyl-methanesulfonamide (**151a)** was prepared in 65% yield from iodobenzene, in 42% isolated yield from bromobenzene and in 81% by from bromobenzene using $Pd(OAc)_2$ / P*t*Bu_3. When using K_3PO_4 (1.0g, 4.7 mmol, 2.3 eqiuvalents), the addition of DMA (1ml) was required and yielded **151a** in 41% from iodobenzene.

1-Cyano-1-phenyl-*N*-benzyl-*N*-methyl-methanesulfonamide 151a: (Found: M^+, 224, $C_{16}H_{16}SO_2N_2$ requires 224); δ_H (200MHz; $CDCl_3$) 2.79 (3H, s, N-CH_3), 4.28 (2H, s, CH_2Ph), 5.14 (1H, s, CH), 7.31-7.44 (5H, m, Ar-H), 7.48-7.53 (2H, m, Ar-H), 7.54-7.63 (3H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 35.9, 55.3, 59.0, 114.1, 128.4×2, 128.7, 128.9, 129.4, 129.6, 130.5, 134.9; ν_{max}(nujol)/cm^{-1} 2312 (C≡N), 1353 (SO_2N), 1151 (CH_2SO_2), 982 and 916 (CNC*H*Ph), 781, 734 and 712 (Ar-CH_2); HRMS (EI): Exact mass calculated for $C_{16}H_{16}O_2N_2S$ $[M]^+$: 300.0933. Found: 300.0934.

Preparation of *N*-benzyl-5-bromoindole **161c**:

To a solution of 5-bromoindole **161a** (1.96g 10mmol) in THF (20ml) was added sodium hydride (0.44g of a 60% dispersion in mineral oil, 11mmol). After evolution of hydrogen ceased, benzyl bromide (1.83g, 11mmol) in THF (10ml) was added drop-wise. After stirring at room temperature for 1 hour analysis by GC showed product and un-reacted starting materials. Sodium hydride (0.1g) was added and stirred another 30min. GC analysis showed only 2% of 5-bromoindole. The mixture was quenched by addition of water and diluted hydrochloric acid to make the suspension slightly acidic. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate. 2.5g of an orange coloured oil was recovered after removal of volatiles. The product solidified on standing. GC showed impurities totaling 17%. The product was purified by column chromatography (33% ethyl acetate, 66% hexane) to give **161c** as a yellow solid (2.1g, 73% yield).

***N*-benzyl-5-bromoindole 161c**: NMR data in agreement with literature values[252]: δ_H (200MHz; $CDCl_3$) 5.33 (2H, s, CH_2Ph), 6.54 (1H, m, Ar-H), 7.08-7.20 (5H, m, Ar-H), 7.26-7.39 (3H, m, Ar-H), 7.82 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 50.5, 101.5, 111.4, 122.1, 123.7, 124.7, 126.9, 128.0, 128.6, 128.8, 129.0, 129.6, 137.2.

2-(*N*-benzyl-5-indolyl)-2-[(benzylmethylamino)sulfonyl]acetonitrile (**151b**) was prepared from **161c** (0.57g, 2.0 mmol) and 2-[(benzylmethylamino)sulfonyl]-acetonitrile (**150a**) by following the above general procedure for palladium catalysed arylation of **150a**.

2-(*N*-benzyl-5-indolyl)-2-[(benzylmethylamino)sulfonyl]acetonitrile / 1-(*N*-benzyl-5-indolyl)-1-cyano-*N*-benzyl-*N*-methyl-methanesulfonamide 151b: δ_H (200MHz; $CDCl_3$) 2.73 (3H, s, N-CH_3), 4.22 (2H, s, CH_2Ph), 5.23 (1H, s, CH), 5.38 (1H, s, CH_2Ph), 6.65 (1H, m, Ar-H), 7.08-7.14 (3H, m, Ar-H), 7.25-7.43 (10H, m, Ar-H), 7.86 (1H, s, Ar-H).

General procedure for the preparation of methanesulfonamides (154):

To ice cold solution of methanesulfonylchloride (4.0ml, 5.7g, 50mmol) in THF (15ml) was added the appropriate secondary amine (105mmol) in THF (20ml). The temperature was maintained below 10°C during the addition. Due to the formation of a thick white suspension, more THF (20ml) had to be added. The suspension was allowed to warm to room temperature and stirred a further 30min. The reaction was diluted with diethyl ether and brine was added. The brine layer was washed with ether and the combined organics dried over anhydrous magnesium sulfate and evaporated to dryness. In most cases the crude product so obtained was pure enough (as judged by GC analysis and ^{1}H-NMR spectroscopy) to be used without further purification.

***N*-methyl methanesulfonamide 154a**: NMR data in agreement with literature values[253] δ_H (200MHz; $CDCl_3$) 2.74 (3H, s, CH_3), 2.88 (3H, s, CH_3N), 5.70 (1H, broad s, NH); δ_C (50 MHz; $CDCl_3$) 29.5, 38.7.

