Level 3 Extended Project H856

Exemplar Folder 1

ocr.org.uk/extendedproject

Extended Project Exemplar 1 - 49/60 A*

Palladium Catalysts

AO1 - Some reservations at the start, with the abstract, introduction approach etc, so seemed to be more concerned with dissertation than with project management. PPR had good evidence of choice and planning and basic plan was fine. Would have liked to have seen more evidence of independence and where the journey was starting from. Presumably an A Level Chemist? Would like to have seen more highlighting of decision making skills and problem solving skills in planning process. Clearly good on deadlines. Needed more evidence of planning reviews/reflection to justify this high a mark. Right level, but too high in it.

AO2 - Clearly a lot of research done. Real depth. Clearly heading for L3, yet.... ? Is it really a wide range? Any evidence of talking to university chemists/postgraduates (address would indicate very near major chemistry dept). Some evaluation of sources, but enough for top marks? Possibly evidence of specialist supervisor syndrome. Was there 'little or no guidance'? Some evidence conflicts here. Slightly more careful training in research and evaluation would have paid off.

AO3 - Clearly impressive achievement here. Major piece of work completed. Right level, but too high in it. Just not the requisite focus on skills for very top marks. Nature and extent of the journey for this one? Doing Chemistry at A level? Was the intention to write a dissertation comparable to those required for university students?

AO4 - Again right level, but a little high in it. Good on evaluating outcomes, less good on process. Case where presentation could have questioned more effectively to tease out skills here. Review of methodology? How well did student communicate with a lay audience?

General points

No reason why not top A* with right focus. Cleary impressive achievement showing commitment and ability. Well organised and presented. Link to career and HE? Worried too much about 5000 words - not our requirement, just a recommendation. Always L3, but just a little high in each one. Not always judged by right criteria.

MoD. 12, 11, 18, 8 = 49

OCR
RECOGNISING ACHIEVEMENT

Extended Project (Level 3)

Unit H856

Unit Recording Sheet

Please read the instructions printed at the end of this form. **One** of these cover sheets, suitably completed, should be attached to the assessed work of **each** candidate.

Unit Code	**H856**		**Year**	**2**	**0**	**0**
Centre Name		**Centre Number**				
Candidate Name		**Candidate Number**				

AO	Criteria			Teacher Comment	Mark
1	• Selected a suitable topic and produced a piece of work that reflects a design formulated with the assistance of their teacher/mentor • Taken an adequate degree of responsibility for their project, planning and managing the work through measures addressing its sequencing, its breakdown into intermediate tasks and monitoring its progress. In a group setting, responsibility will have been taken for closely defined tasks assigned by the group • Developed adequate organisational, IT, decision-making and problem-solving skills necessary to realise the project, responding to changing circumstances • Completed the project within the agreed time schedule **[0 1 2 3 4]**	• Proposed a suitable topic and produced a piece of work that reflects a design negotiated with their teacher/mentor • Taken substantial responsibility for their project, effectively planning and managing the work including sequencing, its breakdown into intermediate tasks and monitoring its progress. In a group setting, responsibility will have been taken for aspects of group work with active participation in group decision-making • Developed proficient organisational, IT, decision-making and problem-solving skills and used them effectively to realise the project, recognising and responding to changing circumstances • Completed the project within the agreed time schedule, meeting most intermediate goals **[5 6 7 8]**	• Proposed a suitable topic and produced a piece of work that reflects a design proposed to their teacher/mentor and with limited negotiation/support of their teacher/mentor • Taken full responsibility for their project, skillfully planning and managing every aspect of the work. In a group setting, responsibility will have been taken for directing and monitoring aspects of group work with some leadership of group decision-making • Developed proficient IT and sophisticated organisational, decision-making and problem-solving skills and used them creatively to realise the project, effectively managing changing circumstances • Completed the project within the agreed time schedule, meeting all, or virtually all, intermediate goals **[9 10 11 12]**	Clearly a suitable topic was produced in an independent manner. Daniel took full responsibility for the project in a mature and conscientious manner. He developed the requisite skills and met all deadlines.	11

2	• A limited range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Guidance on the choice and interpretation of sources has been given by the teacher/mentor • Some understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A limited range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used, where appropriate • Where relevant, some information and/or data has been obtained through working with others in the context of engagement in a business, social-community venture/enterprise or through involvement in a local, regional or international team Extended Project. The learner has participated in a limited way within the context [0 1 2 3 4]	• An appropriate range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Some guidance on the choice and interpretation of sources has been given by the teacher/mentor • An effective understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used effectively to further the aims of the project, where appropriate • Where relevant, a range of appropriate information and/or data has been obtained through working with others in the context of engagement in a business, social-community venture/ enterprise or through involvement in a local, regional or international team Extended Project. The learner has been an active participant within the context [5 6 7 8]	• A wide range of sources has been used to obtain, select, collate and analyse information and data relevant to the project. Little or no guidance on the choice and interpretation of sources has been given by the teacher/mentor • A sophisticated and perceptive understanding of connections and linkages between different types of resource and the complexities inherent in their project has been developed • A wide range of appropriate technology and related technical skills have been used to aid the collection of information and data. E-learning has been used skilfully and critically to further the aims of the project, where appropriate • Where relevant, a wide range of appropriate information and/or data has been obtained working with others in the context of engagement in a business, social-community venture/enterprise or through involvement in a local, regional or international team Extended Project. The learner has offered leadership or direction within the context [9 10 11 12]	Outstanding range of sources examined with very limited guidance. The nature of the links ~~was~~ can be considered one of the clear links of the Extended project, something facilitated by the effective use of technology. Undoubtedly data was collected and filtered through an engaged approach.	12

3	• Some appropriate skills have been selected and used in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is some evidence of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • Some appropriate technologies, including relevant new technologies, have been used to assist the process of problem-solving, decision-making and achieving the planned outcome. There is some evidence of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation **[0 1 2 3 4 5 6 7 8]**	• A range of appropriate skills have been selected and used effectively in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is evidence of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • A range of appropriate technologies, including relevant new technologies, have been used effectively to assist the process of problem-solving, decision-making and achieving the planned outcome. There is evidence of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation **[9 10 11 12 13 14 15 16]**	• A wide range of appropriate skills have been selected and used in a sophisticated manner in relation to the context of the project in order to solve problems, take decisions and achieve the planned outcome. These skills may include problem-solving techniques, analytical techniques, PLTS, functional skills, presentational skills and technical skills of various kinds. There is clear evidence throughout of the critical, creative and flexible use of skills in the furtherance of the project's development and realisation • A range of appropriate technologies, including relevant new technologies, have been used in a sophisticated manner to assist the process of problem-solving, decision-making and achieving the planned outcome. There is clear evidence throughout of the critical, creative and flexible use of technology in the furtherance of the project's development and realisation **[17 18 19 20 21 22 23 24]**	An outstanding range of skills evident including problem-solving, analytical techniques and presentational skills. The planned outcome was fully achieved, enhanced through the flexible use of technology.	23

4	• Although limited in scope, a critical, reflective and independent approach to learning has been developed. A limited attempt has been made to present an accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A limited usage of communication skills and media to present a broadly effective review of the development and outcome of the project [0 1 2 3 4]	• A critical, reflective and independent approach to learning has been developed. They present a thorough and accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A broad usage of communication skills and media to present an effective and comprehensive review of the development and outcome of the project • The presentation has broadly met the needs of its intended specialist and/or non-specialist audience* • They have appropriately addressed the issue of personal, academic and career development beyond the confines, but informed by, their participation in the project, including their development of transferable skills [5 6 7 8]	• An incisive critical, reflective and independent approach to learning has been developed. They present a perceptive, thorough and accurate review of their work covering both development aspects and the eventual outcome of the project. This may relate to the learner's participation and contribution to a group project in a social-community venture/enterprise and/or local, regional or international team project • A sophisticated usage of communication skills and media to present a perceptive, effective and comprehensive review of the development and outcome of the project • The presentation has met all the needs of its intended specialist and/or non-specialist audience. The audience was engaged and entertained* • They have addressed clearly and realistically the issue of personal, academic and career development beyond the confines, but informed by, their participation in the project, including their development of transferable skills. They clearly understand what has been achieved and where it can lead them [9 10 11 12]	Reflective approach characterised by a self-assured yet self-critical approach. Quality of the writing is evidence of the sophistication of the approach The presentation was nuanced, perceptive and shaped to the needs of the audience. Clearly the project has key & shaped future aspirations	12
				Total /60	58

Guidance on Completion of this Form

⇒ action plan

1 **One** sheet should be used for each candidate.

2 Please ensure that the appropriate boxes at the top of the form are completed.

3 Circle the mark awarded for each strand of the marking criteria in the appropriate box.

4 Add the marks for the strands together to give a total out of 60. Enter this total in the relevant box.

Extend Project Portfolio: Contents

1. Project outcome – the dissertation

2. Project Progression Record

3. Plan

4. "Synthesizing our future" – an article that was useful as stimulus material when I was selecting the topic

5. A sample of my research material – three annotated journal articles

6. Two drafts of the dissertation – other drafts were too similar to justify inclusion

7. PowerPoint slides for the presentation

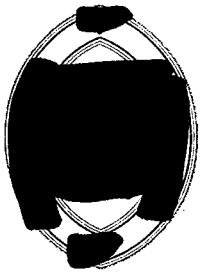
8. Audience feedback on the presentation (two forms are included and have been written by [redacted] and also student [redacted])

9. Evaluation document

OCR
RECOGNISING ACHIEVEMENT

Extended Project Qualification (Level 3)

How can palladium catalysts increase efficiency in the synthesis of aromatic compounds?



Science Supervisor: [redacted]

General Supervisor: [redacted]

Contents

Abstract

Modern synthetic chemists are continually striving to prepare compounds more efficiently, and one method that they are invoking routinely is the use of a palladium catalyst. Palladium is currently an important catalyst in many commercial syntheses due to the large number of high yielding and highly selective pathways it mediates. However, de novo palladium catalytic systems are more esoteric – but crucially, offer marked improvements in efficiency. The often unusual behaviour of palladium has made it the catalyst of choice for those in search of novel, efficient synthetic routes. Coupling reactions of aromatic compounds have been identified as the subset of organic synthesis that is best placed to benefit from the advantages of palladium, and so they will be our focus here. Reactions of this nature are vital to the development of convergent synthetic routes in industry and also to research labs pursuing total synthesis, which necessitate the assembly of complex molecules consisting of multiple substructures. Here we present the palladium-based procedures that have already led to efficient strategies, with particular regard to biaryl synthesis and Heck reactions, and additionally review current research that promises to shape the next generation of palladium-based methodologies.

Introduction

A successful organic synthesis demands the creative application of computational and theoretical techniques in order to identify a molecular framework with a structure well-suited to the desired function, and to then map out a synthetic route which may arrive at the target[1]. Putting together a complex molecule relies on having a library of efficient core reactions at one's disposal; frequently it is compounds exhibiting aromatic motifs that prove to be the core reagents of greatest value. Aromatic compounds are characterised by their delocalised system of pi-electrons, a well-defined geometric structure, relatively high levels of photochemical, thermal and chemical inertness as well as good potential for selective functionalisation[2]. It is therefore no surprise that compounds displaying an aromatic nucleus are ubiquitous in modern synthetic chemistry and are biosynthesised by organisms in every taxonomic kingdom. This is an area of chemistry that has been thoroughly investigated, but of course, many avenues remain unexplored. Here, we will focus on the palladium-catalysed synthesis of compounds exhibiting aromaticity – palladium is extremely versatile and highlights the tremendous power of a transition metal-mediated approach to constructing organic molecules. Whilst palladium-catalysed routes to aromatic compounds have been examined in many articles before, discussions of the strategy in the context of synthetic efficiency are much harder to find; consequently, it is our purpose to investigate the improvements in efficiency offered by these reactions. The combination of a well-behaved and structurally malleable compound class with a procedures based on palladium catalysis, a synthetic methodology that gives rise to highly selective routes, provides an ideal starting point in the search for more efficient strategies in synthesis.

It is necessary but certainly not sufficient to merely identify and synthesise a target compound, the next and arguably more important stage is to refine the efficiency of the synthetic procedure. An efficient reaction scheme may be defined as one which produces a unit quantity of a target compound with the minimum input of resources. Evaluating synthetic efficiency is difficult: industrial chemists and research chemists have markedly different objectives and thus place emphasis on different aspects of efficiency. Industrial chemists will regularly choose reactions requiring cheap and readily available reagents whilst simultaneously attempting to maximise yield, minimise the number of steps, ease product isolation and purification, and reduce energy and time input. These objectives are self-explanatory and quite clearly can be grouped together as a set of economic considerations intended to improve cost effectiveness. Using palladium to improve cost effectiveness may seem paradoxical when the high price of palladium considered, but the efficiency-enhancing characteristics that it able to induce in a reaction tend to greatly outweigh the capital input required. Academic research in organic synthesis may share some of these goals, but the key difference is an emphasis on finding new reactions with inherent properties that are of interest – optimising a reaction to improve profitability is

not the objective. Selectivity and atom economy are two examples of properties that confer greater efficiency; it will become evident that these properties also have economic repercussions and so will be of interest to industry, provided that it is feasible for the procedure to be scaled-up.

To achieve good atom economy is to maximise the proportion (by mass) of the reactants that end up in the final product and minimise waste as a consequence. Quantitatively this may be defined as the ratio of the molecular mass of the desired product to the sum of the molecular masses of all the products. Atom economy is an intrinsic feature of a reaction; this is in contrast to yield, which can be manipulated by altering reaction conditions and recycling the reaction mixture.

Selectivity is another reaction property that must be understood in order to appreciate the utility of organopalladium chemistry in achieving an efficient synthesis. The first division of selectivity to consider is chemoselectivity: this is the extent to which a reaction is effected only at the intended functional group(s); it is often the case that many potentially reactive groups will be present and these must be prevented from taking part in side reactions[2]. Similarly, regioselectivity is the extent to which a compound reacts to give the desired structural isomer. In an unsymmetrical species, this necessitates the preference of one direction of bond breaking and formation over another, and in instances where several identical functional groups are present, there must be discrimination between different the chemical environments[3]. Lastly we come to stereoselectivity; this facet of a synthesis is encompassed in the degree of diastereoselctivity and/or enantioselectivity. These concern the degree to which a single diastereoisomer or enantiomer is produced respectively, achieving the latter objective is difficult due to the identical chemical and physical properties exhibited by chiral molecules; it is the subject of the field of asymmetric synthesis[3]. Quantitative assessment of the level of stereoselectivity is given by the enantiomeric or diastereomeric excess, this is calculated by determining the absolute value of the difference between the mole fraction of the desired stereoisomer and the sum of the mole fractions of the unwanted stereoisomers; it is normally expressed as a percentage[4]. Optical purity is also routinely used to quantify enantioselecitivty – it is the ratio of the specific rotation of the sample to the specific rotation of the pure desired enantiomer; we will not be using this parameter here. As a final note on selectivity, the term "specificity" is used to refer to 100% selectivity – this indicates that selectivity is a strict requirement of the reaction mechanism[4].

Actualising these synthetic objectives is made possible thanks to a range of methods; however, here we will only discuss a single family of techniques, that is, those involving the use palladium to mediate reactions. As we have seen, efficiency is a very broad term encompassing many issues - overall "efficiency" is thus a trade-off between each of the competing factors. For example, consider a very slow reaction which demands expensive reagents, but which offers 100% atom economy and high yield. Clearly, the input of capital and time is high whilst the quantity of reagents required have been minimised – it is the net impact which must be considered. The net impact need not be considered solely in economic terms; it will transpire that the discussion regularly alludes to the terminology of green chemistry and indeed the consequence of improving efficiency is frequently a reduction in environmental impact. Transition elements frequently enable the attainment of efficiency in several of the aforementioned categories simultaneously. The extent to which the catalytic properties of palladium can be exploited in order to address the issue of efficiency, and hence bring great benefits to the chemical industry, will be considered by exploring reactions that clearly illustrate the advantages and disadvantages of palladium-based synthesis.

Biaryl Synthesis

Suzuki and Negishi Coupling

Palladium (Pd) catalysis can be used to great advantage in coupling reactions, that is, reactions leading to the amalgamation of organic fragments via carbon-carbon or carbon-heteroatom bond formation. Molecules consisting of two directly bonded aryl groups (biaryls) are indisputably among

the most important compounds that can be produced in coupling reactions. Biaryl substructures are widespread in medicinal products, such as the antibiotic vancomycin and the potent antileukaemic agent stegnacin, as well as engineering materials including liquid crystals, molecular wires, and conducting polymers such as poly-p-phenylene[5, 6]. Moreover, aryl-aryl bond forming reactions are vital to the modern synthetic approach known as convergent synthesis in which several molecular fragments are assembled separately before being finally coupled in order to assemble the target[7]. Sartans (angiotensin II receptor antagonists) are an important class of antihypertensive drugs that are synthesised using a Pd-based convergent strategy[8]. This class of drugs is also an example of how syntheses already exploiting palladium chemistry can be further enhanced thanks to new advances (The novel ligand mentioned below can be applied to the standard Suzuki reaction normally employed).

Comparing a typical nickel (Ni) catalysed Negishi coupling to the palladium catalysed Suzuki coupling will serve as a useful case study to briefly survey the ways in which efficiency can be enhanced by employing a palladium catalyst in place of a different transition metal. Figure 1.1 below shows a simple two-step synthesis of 2-phenylbenzaldehyde that I have designed; it is based on a similar procedure noted by Cepanec[5]. The reaction scheme affords the product with an overall yield of 82% within a 5.5h period. We can attribute the need for two steps to the fact that a protecting group (in this case, a cyclohexylimino group) is required to avoid complexation between the nickel species and the carbonyl. Deprotection (step two) introduces a further problem; the nickel complex is attacked by the acid (oxidative addition of the acid to the Ni(0)) and so the complex must either be continually replaced or an extraction step must be added to remove the catalyst[9]. The nickel complex is also relatively difficult to work with, it must be kept at 2°C and contact with oxygen should be minimised, Sigma Aldrich also confirm that the compound is hazardous – a faceshield and full-face particle respirator should be worn when using the substance[10]. Lastly, an unfortunate consequence of the reaction conditions is that the arylzinc reagent will undergo a homocoupling, this side reaction cannot be avoided and so an excess of the arylzinc compound must be added[5].

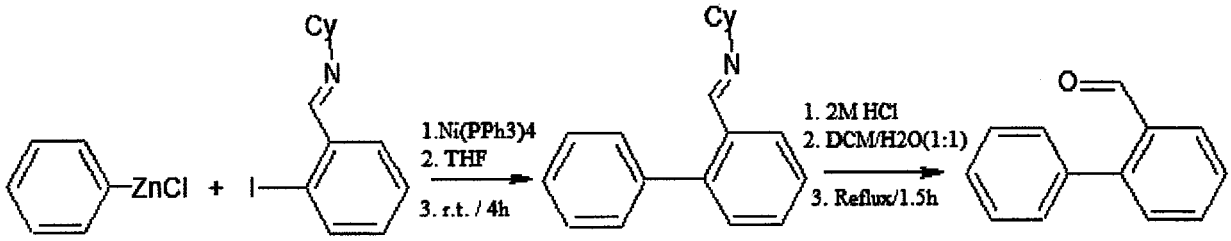


Figure 1.1: Scheme one - – an example of a nickel-catalysed Negishi Coupling

Thimmaiah and Fang reveal that an innovative Suzuki-Miyaura coupling will afford the same product[11]. Not only is the yield much greater at 99%, but the $Pd_2(dba)_3$ confers complete chemoselectivity enabling the reaction to proceed in the absence of a carbonyl protecting group[11]. The number of steps is instantly halved, which leads to a reduction in the amount of apparatus and solvent used, and the synthesis is also much more rapid (four hours per batch is saved), however this is also due to the greater rate of reaction in the second scheme. Industry is likely to be deterred from using the second procedure as a result of the need for a specialised ligand (see figure 1.3) that is not widely produced and is thus costly, however, in association with the Pd-complex the ligand is only required in catalytic amounts as the substance is neither consumed in the reaction, nor chemically altered by the chosen reaction conditions. Moreover, the ligand activates the Pd-complex more strongly than conventional ligands: the reaction proceeds at a faster rate, in milder conditions, and in the presence of a smaller quantity of the expensive Pd compound[11]. The discoverers of the new class of ligands argue that the ligands are easy to prepare and make possible a variety of reactions that have

previously been impossible, for example, they report the synthesis of the novel compound 2,6-dimethyl-2-phenyl-1,10-biphenyl[11]. For this reason, the ligands will be of interest to research groups.

Other ligands, many readily available, can also enhance the reaction (though rate and yield are not enhanced as significantly) and crucially, ligand-free Suzuki cross-couplings have been documented. From the perspective of industry, both schemes could be made more appealing by reducing the amount of the expensive catalyst (catalyst loading) required, the first reaction is effective with a load of 1-5 Mol % while the second procedure was optimised at 1.5 Mol %[11]. Excessive catalyst loads are inefficient in two respects, firstly they unnecessarily increase the cost of the reaction and secondly, the high concentration encourages catalyst particle agglomeration leading to cluster formation, the clusters precipitate out as palladium black – this is uneconomical as it is not a catalytically active species. Astonishingly, the problems associated with the reaction scheme, that is, the use of an exotic ligand and also the need for a relatively high catalyst loading could potentially be overcome concomitantly. The technique in question is the use of so-called "homeopathic" conditions. Predictably, catalyst loading is greatly reduced (to approximately 0.02Mol %), the ligand is excluded, and the reaction is run in ambient conditions[12]. High yields were obtained (up to 95%) though they varied with substrates and were on the whole lower than scheme two [12]. Potential exists to lower catalyst concentrations even further, a 0.0025 Mol % loading was successfully employed to obtain 4-acetylbiphenyl in an 85% isolated yield[12]. Both highly-activating ligands and the opposing technique of homeopathic conditions are clearly worthy of further work; they promise to greatly improve the efficiency with which biaryls are synthesised for both industrial and research purposes

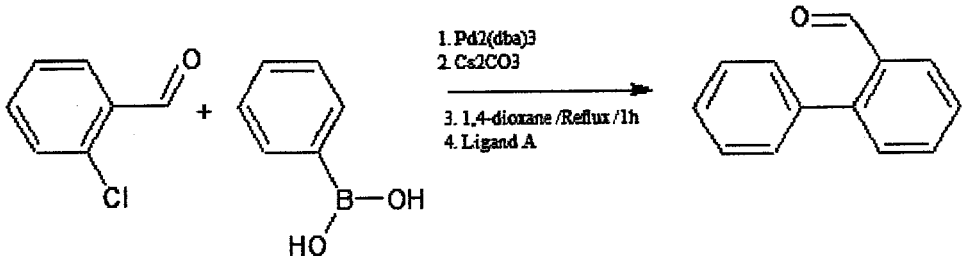


Figure 1.2: Scheme two

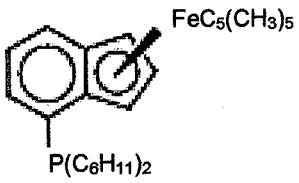


Figure 1.3: The structure of ligand A (a benzoferrocenyl dicyclohexyl phosphine derivative called 4-(Dicyclohexylphosphino)indenyl-pentamethylcyclopentadienyliron)

The simplicity and enormous potential of the Suzuki coupling is emphasised by the fact that a simple example of one is now carried out as a practical at the University of Oxford by second and third year undergraduates – this is testament to the increasing accessibility of organopalladium chemistry to chemists[13]. Use in the setting of a teaching laboratory also confirms that Pd-species are in general safe to handle, markedly so in comparison to Ni-complexes – this is convenient as no special protective gear is required. Scheme two also produces less waste than scheme one due to the absence of competing reactions (no homocoupling is observed in either the scheme recorded in figure 1.2 or the homeopathic procedure). However, the atom economies of both the methods discussed so far are not optimum; by-products from the desired reactions are produced in stoichiometric quantities. Nonetheless, the Suzuki method still offers superior efficiency over the Negishi reaction in this respect, as the by-products are all inorganic facilitating extraction from the reaction mixture.

Reactions yielding biaryls without invoking the power of transition element catalysis are rare, the sole common example is the Gomberg-Bachmann-Hey (GBH) reaction; this reaction instead exploits diazonium salts[14]. Admittedly, the GBH method allows a wide range of biaryls to be produced, but the chemoselectivity is low and subsequently yields rarely exceed 40%[15]. This is a result of the fact that a plethora of side reactions occur; the aryl radicals generated will undergo polymerisation, reduction to the parent arene, and azo coupling to give brightly coloured compounds in cases where the arene to be arylated is activated by an electron-donating group. One would therefore assume that this reaction is of no use in modern synthetic routes owing to its poor efficiency, however, many syntheses have continued to use the GBH reaction and its variants, for instance, a Suzuki coupling strategy to synthesise the NSAID diflunisal in a single step was only developed in October 2009[15]. Previously, a three-step procedure involving a GBH reaction between the diazonium salt of 2,4-difluoroaniline and anisole, followed by ether hydrolysis and Kolbe-Schmidt carboxylation, had been favoured[16].

One-Pot Synthesis

Now with an idea of some of the generic benefits we can exploit by using Pd-based methods, it is possible to turn to a more technically demanding synthesis – a triaryl synthesis. Figure 1.4 (below) shows a completely regioselective one-pot double Suzuki coupling yielding a differentially substituted pyrrole[17]. By assembling a tripartite structure in a single reaction vessel, a target compound can be assembled in fewer reactions and purification steps, with fewer reagents, and with less apparatus. Motivation for the synthesis of these compounds stems predominantly from their use in herbicides; this particular structural motif is prevalent in the protox inhibitor class of herbicides[18]. Two major difficulties must be overcome in order to achieve success in this synthesis, the first is that two sequential coupling reactions must take place in the same reaction vessel, and secondly, both couplings must take place with high regioselectivity: one reagent must attack only. Owing to the relatively nascent nature of Pd-mediated synthesis, there is no sure-fire way of determining an ideal combination of solvent, ligand and base. A common strategy for choosing a suitable catalytic system is a high-throughput screening approach; this involves setting up different reaction conditions on a millilitre scale and allowing the reactions to take place in parallel. Yield and product characterisation are the most important points to consider – yield is in this instance an integral part of the synthetic efficiency as the reaction conditions have been fixed. Following analysis of this nature, it was found that running the reaction under the first three conditions highlighted in the scheme and in the absence of p-fluorophenyl boronic acid produced exclusive monocoupling in the 5-position, even an attempt at forced dicoupling with 24 hours of vigorous reflux was unsuccessful. The next hurdle was to substitute the other boronic acid into the 4-position. Initial attempts to do so involved adding a different, more active catalyst to the reaction mixture in combination with the species to be coupled. Despite the success of this strategy, it was found that even a cheaper strategy could be employed; a new catalyst could be synthesised in situ by addition of a phosphine ligand. A modest 58% yield was obtained. Numerically, this is disappointing, but if we take into account the fact that two regiospecific reactions have taken place without any work-up, isolation or purification in between and that a sequential "couple-halogenate-couple" approach would enable the same product to be isolated in a mere 39% yield after extensive purification, then we can certainly claim that this is an impressive result. The most tangible improvement in efficiency will be the time saved by the reduction in the length of the reaction and the reduction in reagent and apparatus usage.