***N,N*-dimethyl methanesulfonamide 154b**: NMR data in agreement with literature values[254] δ_H (200MHz; $CDCl_3$) 2.72 (3H, s, CH_3), 2.82 (6H, s, CH_3N); mp 48-49^{o}C (Lit 49-50^{o}C[255]).

***N*-benzyl-*N*-methyl methanesulfonamide 154c**: NMR data in agreement with literature values[256] δ_H (200MHz; $CDCl_3$) 2.77 (3H, s, CH_3), 2.83 (3H, s, N-CH_3), 4.31 (2H, s, CH_2Ph), 7.32-7.38 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 34.5, 36.3, 54.2, 128.3, 128.6, 129.0, 130.3.

1-methanesulfonyl-pyrrolidine 154d: NMR data in agreement with literature values [257] δ_H (200MHz; $CDCl_3$) 1.94 (4H, m, CH_2), 2.82 (3H, s, CH_3), 3.33 (4H, m, CH_2N); δ_C (50 MHz; $CDCl_3$) 25.9, 34.7, 48.1; mp 62-63°C (Lit. 68-68.5°C[258]).

***N,N*-diisopropyl methanesulfonamide 154e**: NMR data in agreement with literature values[259] δ_H (200MHz; $CDCl_3$) 1.37 (12H, d, *J* 6.8, CH_3), 2.87 (3H, s, CH_3), 3.78 (2H, sept, *J* 6.8, CH); δ_C (50 MHz; $CDCl_3$) 22.1, 42.3, 48.6; mp 66-67°C (Lit.[259] 72-73°C).

4-methanesulfonyl-morpholine 154f: NMR data in agreement with literature values[260] δ_H (200MHz; $CDCl_3$) 2.81 (3H, s, CH_3), 3.23 (4H, m , CH_2N), 3.80 (4H, m, CH_2O); δ_C (50 MHz; $CDCl_3$) 34.1, 46.0, 66.4; mp 85-86°C (Lit. 91-93°C[260]).

***N*-methyl-*N*-phenyl methanesulfonamide 154g**: NMR data in agreement with literature values[261] δ_H (200MHz; $CDCl_3$) 2.88 (3H, s, CH_3), 3.37 (3H, s, CH_3N), 7.26-7.50 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 35.3, 38.2, 126.3, 127.5, 129.4, 141.5; Exact mass calculated for $C_8H_{11}O_2NS$ $[M]^+$: 185.0511. Found: 185.0512; mp 73-74°C (Lit. 77-78°C[262]).

General experimental experimental procedure for the palladium catalysed arylation reaction of methanesulfonamides:

A screw capped pyrex tube (50ml) was charged with sodium *tert*-butoxide (0.34g, 3.5mmol), aryl bromide (2.0mmol), methanesulfonamide (2.2mmol) and dry toluene (10ml, distilled from sodium). The tube was flushed with nitrogen and a warmed suspension (60°C, 1min) of $Pd(OAc)_2$ (36mg, 0.16mmol, 8mol%) and triphenylphosphine (120mg, 0.46mmol, 23mol%) and an accurately weighed amount of 2-methoxynaphthalene (internal standard) and toluene (3ml) was added. The tube was again flushed with nitrogen and sealed. The mixture was heated to 110°C in a Robosynthon multireactor for 20 hours. Conversion of starting materials and formation of products were measured based on internal standard calculations. The reaction was quenched by the addition of water and was diluted using ethyl acetate.

The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford the crude product. The crude product was purified using column chromatography (10-20% ethyl acetate, 80-90% hexane).

N-benzyl-*N*-methyl phenylmethanesulfonamide (**155a**) was prepared in the reaction between *N*-benzyl-*N*-methyl methanesulfonamide **(154c**) and bromobenzene. The crude product was isolated as a yellow oil (0.64g). A pure fraction of **155a** (0.33g, 59%) was recovered after flash column chromatography (20% ethyl acetate, 80% hexane). **155a** was also prepared in 28% yield by using P*t*Bu_3 as ligand.

***N*-benzyl-*N*-methyl phenylmethanesulfonamide 155a** [263]: δ_H (200MHz; $CDCl_3$) 2.64 (3H, s, N-CH_3), 4.09 (2H, s, CH_2Ph), 4.32 (2H, s, NCH_2Ph), 7.26-7.53 (10H, m, Ar-H).

155b was prepared in the reaction between *N*-benzyl-*N*-methyl methanesulfonamide (**154c**) and *N*-benzyl-5-bromoindole (**161c**). The crude product was isolated as a brown oil (1.17g). A pure fraction of **155b** (0.31g, 38%) was recovered after flash column chromatography (20% ethyl acetate, 80% hexane). **155b** was also prepared in 15% yield by using P*t*Bu_3 as ligand.