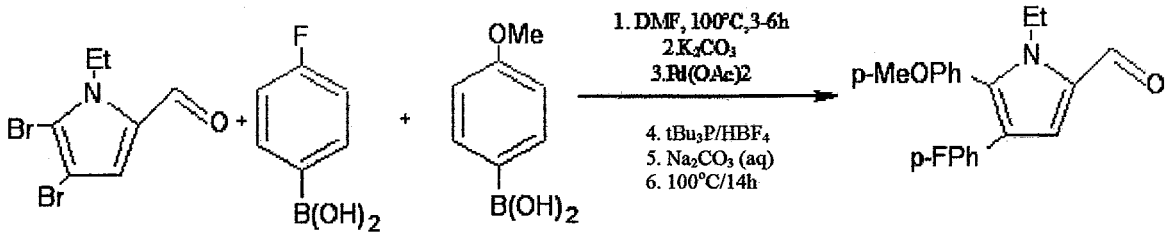


Figure 1.4: A synthesis of a substituted pyrrole to illustrate the "one-pot" concept

The strategy outlined here clearly has laid the foundations for the development of other related syntheses; this same dicoupling technique has been used to prepare substituted pyridines, thiophenes, and most recently, general unsymmetrical triaryls[19,20]. Whilst pyrroles are rarely useful, these latter protocols make the synthesis suitable to a range of applications including organic LEDs (OLEDs) and important pharmaceuticals such as Lipitor, a statin for cholesterol reduction, and Celebrex, an arthritis treatment[19]. What's more, a greatly improved isolation procedure utilising neutral alumina instead of silica has been developed; this has boosted yields to 97% for certain substrate combinations – the palladium catalyst is unaffected by this new procedure, and may continue to be recycled[19]. Without doubt, palladium's scope for one-pot syntheses is of great value; the capacity to amalgamate reaction steps will cut costs in industrial routes whilst the fact that the technique can give rise to quickly converging schemes will almost certainly result in its exploitation by research labs in search of facile total syntheses of complicated natural products.

Heck Reactions: Arylation of Alkenes

Asymmetric Catalysis

The Heck, or Mizoroki-Heck, reaction can be defined as the Pd-catalysed coupling of an alkene and an sp^2 (aryl or alkenyl) halide or triflate[21]. The technique is extremely versatile, thus accommodating many substrates, countless variants exist, and a myriad of innovative efficiency-enhancing modifications have emerged. Heck reactions have proved to be fertile grounds for the development of asymmetric catalytic protocols. This useful characteristic of Heck reactions is illustrated quite unequivocally in Overman's highly enantioselective synthesis of a series of spirooxoindoles exhibiting a single quaternary carbon centre, of which one example is shown below[22]. The most significant aspect of this success was the formation of both enantiomers at will, with only very minor alterations to the reaction conditions being required to change the isomer obtained. Another notable feature of the reaction is that it is an example of a desymmetrising Heck reaction, as chirality has been introduced into a prochiral substrate; no enantiopure starting reagents are called for as is the case for a chiral pool synthesis. This use of cheap, readily available reagents compensates for the high cost of the palladium catalyst. The first procedure in figure 2.1 (top) produced the S-isomer in an 81% yield and 71% enantiomeric excess (e.e.); after conducting the reaction with the addition of PMP, in the presence of DMA and in the absence of silver phosphate, but at the elevated temperature of 110°C, the R-isomer was obtained in 77% isolated yield and 66% e.e. [22]. It is this sensitivity to reaction conditions that confers excellent versatility to the Heck reaction.

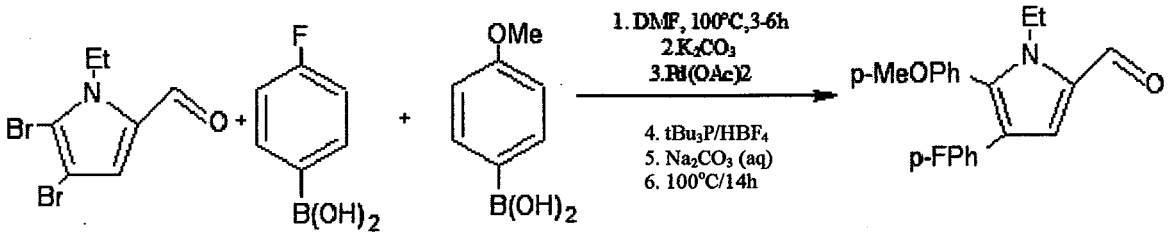


Figure 1.4: A synthesis of a substituted pyrrole to illustrate the "one-pot" concept

The strategy outlined here clearly has laid the foundations for the development of other related syntheses; this same dicoupling technique has been used to prepare substituted pyridines, thiophenes, and most recently, general unsymmetrical triaryls[19,20]. Whilst pyrroles are rarely useful, these latter protocols make the synthesis suitable to a range of applications including organic LEDs (OLEDs) and important pharmaceuticals such as Lipitor, a statin for cholesterol reduction, and Celebrex, an arthritis treatment[19]. What's more, a greatly improved isolation procedure utilising neutral alumina instead of silica has been developed; this has boosted yields to 97% for certain substrate combinations – the palladium catalyst is unaffected by this new procedure, and may continue to be recycled[19]. Without doubt, palladium's scope for one-pot syntheses is of great value; the capacity to amalgamate reaction steps will cut costs in industrial routes whilst the fact that the technique can give rise to quickly converging schemes will almost certainly result in its exploitation by research labs in search of facile total syntheses of complicated natural products.

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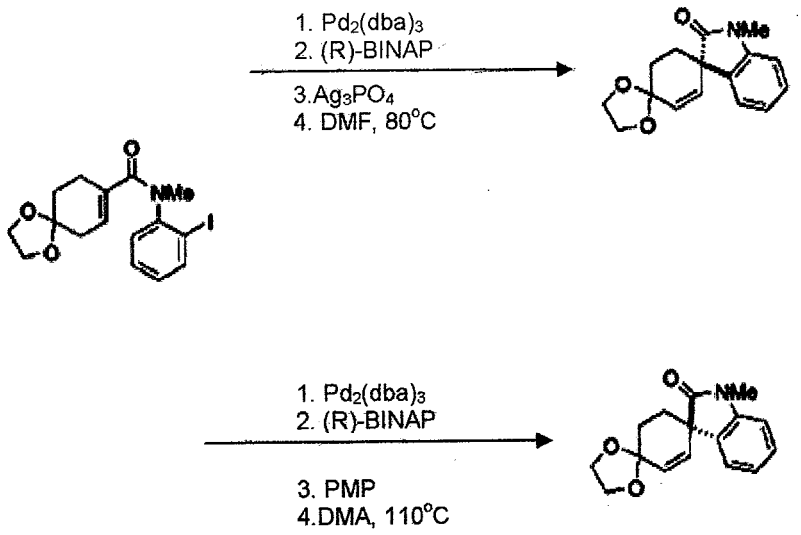

Figure 2.1: A reaction showing one of the first highly asymmetric intramolecular Heck reactions

Whilst the yield and e.e. may not seem impressive when compared to more up-to-date asymmetric syntheses, for examples, modern enzyme catalysed reactions; the reaction effectively illustrates the great ease of controlling the outcome of the synthesis. It is useful to compare the nature of the control over stereochemistry to that achieved by other strategies; first of all we shall consider enzyme-based methods. The enantioselective synthesis of cyanohydrins via biocatalysis with hydroxynitrile lyases is a procedure that has benefited from extensive research since 1908. However, until recently only the (R)-lyase was known, eventually advanced over-expression and cloning techniques have led to the production of the (S)-lyase which yields the other isomer[23]. So, even though each technique allows the acquisition of both isomers, the enzymatic route demands a long search for a mutant that achieves the goal (a 95 year long search in the case of the (S)-hydroxynitrilelyase); asymmetric Heck reactions however have demonstrated control can be placed firmly in the hands of the researchers[24]. Our second comparison will be to methods based on artificial catalysts: either an organocatalyst or other transition-metal catalysts. These approaches tend to take advantage of either an asymmetric induction, in which a reagent, auxiliary or catalyst is able to impart a particular stereochemistry onto the product by virtue of its own chirality, or a kinetic resolution in which one of the enantiomers undergoes a reaction much more rapidly in the presence of a chiral catalyst – the two different products can then be separated more easily. In the Heck reaction, contrary to these other asymmetric catalytic procedures, the enantioselectivity is not a result of the chiral ligand's (i.e. BINAP's) ability to accomplish an asymmetric induction at some point in the catalytic cycle. Instead, an almost alchemical manipulation of the solvent and additives in the reaction mixture has led to fine stereochemical control. As of 2010, the mechanistic interpretation is still under some dispute though it seems that silver phosphate's presence opens up rapid interconversion between the pro-(*R*) and pro-(*S*) intermediates that come into existence following initial oxidative addition[25]. Further work revealed more unusual occurrences. When high-purity Ag_3PO_4 was used, the R-product was the primary product. However, when a fractionally less pure Ag_3PO_4 was employed (or if the high-purity salt was first exposed to light), the S-product was the major product was obtained[25]. This points to the presence of a Ag(0) species perturbing the post-oxidative addition equilibrium. A confirmed explanation of the mechanism will reduce the amount of microscale screening that must be done to select the additives. This exemplifies the fact that the reaction outcome can be controlled by attempting to understand the chemistry - we alluded to this in our discussion of enzymes above. Exploiting very simple procedures to synthesise enantiopure products is one of the synthetic breakthroughs offered by the Heck reaction. Enantioselective reactions can thus be effected without having to spend time either designing and

attempting to synthesise intricate chiral ligands, or performing kinetic resolutions, which only serve to add more (low yielding) steps to the reaction scheme[26]. Nonetheless, determining the alteration that must be made to the reaction conditions in order to invert the stereoselectivity is not necessarily easy. In many instances the high-throughput screening approach is required due to a lack of understanding of the mechanistic chemistry; although this "gets results", most chemists are eagerly awaiting a theoretical basis for new studies.

Supported Catalysts

Mizoroki–Heck reactions continually resurface in the hunt for efficient syntheses. A recurring theme in research in this area is the use of a reaction set-up which promotes easy recycling of the catalyst to maximise catalyst usage and to save time. This technique is not exclusive to Pd-based strategies, but the number of Heck reactions harnessing the benefits is large and so there is a close relationship between this particular reaction and reaction set-up. Supported palladium catalysts have realised this objective, and have additionally enhanced regioselectivity to unprecedented levels owing to the steric hindrance of the catalyst at the catalyst-support interface. A recent technique used in the synthesis of a range of cinnamates appears to be an easy to implement and highly effective strategy. Supporting a $Pd(NH_3)_4Cl_2$ on silica (SiO_2) in a BMIM-PF_6 solvent system enabled Okubo and colleagues to diastereospecifically synthesise a set of alkyl cinnamates with at least 95% yield[27]. In particular, ethyl cinnamate, an important flavouring compound, was isolated in 100% yield after reflux for 1h[25]. The extent of leaching of the catalyst into the solvent did not exceed 0.24% of the initial catalyst load; the investigation demonstrated six reuses of the catalyst with no loss of performance in the system – more work is necessary to reveal the upper limit to this statistic, but this procedure alone will already be of enormous interest to the flavour and fragrance industry[27].

The aforementioned technique of immobilisation (which is an example of heterogeneous catalysis - using a catalyst in a distinct phase to the reaction mixture) is currently eagerly investigated. Unfortunately, reduced reaction rate is often a side-effect of enforcing a heterogeneous catalyst – chemically, this is quite expected. If the system is truly biphasic with minimal leaching, one can only expect reaction to occur at the interface between the substrate and the catalyst surface whilst a homogenously catalysed reaction can take advantage of a catalyst dispersed uniformly throughout the reaction mixture. Two further strategies can be employed to attempt to counteract this: phase-transfer catalysis and a novel method discovered by Kleist based on dissolution and redeposition. Using a phase-transfer catalyst (PTC) is certainly not a concept unique to palladium chemistry, it is extensively put into practice to solve this problem in an array of synthetic applications. Only the Heck reaction has been extensively trialled for use with a PTC and the results show a marginal improvement in reaction rate. On a side note, using a PTC method in an aqueous medium does bring with it an advantage; water is a very cheap and environmentally friendly solvent. An especially useful strategy is binding the substrate to the liquid polymer PEG and conducting a standard homogeneous reaction procedure in an aqueous environment. In normal circumstances, the poor solubility of the Pd-catalyst would render the method useless but the PEG serves as a support and a PTC, thus enabling efficient reaction between the Pd-catalyst and the substrate when they come in to contact[28].

Whilst this is another technique to remember for the industrial chemist searching for green alternatives, it does not enable us to combine the benefits of a catalyst-support method and a fast reaction. For this objective, the only potential solution is to draft in the line of attack suggested by Kleist. Kinetic investigations confirm the expected result that an increased concentration of the leached Pd-catalyst in the solution leads to a greater rate of reaction, the insight of the Kohler lab was to capitalise on the rate increase obtained from a homogeneous catalyst whilst combining it with a catalyst support to aid recycling. Despite the paradoxical nature of this proposal, the objective was accomplished by designing a supported catalyst system that consists of a solid catalyst which is in equilibrium with a dispersed Pd-species in solution. Several systems were tried but incorporating the

palladium into a zeolite cage was most effective[29]. During the reaction, Pd diffused from the zeolite pores to give reaction rates which exceeded any previous Pd-catalysed heterogeneous reaction by at least a factor of ten[29]. Following completion of the reaction, essentially all the Pd is re-deposited onto the support. Kleist et al. believe that the protocol meets all the "requirements for practical applications in laboratory and industry" and indeed, the concept of combining the benefits of homogeneous and heterogeneous catalysis whilst evading their problems has the potential to transform many procedures exploiting traditional Heck reactions.

Future Work

Direct Arylation

Earlier we considered the advantages that can be reaped by employing Pd-catalysis in order to link aromatic structural subunits. The methods already discussed are very good, but they have an inherent drawback that places an upper bound on their efficiency. In all of the reactions discussed above, the coupling partners had to be activated, typically by a halogen on one species and an electropositive group such as boronic acid (which must be further activated by a base) on the other – these additional groups are absent in the product and inevitably form by-products. If these reactions could take place without preactivation, then the process would become much more atom economic, as waste products owing their existence to the preactivating groups would no longer be present. For this reaction to succeed the catalyst must not lead to the formation of homocoupled products, as this would offset any increase in the efficiency of the process. In order to induce this selective cross-coupling, the catalyst must initially react with the first arene substrate, after which total inversion of selectivity must occur such that the Pd-complex will exclusively react with the other arene. Figure 3.1 below outlines how this selectivity could take place within the framework of a simplified yet feasible catalytic cycle.

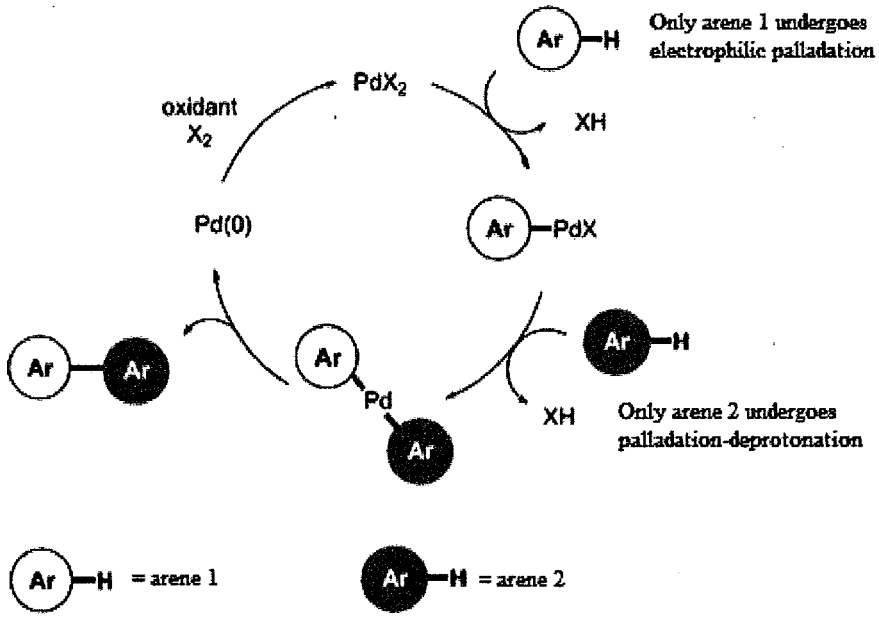

Figure 3.1 (above): A possible direct arylation cycle (adapted from the Fagnou and Stuart publication)[30].

Stuart and Fagnou have reported the first example of a direct arylation[30]. Facilitation of the selectivity inversion was achieved by provoking two different mechanisms: an aromatic electrophillic

palladation followed by a concerted palladation-deprotonation; this was the sequence proposed in the cycle above. Their study has revealed successful couplings between N-acetylindoles and simple substituted benzenes. Figure 3.2 below demonstrates one such reaction. Although the arylindoles are not a widely synthesised class of compounds, they are frequently found in natural products – an example is the diazonamide A, a secondary metabolite of an ascidian that functions as an anticancer agent at nanomolar concentrations – the compound is of interest to medicinal chemists for this reason[31].

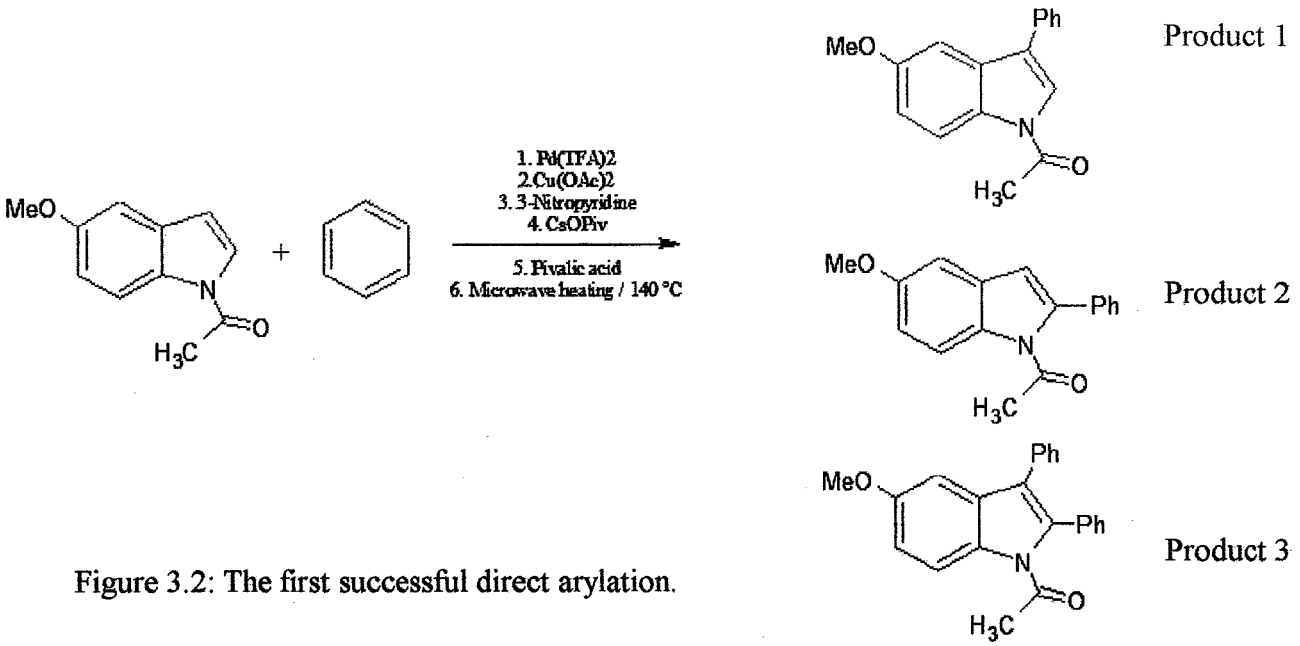

Figure 3.2: The first successful direct arylation.

Further work is much needed before this methodology can make its way into industrial synthetic routes – but the increasing number of publications in this field suggests its emergence is imminent[31]. The catalytic system is suitable for only a small group of substrates, which suggests a series of extensive substrate scope studies should be carried out, and furthermore, the mechanistic efficiency is diminished by the high catalyst loading required (10 mol %) and the requirement for a copper (II) acetate oxidant in stoichiometric quantities. Arguably the most important goal for research in this area is to develop a pathway that incorporates an oxidative concluding step in the cycle, this would enable the oxidant to be removed and the catalyst loading to fall. In addition, to warrant a role in industry, the 84% yield must be improved and research should aim for complete regioselectivity – in this instance, the products were obtained in the ratio 11.2:1:0.4 (product 1:product 2:product 3) although this is high regioselectivity, regiospecificity is the next target. A feature of this reaction which need not change is the heating protocol – microwave irradiation was shown to reduce reaction time from 48h (achieved in an oil bath) to 5h. The result is testament to the synergy between microwave assisted organic synthesis (MAOS) and Pd-mediated reactions. Arguably the most useful instance of this phenomenon is a Buchwald-Hartwig amination of aryl chlorides reported by Diels et al. in which reaction times were reduced from 1 day to 10 minutes – the procedure is directly applicable to a range of syntheses including the natural product lavendamycin and raloxifene[32]. Whilst microwave methods are not the focus of this review, they are relevant to the design of efficient synthetic procedures; volume 266 of the "Topics in Current Chemistry" series provides an excellent account of the increasingly important role of this family of techniques.

Domino Reactions

Above, we established how synthetic efficiency can be greatly ameliorated by the use of the aptly named "one-pot" concept. The idea can be taken a step further: it would be even more efficient if we could trigger a second reaction without having to introduce a new catalyst or modify the existing catalyst following initiation. Carrying out a sequence of two or more discrete reactions, in which subsequent transformations occur at functionalities altered in former steps, is known as a cascade or domino reaction[25]. Domino reactions are simultaneously environmentally sound and elegant in nature. In terms of the principles of green chemistry, the reaction ticks several boxes; among the useful features are the minimisation of solvent and reagent quantities, the reduction in the time and thus energy input required, and the high atom economies achieved. Researchers seeking new domino processes are finding the library of Pd-catalysed reactions to be the most fruitful place to look – this is because Pd has the unique ability to catalyse a variety of bond-forming reactions; C-C, C-O and C-N being the most useful. The other vital characteristic of Pd that we encountered at the start was its high chemoselectivity and regioselectivity, for domino reactions this is vital as it enables functionalisation in the absence of protecting groups.

The total synthesis of okaramine N, an insecticidal alkaloid, argues a compelling case for the importance of domino reactions[33]. Retrosynthetic analysis was used to plan the synthesis, the result of which was the prediction that eight steps would be required, starting from a tetracyclic intermediate synthesised in two-steps (a reductive N-alkylation in the presence of $NaBH_4$ and a Schiff base, followed by an acylation)[34]. Furthermore, the intention was to exploit the Fujiwara–Moritani modification to the Heck reaction; this is a Heck reaction in which an oxidative coupling process enables an arene and alkene to couple without the use of a halogenated aromatic substrate, no halogen-based by-products form and atom economy is therefore enhanced. Consequently, a synthetic goal analogous to the direct biaryl synthesis is achieved.

When the synthesis was eventually attempted, the first five steps (identified in the retrosynthetic analysis) were achieved with a single reaction: an intramolecular cyclisation cascade reaction - almost unrecognisable as a Heck reaction owing to the complexity of the transformation. The cascade has been outlined below to reveal the distinct nature of each of the transformations and to partially elucidate the mechanism. A notable feature of the cascade is that several steps are unexpected yet are still able to proceed with almost total regioselectivity. First of all, the presence of two indole groups suggests that a competing mode of ring closure will operate to give a 7-membered ring formed from the wrong indole. Instead, only the intended indole (the N-unprotected indole) cyclises via a 7-exo-trig 1,2-insertion with almost complete chemoselectivity to give a 7-membered ring. Whilst the feasibility of this mode of ring closure is predicted by Baldwin's rules, consideration of the product reveals that an 8-membered must be generated; fortunately a spontaneous ring expansion in step four rectifies the problem[35]. Following the initial ring formation, β-hydride elimination is the expected step due to the presence of seven optimally located hydrogen atoms. Nonetheless, the reaction again diverges from the anticipated result by heterolytic fragmentation into a tertiary carbocation. Upon termination of this domino reaction, preparation of the target compound is achieved in three straightforward steps[35].

Whilst it is possible to rationalise the result that was obtained, it is difficult to understand how such a process could have been planned in advance. Palladium has been found to catalyse many cascade processes, but their unpredictability has meant that they have only been of academic interest. Nonetheless, the success of this synthesis means that the technique should be earmarked as a potentially useful industrial method.