***N*-benzyl-*N*-methyl (5-*N*-benzylindole)methanesulfonamide 155b**: δ_H (200MHz; $CDCl_3$) 2.61 (3H, s, N-CH_3), 4.06 (2H, s, CH_2Ph), 4.43 (2H, s, NCH_2Ph), 5.37 (2H, s, (indole)NCH_2Ph), 6.58 (1H, d, *J* 2.8, Ar-H), 7.08-7.15 (2H, m, Ar-H), 7.17-7.22 (2H, m, Ar-H), 7.23-7.37 (9H, m, Ar-H), 7.64 (1H, s, Ar-H); δ_C (50 MHz; $CDCl_3$) 34.9, 50.5, 54.4, 58.1, 102.2, 110.2, 120.1, 123.6, 124.4, 126.9, 128.0, 128.5, 128.7, 129.0, 129.4, 130.4, 136.4, 137.4, 138.5; ν_{max}(nujol)/cm^{-1} 1705 (S=O), 1595 and 1327 (SO_2N), 1149 (CH_2SO_2), 719 (Ar-CH_2). HRMS (EI): Exact mass calculated for $C_{24}H_{24}O_2N_2S$ $[M]^+$: 404.1558. Found: 404.1549.

155c was prepared in the reaction between 1-methanesulfonyl-pyrrolidine (**154d**) and *N*-benzyl-5-bromoindole (**161c**). The crude product was isolated as a brown oil (0.85g). A fraction was collected which contained **154d** and **155c** was recovered after flash column chromatography (20% ethyl acetate, 80% hexane) as well as a fraction containing *N*-benzylindole (**170**).

(5-*N*-benzylindole)-methanesulfonyl-pyrrolidine 155c: ν_{max}(neat)/cm^{-1} 2871 (Ar-H), 1715 and 1606 (S=O), 1494, 1455 and 1328 (SO_2N), 1151 (CH_2SO_2), 959 (CH_2S), 778, and 729 (Ar-CH_2); HRMS (EI): Exact mass calculated for $C_{20}H_{22}O_2N_2S$ $[M]^+$: 354.1402. Found: 354.1414.

1-Phenylmethanesulfonyl-pyrrolidine 155d: NMR data in agreement with literature values[257]; δ_H (200MHz; $CDCl_3$) 1.69 (4H, m, CH_2), 3.04 (4H, m, CH_2N), 4.12 (2H, s, CH_2Ph), 7.14-7.31 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 26.0, 48.3, 56.6, 128.7, 128.8, 129.6, 130.8; mp 92.8^{o}C (Lit. 93-94^{o}C[264]).

Diphenylmethanesulfonyl-pyrrolidine 155dd: δ_H (200MHz; $CDCl_3$) 1.72 (4H, m, CH_2), 3.13 (4H, m, CH_2N), 5.25 (1H, s, $CHPh_2$), 7.33-7.46 (6H, m, Ar-H), 7.64-7.72 (4H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 25.7, 48.3, 71.9, 128.3, 128.6, 129.5, 134.7; mp 166-168^{o}C (Lit. 175-177^{o}C[264]).

***N,N*-diisopropyl phenylmethanesulfonamide 155e**: δ_H (200MHz; $CDCl_3$) 1.23 (12H, d, *J* 6.8, CH_3), 3.68 (2H, sept, *J* 6.8, CH), 4.19 (2H, s, CH_2Ph), 7.31-7.47 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.6, 49.1, 61.2, 128.6, 128.7, 128.8, 131.0; ν_{max}(neat)/cm^{-1} 2932 (Ar-H), 1728 (S=O), 1494 and 1329 (SO_2N), 1122 (CH_2SO_2), 976 (CH_2S), 702 (Ar-CH_2). HRMS (EI): Exact mass calculated for $C_{13}H_{21}O_2NS$ $[M]^+$: 255.1293. Found: 255.1294.

***N,N*-diisopropyl diphenylmethanesulfonamide 155ee**; δ_H (200MHz; $CDCl_3$) 1.11 (12H, d, *J* 6.8, CH_3), 3.59 (2H, sept, *J* 6.8 ,CH), 5.22 (1H, s, $CHPh_2$), 7.28-7.42 (6H, m, Ar-H), 7.62-7.73 (4H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.8, 49.9, 76.8, 128.5, 128.9, 130.0, 135.5.

4-phenylmethanesulfonyl-morpholine 155f: NMR data in agreement with literature values[265] δ_H (200MHz; $CDCl_3$) 3.12 (4H, m, CH_2N), 3.63 (4H, m, CH_2O), 4.25 (2H, s, CH_2Ph), 7.33-7.51 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 46.3, 57.0, 66.9, 128.9, 129.0, 130.9; mp 170.9^{o}C (Lit. 174-176^{o}C[264]).

***N*-morpholine diphenylmethanesulfonamide 155ff**: δ_H (200MHz; $CDCl_3$) 3.04 (4H, m, CH_2N), 3.54 (4H, m, CH_2O), 5.32 (1H, s, $CHPh_2$), 7.37-7.44 (6H, m, Ar-H), 7.64-7.75 (4H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 46.3, 57.0, 79.8, 128.9, 129.0, 130.4, 135.8. Structure proposed based on downfield shifts in the ^{1}H and ^{13}C-NMR spectra (compared to **155f**) for the CH adjacent to the sulfonamide group, material not isolated due to minor quantities produced.

***N*-methyl-*N*-phenyl-*C*-phenylmethanesulfonamide 155g** [264]: Exact mass calculated for $C_{14}H_{15}O_2NS$ $[M]^+$: 261.08235. Found: 261.08131.