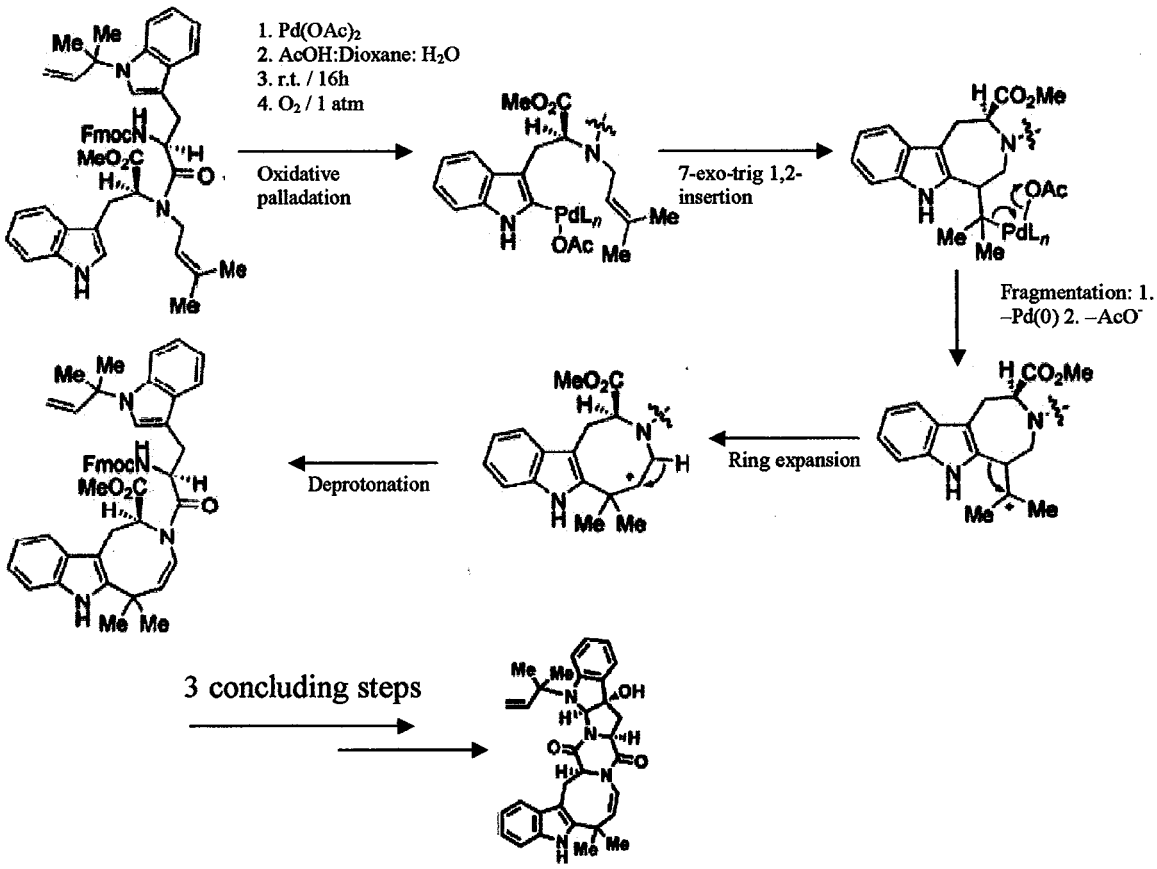

Figure 3.3: The total synthesis of okaramine.

It is a surprise that this synthesis was conceived given the unconventional route it follows, Baran et al. admit that they were "humbled by the large number of completely unforeseen roadblocks" – but of course this should have been expected given the low feasibility of the reaction[35]. Selecting the solvent system was among the most challenging of tasks, but being a Heck reaction great sensitivity to reaction conditions is expected. Omitting acetic acid from the reaction mixture led to no reaction occurring whilst in the absence of water, 7-membered rings were formed exclusively (no ring expansion took place)[36]. A thorough understanding of the subtleties of domino reactions is necessary before the methodology can be applied freely, at the moment the design process is highly labour intensive due to the amount of good fortune and creativity involved.

Conclusions

In recent years, more and more palladium-derived compounds are being recognised as important catalysts in an eclectic assortment of syntheses including the production of industrial feedstock and fine chemicals as well as the assembly of large, intricate natural products. Through our examples we have shown that Pd catalysts enable: high selectivity, high yields, shorter synthetic routes, mild reaction conditions and low toxicity in addition to the tolerance of unprotected functional groups, oxygen, water, and acid. These traits are among the hallmarks of a green and commercially attractive synthesis – an efficient synthesis. Even in light of the great expense of palladium (see appendix B for more information on the price of palladium), the rapid appearance of palladium catalysed reactions in industry over the last 20 years emphasises the extent to which this major drawback is overshadowed.

Perhaps the most important, yet least documented, facet of palladium chemistry that we encountered above is what Fairlamb has aptly termed the "black-box". Research in this field regularly uncovers unexpected and unexplainable phenomena that promise to enhance the efficiency of synthetic

routes, for instance, the idea of homeopathic conditions has led to significantly reduced catalyst loadings in isolated cases, but only when this observation has been fully rationalised can we expect to see it become a standard procedure in the optimisation of reaction conditions. This same conclusion could be drawn from many of the novel protocols that we have investigated, but progress is already discernable in some key areas. Direct arylation without prefunctionalisation of the substrates promises to solve all issues of waste formation with a pathway offering maximum atom economy. Fagnou's untimely death has slowed progress in the field but his lab continue to report direct coupling strategies – it is only a matter of time before a large library of these direct reactions are available for widespread use. A key factor in the pace of this particular development is the concomitant mechanistic elucidation work that has been undertaken – this provides a theoretical base from which substrate and reagent combinations can be postulated. This work serves as an excellent template for research in Pd-mediated synthesis – firstly observing the "black-box" at work and then unpacking the mechanics of its action such that the techniques scope can be broadened.

Palladium's role in synthetic chemistry is perhaps analogous to that of the stem cell in biology – it acts a progenitor from which a plethora of systems can be developed to catalyse a vast range of reactions, and what's more it may be the only viable catalyst for a given transformation.

More often than not, palladium catalysts exhibit the traditional characteristics of an efficient synthesis (high atom economy, yield, and selectivity). Furthermore, modifications to the system (for example, new ligands, solvents or additives) frequently lead to "black-box" phenomena that may enhance palladium's existing efficiency, and lastly, completing the triad of useful properties is palladium's versatility, it catalyses an enormous variety of reactions - a feature useful in its own right - but also vital to the success of one-pot and domino reactions, the most efficient of all reaction schemes[37]. With increasing pressure on chemists to design syntheses that are more environmentally sound and more economical, palladium catalysts will almost certainly feature ever more prominently in 21st century synthetic endeavours.

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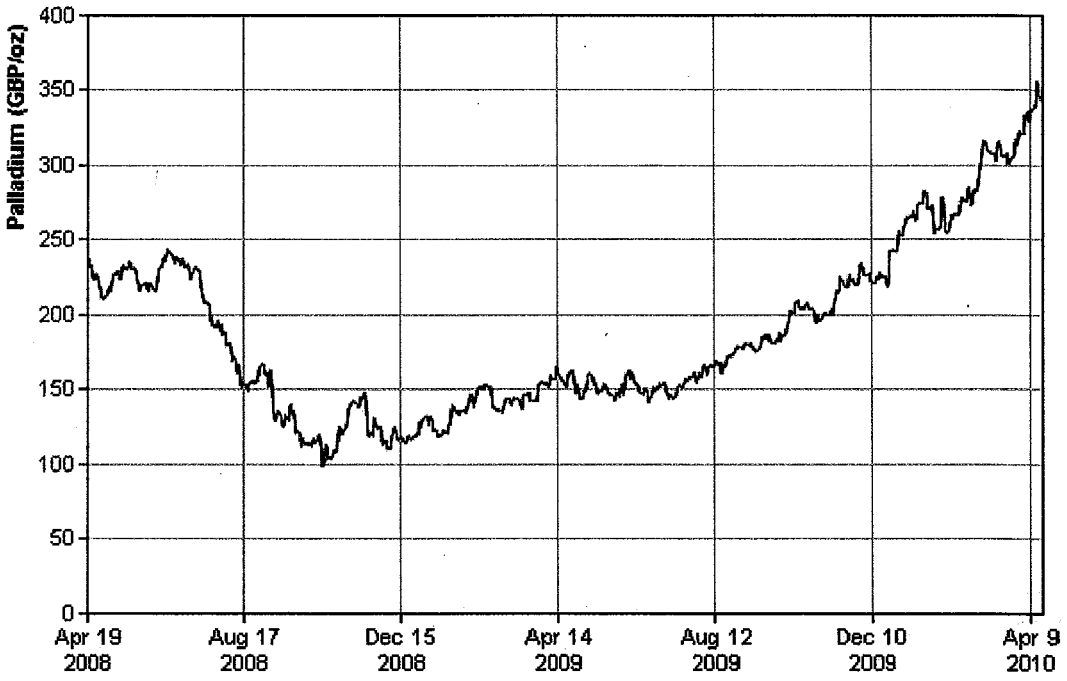
Appendix A: List of Abbreviations

Ac	Acetyl
BINAP	2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMIM-PF_6	1-Butyl-3-methylimidazolium hexafluorophosphate
Cy	Cyclohexylamino
dba	Dibenzylideneacetone
DCM	Dichloromethane
DMA	Dimethylacetamide
DMF	Dimethylformamide
Et	Ethyl
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
Me	Methyl
OPiv	Pivalate (2,2-dimethylpropanoate)
p-	Para-
PMP	1,2,2,6,6-pentamethylpiperidine
r.t.	Room temperature
tBu	Tertiary-butyl
TFA	Trifluoroacetate
THF	Tetrahydrofuran

Source: Negishi, E., De Meijere, A. *Handbook of Organopalladium Chemistry for Organic Synthesis: Volume 1 and Volume 2*, pp. xxxiii - xxxv (Wiley, Hoboken, 2002).

Appendix B

The chart below depicts the fluctuation in palladium price (in British pounds per troy ounce where one troy ounce is approximately equal to 31.10 grams) over the period commencing on the 19th April 2008 and ending on the 18th of April 2010.



Source: Infomine Inc. Dynamic Charting Tool [Online]. Available at : www.infomine.com/investment/charts.aspx?mv=1&f=f&r=2y&c=cpalladium.xgbp.uoz#chart [Accessed on: 18/04/2010]

OCR
RECOGNISING ACHIEVEMENT

Project Progression Record

Level 3 **Line of learning (when taken as part of a Diploma)** n/a

Centre Name _____ **Centre Number** _____

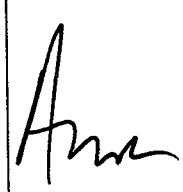
Learner name _____ **Learner Number** _____

The topic chosen must allow the learner

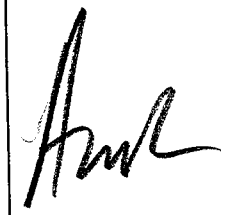
- to be fairly assessed at the standard applicable to the Project level (level 1, 2 or 3).
- the opportunity to meet comparable demands to those made on other learners working at the same level
- to meet all of the Learning Outcomes and Assessment Objectives of the Project.

Activity	Date	Detail	Supervisor's initials	Comments
The date you started your project	09/09/09	I first decided that I would do an extended project in July, 2009 – however, I did not decide the form that the project would take until the date indicated to the left. The evaluation document describes some of the events that preceded my decision to write a dissertation.		

Activity	Date	Detail	Supervisor's initials	Comments
First thoughts about topic and working title	12/09/09	- Efficiency in organic synthesis - An article in the journal "Nature Chemistry" was useful as stimulus material – it outlined the aspects of an efficient synthesis and its role in modern chemistry. - Organotransition metal compounds routinely contribute to efficient strategies owing to their varied catalytic behaviour. This is not a topic I have studied much before and it would be enjoyable to deepen my knowledge in this area. - First working title: "How can transition metal catalysts be used to improve the efficiency of organic synthesis?" - I have agreed with my supervisor that the topic is suitable and this is only a tentative working title and is likely to change.		
	15/09/09	- Having reviewed the literature surrounding the original question, I have decided that its scope is too broad – attempting to discuss more than one transition element would lead to a lot of superficial facts and comments. Instead, I have chosen to focus on the use of palladium alone. I chose palladium because it has been investigated most thoroughly for its catalytic uses. - Second working title: "How can palladium catalysts be used to improve the efficiency of organic synthesis?"		
	17/09/09	- I feel that the discussion could be made more convincing by considering a smaller subset of reactions. - The vast majority of research papers that I have looked at (I have only been looking at abstracts for the moment) have dealt with aromatic reactants. - Furthermore, a large number of pharmaceuticals, industrially important fine chemicals, and academically interesting natural products are substituted aromatic species; hence, I intend to consider how palladium can assist organic syntheses involving this subset of compounds alone. - The final title can be found below.		

Activity	Date	Detail	Supervisor's initials	Comments
What is the title of the project? This could be phrased as a question, hypothesis or statement.	22/09/09	- "How can palladium catalysts increase efficiency in the synthesis of aromatic compounds?" - I did not require any assistance in the development of my final title.		
What do you hope to achieve by the time you complete the project?	08/10/09	1. To produce a dissertation that: a) Explores the most important palladium catalysed reactions and investigates the improvements to synthetic efficiency that they offer to industrial and research chemists over alternative methods. b) Takes into account the disadvantages and problems that palladium chemistry can introduce and thus determines the net utility of the synthetic methods explored. c) Investigates some of the recent discoveries in the field of palladium catalysis and subsequently assesses the extent to which they can be employed in industry and research to construct efficient synthetic routes. 2. Extended essay writing is not present in the chemistry A-level syllabus, thus I would like to have had the chance to thoroughly investigate an area of interest and then produce a piece of extended writing adopting the conventions of formal scientific writing. 3. Enhance project management skills, in particular, the ability to plan effectively and work to deadlines over an extended period. 4. Develop research skills, such as the ability to use (and properly cite) academic research papers to extract information– something that I will need to do regularly at university.		