***N,N*-diisopropyl (1-naphthyl)methanesulfonamide 155h**: δ_H (200MHz; $CDCl_3$) 1.32 (12H, d, *J* 6.8, CH_3), 3.74 (2H, sept, *J* 6.8,CH), 4.68 (2H, s, CH_2Ar), 7.45-7.66 (4H, m, Ar-H), 7.88 (2H, t, *J* 7.7, Ar-H), 8.20 (1H, d, *J* 8.4, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.7, 49.1, 58.4, 124.5, 125.4, 126.1, 126.8, 128.9, 129.6, 130.6, 131.6, 132.5; Exact mass calculated for $C_{17}H_{23}O_2NS$ $[M]^+$: 305.1450. Found: 305.1452.

***N,N*-diisopropyl di-(1-naphthyl)methanesulfonamide 155hh**: δ_H (200MHz; $CDCl_3$) 1.11 (12H, d, *J* 6.8, CH_3), 3.68 (2H, sept, *J* 6.8, CH), 7.19 (1H, s, $CHAr_2$), 7.45-7.66 (6H, m, Ar-H), 8.20 (4H, d, *J* 8.4, Ar-H), 8.36 (2H, d, *J* 8.6, Ar-H), 8.46 (2H, d, *J* 7.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.7, 50.0, 64.4, 122.7, 125.3, 125.6, 127.0, 128.4, 129.0, 129.4, 131.0, 132.0, 134.1. Structure proposed based on downfield shifts in the ^{1}H and ^{13}C-NMR spectra (compared to **155h**) for the CH adjacent to the sulfonamide group, material not isolated due to minor quantities produced.

***N,N*-diisopropyl (2-methylphenyl)methanesulfonamide 155i**: δ_H (200MHz; $CDCl_3$) 1.34 (12H, d, *J* 7.0, CH_3), 2.49 (3H, s, CH_3), 3.79 (2H, sept, *J* 7.0, CH), 4.20 (2H, s, CH_2Ar), 7.18-7.28 (3H, m, Ar-H), 7.33-7.41 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 19.8, 22.4, 48.7, 58.4, 125.9, 128.0, 128.4, 130.6, 131.9, 138.0; ν_{max}(nujol)/cm^{-1} 1461 and 1321 (SO_2N), 1121 (CH_2SO_2), 980 (CH_2S), 782, 758 and 712 (Ar-CH_2).Exact mass calculated for $C_{14}H_{23}O_2NS$ $[M]^+$: 269.1450. Found: 269.1431.

***N,N*-diisopropyl di-(2-methylphenyl)methanesulfonamide 155ii**: δ_H (200MHz; $CDCl_3$) 1.14 (12H, d, *J* 6.8, CH_3), 2.54 (6H, s, CH_3), 3.69 (2H, sept, *J* 6.8, CH), 5.86 (1H, s, $CHAr_2$), 7.13-7.26 (6H, m, Ar-H), 8.08 (2H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 20.6, 22.6, 49.9, 67.0, 126.3, 128.1, 129.9, 130.8, 133.3, 137.1. Structure proposed based on downfield shifts in the ^{1}H and ^{13}C-NMR spectra (compared to **155i**) for the CH adjacent to the sulfonamide group, material not isolated due to minor quantities produced.

***N,N*-diisopropyl (4-methoxyphenyl)methanesulfonamide 155j**: δ_H (200MHz; $CDCl_3$) 1.23 (12H, d, *J* 6.8, CH_3), 3.66 (2H, sept, *J* 6.8, CH), 3.84 (3H, s, OCH_3), 4.12 (2H, s, CH_2Ar), 6.94 (2H, d, *J* 8.6, Ar-H), 7.35 (2H, d, *J* 8.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.4, 48.8, 55.2, 60.3, 113.9, 121.7, 131.8, 159.7; Exact mass calculated for $C_{14}H_{23}O_3NS$ $[M]^+$: 285. 1399. Found: 285.1410.

***N,N*-diisopropyl di-(4-methoxyphenyl)methanesulfonamide 155jj**: δ_H (200MHz; $CDCl_3$) 1.12 (6H, d, *J* 6.8, CH_3), 1.14 (6H, d, *J* 6.8, CH_3), 3.63 (2H, sept, CH), 3.81 (6H, s, OCH_3), 5.19 (1H, s, CH), 6.90 (4H, d, *J* 8.6, Ar-H), 7.59 (4H, d, *J* 8.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 22.7, 48.8, 55.6, 72.9, 117.5, 129.1, 132.1, 159.8. Structure proposed based on downfield shifts in the ^{1}H and ^{13}C-NMR spectra (compared to **155j**) for the CH adjacent to the sulfonamide group, material not isolated due to minor quantities produced.

***N,N*-dimethyl phenylmethanesulfonamide 155k**: NMR data in agreement with literature values[266] δ_H (200MHz; $CDCl_3$) 2.72 (6H, s, CH_3), 4.26 (2H, s, CH_2), 7.35-7.46 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 38.0, 56.2, 128.8, 128.9, 130.8, quaternary carbon not detected; ν_{max}(nujol)/cm^{-1} 1741 (S=O), 1336 and 1187 (SO_2N), 1154 (CH_2SO_2), 706 (Ar-CH_2); Exact mass calculated for $C_9H_{13}O_2NS$ $[M]^+$: 199.0667. Found: 199.0680; mp 94-95^{o}C (Lit 100-101^{o}C[255]).

Ethanesulfonamides *N*-benzyl-*N*-methyl ethanesulfonamide (**175a**) and 1-ethanesulfonyl-pyrrolidine (**175b**) as well as α-toluenesulfonamide (**155d**) were prepared using the general procedure for the preparation of methanesulfonamides (**154**) (as described above).

175a was prepared from ethanesulfonyl chloride and *N*-methylbenzylamine in 95% yield.

***N*-benzyl-*N*-methyl ethanesulfonamide 175a**: δ_H (200MHz; $CDCl_3$) 1.41 (3H, t, *J* 7.6, CH_3), 2.80 (3H, s, CH_3N), 3.06 (2H, q, *J* 7.6, CH_2), 4.39 (2H, s, CH_2Ph), 7.30-7.44 (5H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 8.3, 34.6, 45.2, 54.2, 128.2, 128.5, 128.9, 136.3; ν_{max}(neat)/cm^{-1} 2942 (Ar-H), 1495 and 1328 (SO_2N), 1150 (CH_2SO_2), 993 and 942 (CH_2S), 778, 791 and 742 (Ar-CH_2); Exact mass calculated for $C_{10}H_{15}O_2NS$ $[M]^+$: 213.0824. Found: 213.0830.

175b was prepared from ethanesulfonyl chloride and pyrrolidine in 98% yield.

1-Ethanesulfonyl-pyrrolidine 175b [267]: δ_H (200MHz; $CDCl_3$) 1.33 (3H, t, *J* 7.3, CH_3), 1.90 (4H, m, CH_2), 2.97 (2H, q, *J* 7.3, CH_2), 3.33 (4H, m, CH_2N); δ_C (50 MHz; $CDCl_3$) 8.2, 26.1, 44.3, 48.0; Exact mass calculated for $C_6H_{13}O_2NS$ $[M]^+$: 163.0667. Found: 163.0655.

Preparation of *N*-(2-bromophenyl)-*N*-methylmethanesulfonamide **179a**:

2-Bromoaniline **177** (3.4g, 20 mmol) in THF (10ml) was added dropwise to a stirred solution of methanesulfonyl chloride (1.15g, 10 mmol) in THF (20ml). The resulting solution was refluxed for 16 hours where after it was cooled and diluted with diethyl ether (50ml) which resulted in the formation of a white precipitate. After filtration of the precipitate the solvent was evaporated *in vacuo*. The residue was diluted using diethyl ether (50ml) and hexane was added until a cloudy solution was formed. Extraction with dilute hydrochloric acid (5%m/V, 3×50ml), drying over anhydrous $MgSO_4$ and evaporation of the solvent afforded a yellow oil (1.94g **178**, 78% yield).

***N*-(2-bromophenyl)methanesulfonamide 178**: NMR data in agreement with literature values [268] δ_H (200MHz; $CDCl_3$) 2.94 (3H, s, CH_3), 7.01 (1H, dt, *J* 7.8 and 1.6, Ar-H), 7.26 (1H, dt, *J* 7.8 and 1.6, Ar-H), 7.30 (1H, broad s, N-H), 7.51 (1H, dd, *J* 7.8 and 1.6,

Ar-H), 7.55 (1H, dd, *J* 7.8 and 1.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 40.4, 116.7, 124.1, 127.1, 129.0, 133.2, 135.2; ν_{max}(nujol)/cm^{-1} 3298 (N-H), 1462 and 1325 (SO_2N), 1277 (Ar-N), 1152 (CH_2SO_2), 979 (CH_2S), 746 (Ar-CH_2); Exact mass calculated for $C_7H_8O_2NSBr$ $[M]^+$: 248.9459. Found: 248.9458; mp 77-78°C (Lit. 76-77°C[268]).

To a cold (-5°C) solution of **178** (1.5g, 6 mmol) in THF (10ml) was added NaH (60% in mineral oil, 0.40g, 10 mmol). The mixture was allowed to reach room temparature where after it was cooled to –5°C. MeI (1.7g, 12 mmol) in THF (5ml) was added and the mixture was allowed to warm to room temperature. Analysis of the reaction mixture by tlc and GC revealed mainly **178**. The reaction mixture was heated to 60°C for 1hour during which more MeI was added (1.4g, 10 mmol). After cooling to room temperature the reaction mixture was treated with diethyl ether and water. The organic layer was washed with brine and then concentrated to a brown oil. The crude product was treated with hot hexane (10ml, to remove mineral oil) to yield a brown oil (1.15g) which was recrystallised from ethyl acetate and hexane to afford light yellow crystals, *N*-(2-bromophenyl)-*N*-methylmethanesulfonamide (**179a**, 0.95g, 60% yield).