Activity	Date	Detail	Supervisor's initials	Comments
What form will the assessment evidence for the project take? (ie design, performance, report with findings from an investigation, artefact, [*dissertation – level 3 only*])	09/09/09	A dissertation based on literature (as opposed to one based on my own research). Choosing the form of assessment was the first decision I had to make.		
Have you produced an outline plan to show your project timeline?	16/09/09	I have produced a plan which is included in my portfolio. After each stage of the project was completed, I briefly reviewed the task's outcome – these notes are recorded in a separate column on the plan.		
What will you need to achieve your project? eg tools, equipment, techniques and technologies	06/10/09	I will require: 1. Access to Reading University Library and their e-resources; it will be especially important that I gain access to e-journals. I will attempt to obtain an ATHENS login such that I can use these facilities from home. 2. Software that enables the accurate drawing of chemical structures, and ideally a tool that aids the planning of synthetic routes. 3. Access to bibliography management software. 4. Access to a photocopier in the library in order to copy articles that are not available as an electronic resource. I will need to purchase a photocopying card at the library for a small fee. 5. Access to the internet and word processing software. Further details of technology usage can be found in the plan and the evaluation document.		

Activity	Date	Detail	Supervisor's initials	Comments
Will you or have you used a range of sources for your information?	06/12/09	Yes. I intend to use books, non-peer-reviewed journals (magazines), peer-reviewed journals, as well as websites. This will provide me with material based on both primary and secondary research. Research papers will detail the results of a scientific investigation (primary research) – and will relate to a precise topic only. Books and review articles will themselves be based on the research of others (secondary research) and will provide a broader content.		
Is the information selected suitable and sufficient to fit the question/task/brief?	09/02/10	Yes. Inevitably, there was a mixture of useable and irrelevant material in each source that I used. My decision to download more papers than I intended to use was important as this meant that I could be more selective – I have now chosen the papers that I intend to use. Many of the papers were focussed on theoretical aspects of chemistry as opposed to my particular subject (i.e. efficiency in synthesis); nonetheless, I have carefully read and interpreted the papers in order to extract useful points and make relevant deductions.		
Have you identified any links with other areas of study or areas of interest which relate to your project?	27/02/10	- Despite the fact that I put forward the project as one based on organic chemistry, it is inextricably linked with both economic and environmental issues. These are two aspects which are studied extensively by industrial chemists, but only receive passing references in the chemistry A-level syllabus. Writing the dissertation has helped me realise that a deep knowledge of the chemistry behind efficient processes is essential to the development of environmentally and economically sound industrial synthesis design. - Explanations for why certain chemical behaviour occurs and descriptions of reaction mechanisms were also areas of interest that I regularly encountered in the research material. Whilst I did incorporate some of this into my project, it was normally not relevant and so was not included. Nonetheless, they were interesting to read.		

Activity	Date	Detail	Supervisor's initials	Comments
What skills need to be applied to use the information you have collected?	07/12/09	- Since I was not able to take books out of the university library, I had to find the relevant content and then photocopy the useful pages. The books were often very large and so reading skills, such as scanning and skimming, were important. Google Books also helped me to locate relevant sections – but not all the books I used were available to view on google books. - I have more time to look over the research papers as these were downloaded to a USB flash drive. Owing to the large number of papers, I still need to work quickly to keep to my schedule. Similar speed reading techniques will come in useful in order to eliminate the least useful papers. - In order to analyse the information contained in the papers I will need to understand the content. Hence, I need to keep reference books at hand to look up any unfamiliar topics. I will also use the internet if I am in doubt about a deduction or comment I would like to include. - Lastly, I will need to assess the sources in terms of their accuracy and reliability. It will also be important to consider the authorship of each sources as well as the source's age. My notes have been recorded in my evaluation document.	AMR	
Did you apply the tools, equipment, techniques and technologies to use the information that has been collected to complete your project?	22/02/10	Yes. The "outcome" column of my plan details the way in which the technology was used and the skills I developed are recorded in the evaluation document.	AMR	

Activity	Date	Detail	Supervisor's initials	Comments
What outcomes/objectives have you achieved so far (mid-term review)?	05/01/10	I have completed the first three sections of my plan – confirming the topic, acquiring access to the necessary resources, and completing the research. Additionally, I have started to write the dissertation – but progress has been slow due to university interviews and preparation for exams. Only a table of contents and the introduction has been written. Despite the lack of written progress, the fact that I have read through all my research documents means that I have gained a good idea of the direction that the dissertation will take. The initial objectives of my dissertation that I identified above seem to be achievable based on the material I have obtained.		
Evaluation of own learning and performance so far (mid-term review).	05/02/10	- Even though I feel that I have identified the sections of my dissertation, and thus have a clear idea of what I will be writing about, I am concerned that the dissertation will take longer to write than I had planned. Coupled with the fact that exams will dominate most of January, I may need to amend the plan. - I have enjoyed working independently, guidance from my supervisor has been minimal; however, the advice I did receive was useful – most notably, that I should aim for about one source per 100 words (this is a guideline often used by postgraduates) and that I should structure the research by starting with books and review articles. Guidance of this nature definitely facilitated autonomy.		

Activity	Date	Detail	Supervisor's initials	Comments
What have you changed after reviewing your work?	08/02/10	- Whilst writing the dissertation I have decided that a case study style will make the technical points easier to express and also more accessible. What I mean by this is that I will refer to specific examples to evaluate the degree to which a methodology confers greater efficiency to a synthesis. However, I will need to assess whether the examples have the potential for a wide range of applications or are merely special cases illustrating a point of academic interest. - I will attempt to speed up without reducing the quality of the work such that I can produce a first draft by mid February.		
Final phase - Do you feel that you have achieved all of the outcomes/objectives of your project?	19/04/10	Yes, I feel that I have accomplished all of my objectives. Completing the work has prepared me well for future pieces of scientific writing – though it should be noted that most future pieces of work will have to be produced much more rapidly than this project. Developing a refined style of scientific writing will take a long time, but writing an Extended Project dissertation has been an enjoyable way to start this process. Furthermore, the research that was necessary to write the dissertation was extremely interesting in its own right – it has been rewarding to slowly build up my chemical knowledge. For example, my knowledge of scientific terminology has greatly increased, and I have also become familiar with the so-called "trivial" names for chemical compounds that are used ubiquitously by scientists but rarely encountered in a school environment.		

Activity	Date	Detail	Supervisor's initials	Comments
Presentation of Portfolio • written section (compulsory, even if the outcome is a performance or artefact) • other evidence can be DVD, photographs, slides, CD, artefact, digital technologies etc	25/04/10	The portfolio consists of: 1. Project Progression Record 2. Plan 3. Some of the research material I used and the article in "Nature Chemistry" that played a role in motivating the topic. 4. Two drafts of the dissertation 5. Final dissertation (and a bibliography outlining the sources used) 6. The powerpoint slides that accompanied the review presentation 7. An evaluation document - I have consolidated the notes I produced during the ongoing evaluation process and also included a concluding section which considers transferable skills and personal development.	AMR.	

Activity	Date	Detail	Supervisor's initials	Comments
Describe how you have presented your project to an audience	23/04/10	- The presentation took the form of powerpoint presentation – the oral component of the presentation was delivered using brief notes. The presentation reviewed the way in which I completed the project as well as covering some of the scientific conclusions I was able to draw. It lasted just under 15 minutes. The audience was small (2 students and 2 members of staff) – but this suited the technical nature of the project. - I did not require help in creating the presentation or setting up the computer and projector. - I used the internet to review some of the important features of a good presentation, particular relating to delivery. Advice I found included: make eye contact with each member of the audience, use gestures and body language as opposed to remaining stationary, ensure the computer equipment is working before the presentation and do not read from notes for extended periods of time.	AML	
Have you evaluated your project, taking into account any feedback from your audience?	22/04/10	Yes. A full evaluation including both notes from the ongoing evaluation process as well as some concluding remarks can be found in my separate evaluation document.	AML	
Date of project submission to teacher	26/04/10	The project was submitted on the agreed date.	Ann	

Dissertation plan: "How can palladium catalysts increase efficiency in the synthesis of aromatic compounds?"

Task	Proposed time of completion	Details	Outcome
Confirm topic	Late September 2009	I have decided that the field on which I intend to base the project is the use of transition metal catalysis in the design of efficient organic syntheses. However, I will need to scan the relevant sections in several textbooks and look at some review papers to familiarise myself with both the well-established information and current research in this field such that I can be sure that there is sufficient to write about. Working title: "How can transition metal catalysts be used to improve the efficiency of organic syntheses?"	Having read chapter 48 in "Organic Chemistry" (Clayden et al.) as well as the RSC tutorial text. "Organotransition metal chemistry", I have decided that the synthetic role of palladium will be a topic that is both interesting and pertinent to current research. I would not be able to pursue each topic in much depth if I were to focus on more than one transition metal. Palladium appears to be the most versatile catalyst, and is hence the most widely researched transition metal. I will also be focussing on reactions yielding aromatic compounds – details of the development of the final title can be found in the Project Progression Record.
Acquire access to necessary research material or other resources	Mid October 2009	1. Attempt to obtain access to ATHENS – this will provide access to all the academic e-resources at Reading University from any computer with internet access. 2. Desired research resources: Research papers in relevant journals, specialist books, websites, and videos of lectures. 3. Desired software: a) I intend to use approximately 50 references (based on the one reference per 100 words guideline), and so a bibliography management program would be useful. b) A large number of chemical structures and diagrams will be included, thus appropriate software to create these myself would	- It has proven to be impossible to obtain an ATHENS username – the University have been unwilling to provide me with one. Instead, I have obtained walk-in user rights at the university library which will enable me to visit the library and access their e-resources under staff supervision. - The library has allowed me to access the specialist books that I require. However, they did not have the following book (and were unable to order it in): "The Mizoroki-Heck Reaction" by Martin Oestreich. I resolved this issue by using "Google Books" (the tool I used to locate the book in the first place) which provided limited access to the book – this proved sufficient for my purposes. - Access to the e-resources has enabled me to get hold of a wide range of journal articles in pdf

		be useful. c) I would like to make an effort to include my own judgements/conclusions/predictions and thus access to a database of reactions such as crossfire, or a tool with a synthesis planning facility such as reaxys, will greatly facilitate my attempts to analyse the research myself.	format. - I used the MIT Opencourseware and the Berkeley Webcast websites to watch some lectures covering catalysis and organometallics. These did not turn out to be very useful and offered no insight beyond what I obtained in my initial reading of some textbooks. - All the professional bibliography management programs were quite expensive to purchase – so I decided to use the 30-day free trial of EndNote, even though the trial will expire well before the end of my project. This is because I intend to complete the bulk of my research within the trial period, importing all the relevant references I find. I will be able to export them to Microsoft Word towards the end of the free trial. It will then be easy to remove any redundant references, and furthermore, I can manually add any extra references that I may need. This will reduce the time I have to spend typing out references in a specific format. - In order to draw chemical structures and reaction schemes, I have downloaded ACD/ChemSketch produced by ACD/Labs. This is a very sophisticated piece of software that is only available without charge when used for educational purposes. The commercial version is very similar but costs $695. - Reading university is currently running a trial of Reaxys – this is a powerful workflow tool used by professional synthetic chemists. I have been granted access to this as part of my walk-in user agreement – but again I must be logged in under staff supervision. The synthesis planner feature is the aspect I intend to exploit; it will be very useful in helping me design and confirm the feasibility of

			example reactions to illustrate points in my dissertation.
Carry out the research	Early December 2009	1. I will use the internet, to search for research papers and books. Google Scholar and Google Books will be the primary tools I use to locate potentially useful material. Following this, I will need to use the Reading University's "Unicorn Library Catalogue" in order to determine whether or not I will be able to obtain the material at the library. 2. The chemistry liaison librarian at the library has offered to provide some basic training in the use of their e-resources – I intend to complete this training on my first visit to the library.	- I found lots of relevant research papers and books; I selected them based on the abstract and introduction respectively, obviously the title was an important guide as well. - The training was very useful, it allowed me to confidently download the papers that I required, use the online tool reaxys, and furthermore, locate books and papers (this was required when a journal was not available as an electronic resource).
Mid-term review	Early January 2010	This task should not take long – it will probably last no more than 30 minutes. Hence, I intend to start the next task, that is, the writing of the dissertation, in December 2009, only stopping to review the project at a convenient time in January. Ideally, the review will take place before the commencement of exams.	This has been completed and my thoughts have been noted in the project progression record.
Write dissertation	Mid March 2010	- At this point I will have a large amount of annotated research, but I will probably not be certain of the structure of my dissertation. So, it will be necessary to decide upon the major subheadings of the dissertation. Following this I will need to write an introduction – this should outline the project's rationale and also introduce some of the essential terminology. - Due to the large amount of technical vocabulary used, only the terms that are most important will be introduced. It will be assumed that the reader has access to the internet or suitable textbooks in order to look up unfamiliar jargon. - I aim to start work on the	- Four drafts were produced in total – with the first draft being completed by mid February. In my portfolio I have included only two drafts and the final dissertation (the other two drafts being too similar to warrant inclusion). - It was quite easy to group the papers by the type of reaction they discussed. – This motivated my decision to divide the body into three main sections: Biaryl Synthesis, Heck Reactions, and Future Work. The first two sections deal with two well-known "types" of reaction – although some of the special protocols were very modern, whilst the final section covers two strategies which are in

		dissertation as soon as the January exams have finished.	development and require significantly more research before they can be employed on a large scale.
Produce and deliver the presentation	Early April 2010	I will need to produce a powerpoint presentation and an accompanying talk that outlines the way in which I conducted the project as well as some of the main conclusions I reached. I intend it to be approximately 10-15 minutes and the audience will be non-specialist – that is, I will assume some general scientific knowledge, but no detailed knowledge of the project topic.	- The audience was engaged and remained attentive throughout the presentation. - It lasted nearly 15 minutes as intended. - I was able to successfully deal with the questions that I received.
Evaluation	Mid April 2010	I intend to make notes regarding the progress of my project as it proceeds – I will use the notes produced from this ongoing evaluation to write an evaluation document.	In addition to writing up the brief notes I produced as the project progressed, I included a final evaluation in order to reflect on the project at its completion.
Submit project	Late April 2010		The project was submitted for marking on the 26th April, 2010. This was the date that had been decided upon in advance.