***N*-(2-bromophenyl)-*N*-methylmethanesulfonamide 179a**: δ_H (200MHz; $CDCl_3$) 3.08 (3H, s, CH_3), 3.30 (3H, s, CH_3N), 7.25 (1H, dt, *J* 7.6 and 1.6, Ar-H), 7.39 (1H, dt, *J* 7.8 and 1.6, Ar-H), 7.52 (1H, dd, *J* 7.8 and 1.6, Ar-H), 7.68 (1H, dd, *J* 7.8 and 1.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 38.1, 39.9, 123.8, 128.6, 130.0, 132.1, 133.8, 139.7; ν_{max}(nujol)/cm^{-1} 1461 and 1339 (SO_2N), 1149 (CH_2SO_2), 1149 and 1027 (CH_2S), 890, 773, 730 and 696 (Ar-CH_2); HRMS (EI): Exact mass calculated for $C_8H_{10}O_2NS$ $[M]^+$: 262.9616. Found: 262.9612; mp 68-69°C.

N-benzyl-*N*-(2-bromophenyl)methanesulfonamide (**179b**) was prepared in 22% yield as a yellow oil following the above procedure from *N*-(2-bromophenyl)methanesulfonamide (**178**, 2.0g, 8 mmol) and benzyl bromide (2.0g, 12.7 mmol).

***N*-benzyl-*N*-(2-bromophenyl)methanesulfonamide 179b**: δ_H (200MHz; $CDCl_3$) 3.09 (3H, s, CH_3), 4.60 (1H, d, *J* 14.4, CH_2Ph), 5.13 (1H, d, *J* 14.4, CH_2Ph), 7.07-7.15 (1H, m, Ar-H), 7.16-7.23 (2H, m, Ar-H), 7.29 (5H, s, Ar-H), 7.62-7.69 (1H, m, Ar-H); δ_C

(50 MHz; $CDCl_3$) 41.4, 54.3, 124.1, 127.9, 128.0, 128.4, 129.2, 130.0, 133.8, 134.3, 135.7, 137.1; mp 71-72^oC

Preparation of *N*-[(2-bromobenzyl)-methyl]-*N*-methylmethanesulfonamide **185**:

A solution of 2-bromobenzyl bromide (**183**, 5g, 20 mmol) in THF (20ml) was added to a solution of methylamine in ethanol (5ml of a 33% in ethanol, ~40 mmol). After stirring for 30min a white precipitate had formed while analysis by GC revealed incomplete conversion of **183**. After addition of methylamine solution (1ml) and stirring for 30min the reaction was complete. Filtration of the precipitate followed by partitioning the filtrate between ether and brine and concentration of the organic layer afforded crude *N*-methyl-(2-bromobenzyl)amine (**184**, 3.3g, 82% yield). The crude **184** was dissolved in THF (20ml) and slowly added to a cold solution (~5^oC) of methanesulfonyl chloride (1.0g, 8.7 mmol) in THF (10ml). After stirring for 30min the reaction mixture was filtered and evaporated to dryness. Partitioning between ether and brine, drying and evaporation afforded **185** as a yellow oil (2.1g, 87% yield).

***N*-[(2-bromobenzyl)-methyl]-*N*-methylmethanesulfonamide 185**: δ_H (200MHz; $CDCl_3$) 2.87 (3H, s, CH_3), 2.92 (3H, s, CH_3N), 4.48 (2H, s, NCH_2Ar), 7.20 (1H, t, *J* 7.2, Ar-H), 7.38 (1H, t, *J* 7.6, Ar-H), 7.52 (1H, d, *J* 7.2, Ar-H), 7.59 (1H, t, *J* 7.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 35.1, 36.5, 53.6, 123.7, 128.2, 129.6, 130.0, 133.1, 135.2; ν_{max}(neat)/cm^{-1} 2922 and 2854 (Ar-H), 1455 and 1320 (SO_2N), 1141 (CH_2SO_2), 1027, 1008 and 955 (CH_2S), 791 and 754 (Ar-CH_2); Exact mass calculated for $C_9H_{12}O_2NSBr$ $[M]^+$: 276.9772. Found: 276.9756; mp 59.9^oC.

Preparation of 2,2'-dibromobiphenyl **189**: [199]

A solution of 1,2-dibromobenzene (11.8g, 50 mmol) in dry THF (100ml) was cooled to –80^oC. *n*-BuLi (25ml of a 1.0M solution in hexane) was added dropwise by syringe while maintaining the reaction mixture temperature below –60^oC. The stirred reaction mixture was allowed to warm up to 0^oC upon which dilute hydrochloric acid (20ml, 5% m/V) was added carefully. The aqueous layer was washed with diethyl ether (3x20ml) and the organic extracts were combined with the THF layer. The solvent was

removed *in vacuo* to ~10g of a yellow residue which was crystallised from ether and ethanol to afford **189** as white crystals (3.4g, 47% yield).