* Early = week one of the month; mid = week two - week three of the month; late = before the end of the month

** No amendments to the plan were necessary during the course of the project – all deadlines were kept to.

Synthesizing our future

Chemistry has a central role in science, and synthesis has a central role in chemistry. Ryoji Noyori from Nagoya University considers where synthetic chemists should focus their efforts.

Chemistry attempts both to understand the structures and characteristics of substances in minute details at the atomic and molecular levels, and to create new compounds with desirable properties and functions. One clear direction, both now and in the future, of this core science is to merge with other fields to produce more interdisciplinary science. In view of its significance, chemistry demands the highest level of scientific creativity and insight to explore its limitless possibilities.

With the characteristics described above, chemistry has rapidly expanded into the field of life sciences, as prophesized by James Watson (the 1962 Nobel Laureate for Physiology or Medicine) when he said "Life is simply a matter of chemistry." When DNA was found to have a double-helical structure in 1953, chemistry really began to enter the core region of life sciences. The decoding of the human genome in 2003 led to a new world of chemical science. Thanks to advanced technologies and the diligent work of scientists in many fields, we are now able to elucidate the precise atomic-level structures of large biomolecules such as DNA, RNA, proteins and polysaccharides.

Consequently, the focus of much chemical research has been moving from structure to function. As dynamic interactions between large biopolymers and small organic molecules often control the processes in living organisms, it seems certain that scientists will soon be able to elucidate the chemical mechanisms of cell functions and perhaps even of human thought and memory. We still have few solutions to the problem of creating peaceful human existence, but furthering our understanding of precise biological mechanisms through chemical biology and chemical genomics aided by advanced biomolecular imaging technologies will lead to the discovery of rational and more effective drugs in the post-genome era.

Although the properties of molecules and their assemblies remain unpredictable solely from their constituent elements, the possibilities for atomic and molecular manipulation are unlimited. Chemical synthesis provides a logical basis for the biosciences and materials sciences, and their technological applications. Synthetic chemistry enables the flexible manipulations of elements — we can create value-added substances from abundant natural resources such as oil, coal and biomass. In principle, we can create molecules that have all kinds of properties at will. In view of the very nature of chemistry, its integration with other research fields will have enormous scientific and technological impacts.

> "Chemical synthesis has now reached an extraordinary level of sophistication, but there is vast room for improvement." - Include a Section on future/latest research that discusses these improvements

Looking at the course of human history, we see that man-made substances and materials have played a significant part in determining the quality of life. Although chemical synthesis has now reached an extraordinary level of sophistication, there is still vast room for improvement. Chemical synthesis must pursue 'practical elegance'[1] — that is, it must be logically elegant but must at the same time lead to practical applications. Many of the stoichiometric reactions used at present, although useful, can and should be replaced by more efficient catalytic processes.

- Practical issues relate to the industrial roles of Syntheses

- Logical elegance relates to academic pursuits such as "Total Synthesis"

Catalysis has been, and will remain, one of the most important research subjects, because this is the only rational means of producing useful compounds in an economical*, energy-saving and environmentally benign way*. According to a promotional brochure from the renowned German

* This is what efficiency can be defined as: i.e. the extent to which a process is economical and environmentally friendly

chemical company BASF, more than 80% of globally produced chemicals are made using catalytic processes. The importance of efficient heterogeneous, homogeneous and biological catalysts[2] is continually increasing. Practical catalysts must enable reactions that are rapid, capable of being scaled up, and selective in the products formed. Molecular catalysts displaying chiral efficiency that rivals or exceeds that of enzymes are highly desirable[3, 4, 5].

* These issues are ways to achieve efficiency e.g. increasing selectivity reduces waste => more economical

At the same time, industry demands the development of thermally stable, salt-, poison- and acid/base-resistant synthetic enzymes, because naturally existing enzymes are not robust. Catalysis is thus critical to the production of commodity chemicals and also new substances in research laboratories. In providing a path of lower activation energy, however, it does not improve the ability to conduct endothermic processes, which require the investment of extra energy or the use of special product-separation technology to shift chemical equilibria to favour the formation of a desired product.

There are many reactions that do not work under thermal conditions. To enhance the power of synthetic chemistry, photosynthetic catalysis enabling otherwise energetically forbidden transformations needs to be explored in greater depth. Similarly, current step-by-step organic syntheses must be a combination of all thermodynamically downhill reactions, limiting the overall efficacy. Therefore, cascade syntheses[6], or those that combine multiple components in a single step[7], are particularly appealing. An intricately designed device that can integrate multiple catalysts along with suitable cofactors to achieve this without the necessity of human intervention is a worthy goal.

- Cascade reactions (aka domino reactions) should be considered an important part of current and future research

Ideally, we should aim at synthesizing target compounds with a 100% yield and 100% selectivity and avoid the production of waste. This process must be economical, safe, resource-efficient, energy-efficient and environmentally benign. In this regard, the atom economy[8] and the E-factor[9] should be taken into account. The 3Rs (reduction, recycling and reuse) of resources are particularly important. Such 'green chemistry'[10] is creative and brings about prosperity, and at the same time takes responsibility for society at large. Any efficient chemical processes must also be socially acceptable. Green chemistry is not a mere catchphrase. It is an indispensable principle of chemical research that will sustain our civilized society in the twenty-first century and further into the future. Green chemistry must therefore be promoted and supported by the scientific community as well as by governments, industry, and all other sectors of society. - Efficiency encompasses green chemistry

Science is destined to be more closely involved with society in this century. It should be no surprise that 'Chemistry: the key to our future' is the slogan of the 2010 Chemistry Olympiad, to be held in Tokyo. In contrast, uncontrolled, excessive economic activity based on science and technology has brought with it a range of global issues. Scientists' efforts should be directed towards solving a range of existing or predicted social and global issues associated with energy, materials, the environment, natural disasters, water, food and health. Chemists have an immense responsibility to tackle these problems; however, the prevalent over-specialization in science tends to make it difficult to find solutions because there are usually multiple causes. To remedy this situation, we need a more broadly based science education, which will better equip future chemists to tackle the issues outlined above.

Science is, in principle, objective. But it is human intelligence and endeavour that discover and create scientific knowledge. The scientific world should be borderless; scientists from both advanced and emerging nations — with different backgrounds and values — must cooperate for the survival of our species within the confines of our planet. This is the greatest challenge facing chemists in conducting their research.

Source: Noyori, R. Synthesising Our Future. Nature Chemistry **1**, 5-6 (2009).

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Regioselective Dicouplings: Application to Differentially Substituted Pyrroles

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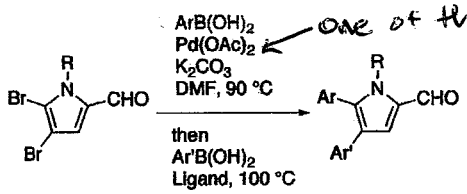
ABSTRACT



one of the cheapest Pd catalysts

In an effort to develop a more concise route to differentially substituted pyrroles (such as that found in the lamellarins), a completely regioselective one-pot double Suzuki coupling has been discovered. The key feature is the use of a ligand-free palladium catalyst under optimized conditions, which results only in coupling of the C5 bromide. At this point, addition of a second boronic acid and a phosphine ligand enables coupling at the remaining C4 bromide.

The one-pot concept is a useful heuristic for improving efficiency

As part of our ongoing interest in the synthesis of the lamellarin family of natural products, we were interested in methods that could reduce the overall length of our first generation synthesis.[1] In examining this synthesis, it became apparent that the most promising way to reduce the number of steps was to focus on the coupling and halogenation steps. Because each one of the three aryl subunits is installed via a Suzuki coupling, this required three separate halogenations and three separate couplings. As such, just the installation of the aryl subunits accounted for over half of the total length of the synthesis (6 out of 11 steps).

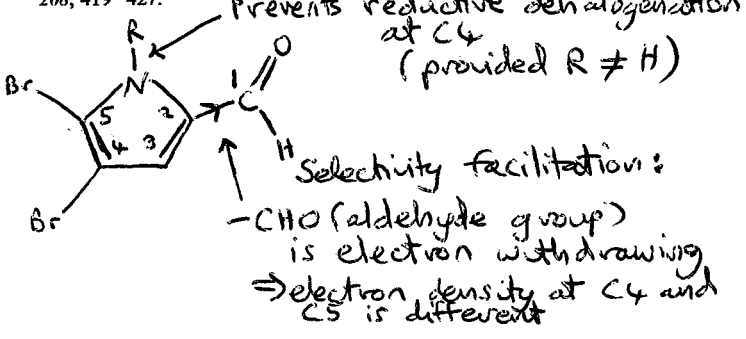
Reducing the no. of steps saves time, labour, and resources.

In contemplating ways to reduce the number of halogenation/coupling steps, we found that one potential solution would be to explore the option of regioselective couplings on polyhalopyrroles and to conduct more than one coupling in the same pot (one-pot polycouplings). Taking this approach to its extreme, we could reduce the six steps for the installation of the aryl subunits to two steps − one triple halogenation followed by one triple coupling. As a result, our lamellarin synthesis would be reduced from 11 steps to 7 − a tremendous improvement.

Lamellarins are cytotoxic to cancer cells

The idea of regioselective couplings of polyhaloheteroaromatics has been attracting greater attention in recent years, so although it had not been studied in the context of pyrroles, it appeared promising.[2] However, the concept of conducting more than one coupling in the same reaction vessel is quite rare. Indeed, within the area of heteroaromatic systems, there are only two existing examples.[3]

To explore the potential of this regioselective polycoupling approach, we began our efforts with pyrrole aldehyde **1**. This substrate was selected for several reasons. First, for successful regioselectivity in the coupling of polyhaloheteroaromatics, there is a clear requirement for some degree of electronic difference between the different halogenated centers.[4] For the pyrrole ring system, this can be most readily achieved by substitution with an electron-withdrawing group. Further, because previous studies had indicated that the pyrrole nitrogen would need to be protected to avoid extensive reductive dehalogenation at C4 and to simplify product analysis by avoiding deprotection under the reaction condi-



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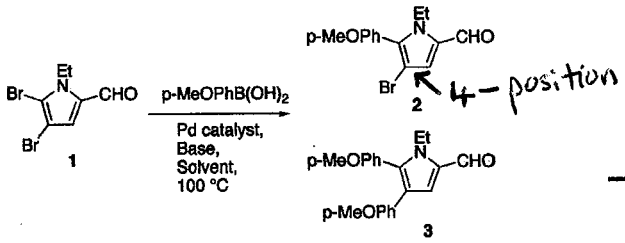
tions, an *N*-alkyl group was selected.[5] Ultimately, pyrrole aldehyde **1** was prepared via a slight modification of the literature procedure.[6]

Treatment of aldehyde **1** with *p*-methoxyphenyl boronic acid under standard Suzuki conditions did afford a separable mixture of products from which monocoupled product **2** and dicoupled product **3** could be isolated in 32 and 29% yield, respectively (Table 1, entry 1). Armed with this encouraging result, several modifications with respect to the palladium catalyst, activator, and solvent were studied. Very rapidly, it was noted that a ligand-free palladium catalyst dramatically reduced the amount of dicoupled product that was observed. In conjunction with this catalyst, potassium carbonate afforded the best selectivity, although a number of other bases were effective but afforded lower conversions or simply lower isolated yields (Table 1, entries 3 and 5−7). Finally, shifting to an ethereal solvent proved to slightly increase the amount of double coupling when using potassium carbonate as the base (Table 1, entry 8), and an acetone/water mix afforded a very complex mixture of products (Table 1, entry 9).

Table 1. Regioselective Monocoupling Studies

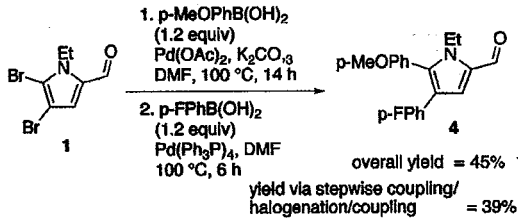


entry	catalyst	base	solvent	% yield (2/3)
1	$Pd(Ph_3P)_4$	Na_2CO_3	DMF	32/29
2	$Pd(Ph_3P)_4$	K_2CO_3	DMF	42/5
3	$Pd(OAc)_2$	Na_2CO_3	DMF	45/18
4	$Pd(OAc)_2$	K_2CO_3	DMF	56/<5
5	$Pd(OAc)_2$	K_2CO_3	DMF	28/7
6	$Pd(OAc)_2$	Cs_2CO_3	DMF	31/5
7	$Pd(OAc)_2$	$Ba(OH)_2$	DMF	complex mix
8	$Pd(OAc)_2$	K_2CO_3	dioxane	48/8
9	$Pd(OAc)_2$	K_2CO_3	H_2O/acetone	complex mix

The end result of these optimizations was a catalyst system (palladium acetate, potassium carbonate, DMF) that completely avoided any coupling at the 4-position. Indeed, coupled product **2** could be resubjected to the coupling conditions, and no trace of dicoupled product was observed even after 24 h at 100 °C. Thus, high regioselectivity could be achieved. At the same time, the question remained as to how to now accomplish the second coupling.