2,2'-dibromobiphenyl 189: NMR data in agreement with literature values[269] δ_H (200MHz; $CDCl_3$) 7.26-7.33 (4H, m, Ar-H), 7.40 (2H, d, *J* 7.2, Ar-H), 7.71 (2H, d, *J* 7.4, Ar-H); δ_C (50 MHz; $CDCl_3$) 123.7, 127.3, 129.5, 131.1, 132.7, 142.2; mp 74.5°C (Lit. 74-76°C[270]).

Reaction between 2,2'-dibromobiphenyl (189) and *N,N*-diisopropyl methane sulfonamide (154e):

A screw capped pyrex tube (50ml) was charged with sodium *tert*-butoxide (0.24g, 2.5mmol), **189** (288mg, 1 mmol), **154e** (179mg, 1 mmol) and dry toluene (5ml, distilled from sodium). The tube was flushed with nitrogen and a warmed suspension (60°C, 1min) of $Pd(OAc)_2$ (22mg, 0.1 mmol, 10mol%) and tricyclohexylphosphine (56mg, 0.2 mmol, 20mol%) and an accurately weighed amount of 2-methoxynaphthalene (internal standard) and toluene (3ml) was added. The tube was again flushed with nitrogen and sealed. The mixture was heated to 110°C in a Robosynthon multireactor for 20 hours. Conversion of starting materials and formation of products were measured based on internal standard calculations. The reaction was quenched by the addition of water and was diluted using ethyl acetate. The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford the crude product as a brown oil (0.5g). The crude product was purified using column chromatography (10-20% ethyl acetate, 80-90% hexane). A fraction containing **192** was recovered.

2-*t*-Butoxy-2'-(*N,N*-diisopropyl-sulfonamidomethyl)-biphenyl 192: δ_H (200MHz; $CDCl_3$) 1.07 (9H, s, *t*-Bu), 1.14 (12H, d, *J* 6.8, CH_3), 3.49 (2H, m, CH), 4.22 (2H, m, CH_2), 7.06-7.44 (7H, m, Ar-H), 7.74 (1H, m, Ar-H); ν_{max}(nujol)/cm^{-1} 1715 (S=O), 1332 (Ar-O), 1187 and 1163 (SO_2N), 977 (CH_2S), 747 (Ar-CH_2); Exact mass calculated for $C_{23}H_{33}O_3NS$ $[M]^+$: 403.2181. Found: 403.2142.

When the above reaction was repeated using $Pd(OAc)_2$ (18mg, 0.08 mmol, 8mol%) and PPh_3 (60mg, 0.23 mmol, 23mol%), the crude product (0.35g) was analysed by GC-MS to contain mainly 2,2'-dibromobiphenyl (**189**) as well as small amounts of what is

proposed to be 1-*N*,*N*-diisopropyl-sulfonamido-fluorene (**190**) and 2-*N*,*N*-diisopropyl-sulfonamidomethyl-biphenyl (**193**).

1-*N*,*N*-diisopropyl-sulfonamido-fluorene 190: Exact mass calculated for $C_{19}H_{23}O_2NS$ $[M]^+$: 329.1450. Found: 329.1473.

2-*N*,*N*-diisopropyl-sulfonamidomethyl-biphenyl 193: Exact mass calculated for $C_{19}H_{25}O_2NS$ $[M]^+$: 331.1606. Found: 331.1635.

6.4 Procedures Relating to Chapter 5

General procedure for the palladium catalysed arylation of acetoacetates:

A screw capped pyrex tube (50ml) was charged with powdered potassium phosphate (2.4g 11.3 mmol), dry toluene (10ml, distilled from sodium), ethyl acetoacetate (0.57g, 4.4mmol), and bromobenzene (0.64g, 4.1mmol). $Pd(OAc)_2$ (9mg, 0.04mmol, 1mol%) and 2-di-*tert*-butylphosphino-2'-methylbiphenyl (24mg, 0.08mmol, 2mol%) were added. The tube was flushed with nitrogen and heated to 90^{o}C in a Robosynthon multireactor for 15 hours. The amount of bromobenzene and ethyl phenylacetate remaining in the reaction mixture was determined by GC analysis based on internal standard calculation. Isolation was done by addition of water and dilute hydrochloric acid to acidify the mixture followed by extraction into ethyl acetate. After solvent removal the crude product was isolated and analysed by ^{1}H-NMR. In cases where the isolated yield was determined the crude product was purified by either flash column chromatography (20% ethyl acetate in hexane) or by fractional distillation (ethyl phenylacatate for example; 80-120^{o}C at 2mbar).

***tert*-Butyl phenylacetate 194a**: NMR data in agreement with literature values[62] δ_H (200MHz; $CDCl_3$) 1.48 (9H, s, *t*-Bu), 3.56 (2H, s, CH_2Ph), 7.27-7.39 (5H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 28.2, 43.1, 81.4, 127.5, 128.6, 129.7, 135.2, 171.6.

Ethyl phenylacetate 194b: NMR data in agreement with literature values[62] δ_H (200MHz; $CDCl_3$) 1.28 (3H, d, *J* 7.2, CH_3), 3.64 (2H, q, *J* 7.2, CH_2Ph), 4.18 (2H, s,

OCH_2), 7.24-7.42 (5H, m, PhH); δ_C (50 MHz; $CDCl_3$) 14.2, 41.4, 60.7, 127.1, 128.5, 129.3, 134.2, 171.5.

Ethyl 4-methoxy-phenylacetate 194c: NMR data in agreement with literature values[271] δ_H (200MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.2, CH_3), 3.58 (2H, s, CH_2Ar), 3.81 (3H, s, OCH_3), 4.15 (2H, q, *J* 7.2, OCH_2), 6.83 (2H, d, *J* 9.2, Ar-H), 7.22 (2H, d, *J* 9.2, Ar-H); Exact mass calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943. Found: 194.0946.

Ethyl 4-aceto-phenylacetate 194d: NMR data in agreement with literature values[19] δ_H (200MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.2, CH_3), 2.60 (3H, s, CH_3), 3.68 (2H, s, CH_2Ar), 4.17 (2H, q, *J* 7.2, OCH_2), 7.40 (2H, d, *J* 9.6, Ar-H), 7.93 (2H, d, *J* 9.6, Ar-H); δ_C (50 MHz; $CDCl_3$) 14.1, 26.6, 41.7, 61.5, 128.8, 129.9, 136.0, 139.9, 171.0, 197.8; ν_{max}(nujol)/cm^{-1} 1730 (Ester C=O) and 1678 (ketone C=O), 1268, 1182 and 1020 (C-O).

Ethyl 1-naphthylacetate / naphthalen-1-yl-acetic acid ethyl ester 194e: NMR data in agreement with literature values[272] δ_H (200MHz; $CDCl_3$) 1.24 (3H, t, *J* 7.4, CH_3), 4.10 (2H, s, CH_2Ar), 4.17 (2H, q, *J* 7.4), 7.43-7.61 (4H, m, Ar-H), 7.79-7.95 (2H, m, Ar-H), 8.03 (1H, d, *J* 10.3, Ar-H); ν_{max}(neat)/cm^{-1} 3048 (Ar-H), 1733 (C=O), 1251 and 1175 (C-O), 780 (Ar-CH_2).

Ethyl 2-phenylacetoacetate / ethyl 2-phenyl-3-oxobutanoate 195 [273]: NMR analysis revealed **195** exist as a 2.2:1 mixture of the keto and enol tautomers in $CDCl_3$ solution: **195 Keto tautomer**: δ_H (200MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.2, CH_3), 2.21 (3H, s, CH_3), 4.25 (2H, q, *J* 7.2, CH_2), 4.71 (1H, s, CH), 7.15-7.40 (5H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 14.1, 29.6, 61.5, 65.7, 128.8, 129.2, 131.1, 132.7, 168.4, 201.3; ν_{max}(neat)/cm^{-1} 3453 (O-H), 2927 (Ar-H), 1734 (ketone C=O), 1689 (ester C=O), 1599 (C=C), 1263 and 1178 (CH-C(O)), 1018 (C-O), 752 and 701 (Ar-CH); Exact mass calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943. Found: 194.0946.

195 Enol tautomer: δ_H (200MHz; $CDCl_3$) 1.21 (3H, t, *J* 7.2, CH_3), 1.88 (3H, s, CH_3), 4.20 (2H, q, *J* 7.2, CH_2), 5.33 (1H, s, OH), 7.15-7.40 (5H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 14.1, 19.8, 60.5, 104.3, 126.8, 127.9, 128.1, 135.2, 172.5, 173.7.

Ethyl 2-phenylpropionate 202: NMR data in agreement with literature values[274] δ_H (200MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.0, CH_3), 1.46 (3H, t, *J* 7.0, CH_3), 3.67 (1H, q, *J* 7.0, CH), 4.24 (2H, q, *J* 7.0, CH_2), 7.22-7.32 (5H, m, Ph-H).

Ethyl 2-methyl-2-phenylacetoacetate / 2-methyl-3-oxo-2-phenyl-butyric acid ethyl ester 203: NMR data in agreement with literature values[275] δ_H (200MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.0, CH_3), 1.77 (3H, s, CH_3), 2.14 (3H, s, CH_3), 4.23 (2H, q, *J* 7.0, CH_2), 7.18-7.41 (5H, m, Ph-H).

General procedure for the arylation of ethyl acetoacetate using a copper catalyst:
A screw capped pyrex tube (50ml) was charged with powdered potassium carbonate (1.1g 8 mmol), dry solvent (DMSO, DMF, NMP, dioxane or toluene, 10ml), ethyl acetoacetate (0.52g, 4 mmol), and iodobenzene (0.41g, 4 mmol). CuI (80mg, 0.4mmol, 10mol%) and 2-methoxynaphthalene (internal standard) were added. In experiments where ethylenediamine was used, distilled ethylenediamine was added by microsyringe (60µL, d=0.899, 0.9 mmol). The tube was flushed with nitrogen and heated to 80^{o}C in a Robosynthon multireactor for 20 hours. The amounts of iodobenzene and ethyl phenylacetate in the reaction mixture were determined by GC analysis based on internal standard calculation.

CHAPTER 7

REFERENCES AND NOTES

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