The first solution was to add a more active catalyst with the second boronic acid. Because tetrakis(triphenylphosphine) palladium(0) had already been shown to affect coupling at both the 4- and 5-positions, this was selected as the second catalyst. Thus, after TLC indicated complete consumption of starting material, a second boronic acid was added, along with tetrakis(triphenylphosphine) palladium(0). Much to our delight, this did lead to the formation of the desired double-coupled product **4** in 45% yield (Scheme 1).

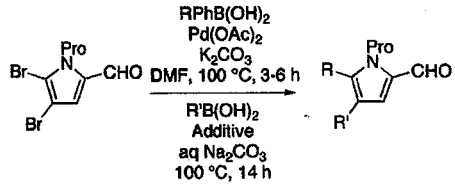
Scheme 1. First Regioselective Double Couplings



Although the yield may seem modest, it is an improvement over the three-step synthesis starting from 4-bromo-1-ethylpyrrole-2-carbaldehyde, which affords **4** in a 39% yield overall. Using this stepwise approach (coupling, halogenation, coupling) also enabled us to confirm the suspected regiochemical outcome of the first coupling with dibromide **1**.

The next question was whether the addition of two different catalysts was necessary. On the surface, it appeared that there might be a different approach to go from a ligand-free system to a phosphine-ligated system − simple addition of a phosphine. As a result, the first stage of the coupling was performed as before, but now, along with the second boronic acid, two equivalents of triphenylphosphine (relative to palladium acetate) were added. Gratifyingly, this resulted in an improved 48% yield of double-coupled product **4** (Table 2, entry 2). Indeed, an even better result was obtained by employing the stabilized phosphonium salt form of tri-*tert*-butylphosphine popularized by Fu.[7] Now the isolated yield was 58% (Table 2, entry 3).

Table 2. Additional Regioselective Double Couplings



entry	Pro	R	R′	additive	% yield
1	Et	*p*-MeOPh	*p*-FPh	$Pd(Ph_3P)_4$	44
2	Et	*p*-MeOPh	*p*-FPh	Ph_3P	48
3	Et	*p*-MeOPh	*p*-FPh	tBu_3P/HBF_4	58
4	Et	*p*-FPh	*p*-MeOPh	tBu_3P/HBF_4	51
5	Et	*p*-MeOPh	stryenyl	tBu_3P/HBF_4	56
6	MEM	*p*-MeOPh	*p*-FPh	tBu_3P/HBF_4	54

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These same reaction conditions were equally effective with other boronic acids, including alkenyl boronic acids (Table 2, entry 5). The alkyl group on the pyrrole nitrogen could be modified as well to other potentially more readily removable groups such as the MEM group (Table 2, entry 6).[8] This observation now opens the door for numerous synthetic applications of this one-pot, double-coupling route to substituted pyrroles such as the lamellarins, Lipitor, and the prodigiosins.[9]

In conclusion, we have reported the ability to regioselectively couple 4,5-dibromopyrrole aldehydes and to carry out two couplings in the same reaction pot by simply adding a phosphine ligand to generate a more active catalyst for the second coupling. This approach has the potential to be of great benefit in the rapid and convergent synthesis of substituted pyrroles. The extension of this method to pyrroles with other substitution patterns and even to other heteroaromatic systems is underway and will be reported in due course.

Acknowledgment. We thank the Research Foundation and the Leukemia Research Foundation for financial support of this research.

Supporting Information Available: Full spectral data and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Interestingly, allyl and benzyl protecting groups caused the reaction to only proceed part of the way to completion and, in the case of the allyl protecting group, completely shut down the second coupling, even under the added phosphine conditions. The origin of this change in behavior is the object of current study.

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REPORTS

The Catalytic Cross-Coupling of Unactivated Arenes

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The industrially important coupling of aromatic compounds has generally required differential prefunctionalization of the arene coupling partners with a halide and an electropositive group. Here we report that palladium, in conjunction with a copper oxidant, can catalyze the cross-coupling of *N*-acetylindoles and benzenes in high yield and high regioselectivity across a range of indoles without recourse to activating groups. These reactions are completely selective for arene cross-coupling, with no products arising from indole or benzene homo-coupling detected by spectroscopic analysis. This efficient reactivity should be useful in the design of other oxidative arene cross-couplings as well.

The immense scientific and commercial value of biaryl molecules is illustrated by their ubiquity as building blocks in light-emitting diodes, electron transport devices, liquid crystals, and medicinal compounds (*1*). The structural simplicity of biaryl compounds belies their preparative complexity, and the search for efficient and convergent syntheses has captivated the attention of synthetic chemists for more than a century. Over the past 30 years, biaryl cross-coupling reactions based on carbon fragment preactivation have revolutionized our ability to forge the carbon-carbon biaryl linkage (*1*, *2*). Of these reactions, the most widely accepted and used are the palladium-catalyzed cross-coupling reactions (such as the Suzuki reaction) of aryl halides and aryl organometallics (*3*). As is common today, these reactions are dependent on preactivation of the two aromatic carbon fragments with halides and electropositive groups, such as boronic acids or stannanes (*4*). Incorporation of these functional groups can require several synthetic steps, generating waste from reagents, solvents, and purification, and (upon fragment cross-coupling) can produce undesired organometallic by-products. As a means of reducing our dependence on preactivation, increased attention is being focused on direct arylation processes that replace one of the preactivated substrates with the simple arene itself [for a review, see (*5*)]. Important advances have been made, particularly in the past decade, and more can certainly be anticipated. In stark contrast, the investigation of cross-coupling reactions that are devoid of arene preactivation is rarely considered, and a high-yielding process with simple unactivated arenes has yet to be described [for a recent report that shows the challenge in achieving high selectivity, see (*6*); for copper-catalyzed and iron-catalyzed reactions between 2-naphthol and 2-naphthylamine, see (*7*) and (*8*).

Substantial hurdles impede the conception of a catalytic arene cross-coupling process that does not involve substrate preactivation. In addition to issues of reactivity and regioselectivity, the catalyst must avoid the generation of unwanted arene homo-coupling that would consume the starting material and generate unwanted by-products (*9*–*12*). To meet this demand, the catalyst must be able to react with one arene in the first step of the catalytic cycle and then invert its selectivity in the second step to react exclusively with the other arene (Fig. 1). Achieving such an inversion in reactivity and selectivity is simultaneously the most daunting challenge and the most crucial prerequisite.

Here, we describe the discovery, development, and study of reactions that meet these challenges and validate this long-sought synthetic strategy (Scheme 1). Notably, no products of arene homo-

coupling are detected in the crude reaction mixture, indicating that a complete inversion in catalyst selectivity occurs at the crucial arene metallation steps of the catalytic cycle. Furthermore, although several regioisomeric products could be formed by reaction at different aromatic C-H bonds, markedly high regioselectivity is obtained. Although the precise sequence of reaction steps cannot presently be described, the demonstrated dichotomous behavior of palladium in the presence of electron-rich heteroaromatics and simple arenes should be applicable to other arene combinations. Given the value of the products and the efficiency with which they can be prepared by the use of this method, our observations should enable the development of this strategy for the synthesis of industrially and medicinally important biaryl molecules.

Our ongoing work in palladium-catalyzed direct arylation led us to believe that the crucial reactivity-selectivity inversion for arene cross-couplings was an achievable goal. It has been shown that palladium(II) complexes can react via an electrophilic aromatic metallation mechanism (S_EAr) with good selectivity for electron-rich arenes (Fig. 2) (*13*–*15*). In 2006, we discovered that a recently described proton transfer–palladation mechanism (*16*) can exhibit complementary reactivity to the S_EAr pathway (*17*, *18*). With simple arenes, this concerted palladation-deprotonation pathway can depend on arene C-H acidity rather than arene nucleophilicity. Important to the current goal, the palladium complexes associated with these two potentially complementary pathways are analogous to the palladium(II) species at step 1 and step 2 of the catalytic cycle in Fig. 1B. We hypothesized that, if the mechanistic duality associated with these two complementary reactivity modes could be accessed within the confines of a single catalytic cycle, the elusive entry point for selective arene cross-coupling could be achieved.

An extensive investigation of reaction conditions with a range of substrates, palladium catalysts, and additives led to the establishment of the conditions described in Table 1. A survey of electron-rich arenes, in conjunction with benzene as the second coupling partner, revealed that indoles exhibited promising reactivity. The indole nitrogen substituent also dramatically influences the reaction. In initial screens, the free *N*-H indole did not react, whereas *N*-methylindole produced self-dimerization predominantly. In contrast, the use of *N*-acetylindole gave more promising results, which was selected for further catalyst development studies. Optimal catalytic reactivity was achieved with a palladium trifluoroacetate (TFA) catalyst in combination with catalytic quantities of 3-nitropyridine and cesium pivalate (2,2-dimethylpropionate). Although the addition of these last two additives is not crucial to achieve catalytic turnover, superior turnover numbers and reproducibility are associated with their use. We believe that the pyridine additive may be acting to stabilize the palladium(0) before re-oxidation, preventing or slowing the formation of palladium black, which precipitates from the reaction mixture (*19*). The beneficial impact of the catalytic quantity of cesium pivalate is less clear, but it may interact with the $Pd(TFA)_2$ to generate palladium pivalate early in the reaction. The optimal solvent for the reaction was discovered to be pivalic acid, and a screen of stoichiometric oxidants revealed that copper(II) acetate [$Cu(OAc)_2$] could provide efficient catalytic turnover. The combination of these efforts led to the establishment of optimized conditions involving the treatment of *N*-acetylindole with an excess of benzene (~30 equivalents) with 2 to 10 mole percent $Pd(TFA)_2$, 2 to 10 mol % 3-nitropyridine, 40 mol % cesium pivalate, and 3 equivalents Cu $(OAc)_2$ in pivalic acid (2,2-dimethylpropionic acid) under thermal or microwave heating from 110° to 140°C (*20*).

Table 1. Development of a catalytic indole-benzene cross-coupling reaction. The products **1**, **2**, and **3** correspond to those illustrated in Scheme 1, in which R=R'=H. $Pd(TFA)_2$ and (if relevant) $Cu(OAc)_2$, 3-nitropyridine, cesium pivalate (CsOPiv), and/or *N*-acetylindole were added to a Schlenk tube or microwave vessel, which was followed by the addition of benzene (~30 equivalents), pivalic acid, and heating according to the indicated method. Oxidant (equivalent), additive (mol %), and Pd (mol %) values were calculated relative to *N*-acetylindole. Unless

otherwise indicated, the values for percent conversion (% conv.), **1:2:3** ratio, and percent yield **1** were determined by GC-MS. The asterisk denotes isolated yield. nd, not determined.

Entry	Mol % Pd	Oxidant (equiv.)	Additive (mol %)	Heating method	T (°C)	Time (h)	% Conv.	1:2:3	% Yield 1
1	100	None	None	Oil bath	110	24	75	4.4:1:2.6	55
2	10	$Cu(OAc)_2$	CsOPiv (40)	Oil bath	110	24	67	27:1:0.3	64
3	0	$Cu(OAc)_2$	3-Nitropyridine (10) CsOPiv (40)	Oil bath	110	24	0	nd	0
4	10	$Cu(OAc)_2$	3-Nitropyridine (10) CsOPiv (40)	Microwave	140	5	100	8.9:1:0.3	87*
5	5	$Cu(OAc)_2$	3-Nitropyridine (5) CsOPiv (40)	Microwave	140	5	92	13.8:1:0.3	84
6	2	$Cu(OAc)_2$	3-Nitropyridine (2) CsOPiv (40)	Microwave	140	5	66	27:1:0	63

A drawback of the thermal heating protocol was the prolonged reaction time (typically 48 hours) required to achieve high conversions with 10 mol % palladium. Notably, a change to microwave heating at 140°C provides a 92% conversion with 5 mol % $Pd(TFA)_2$ in less than 5 hours with a 13.8:1:0.3 ratio of the **1**:**2**:**3** isomers and an 84% gas chromatography–mass spectroscopy (GC-MS) yield of the C3 isomer **1** (entry 5 in Table 1). This acceleration is also accompanied by slight drop in C3:C2 selectivity; however, an improvement in C3:C2 regioselectivity occurs with decreased catalyst loadings. For example, with 2 mol % palladium, a 27:1 C3:C2 regioisomeric ratio is obtained with 66% conversion of *N*-acetylindole (33 turnovers of the palladium catalyst) (entry 6 in Table 1). Under these conditions, the reaction is completely selective for arene cross-coupling, and no compounds arising from indole or benzene homo-coupling are detected by crude proton nuclear magnetic resonance spectroscopy and GC-MS analysis. This finding indicates that the crucial reactivity-selectivity inversion described in Fig. 1 can occur with high precision and fidelity.

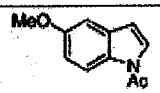
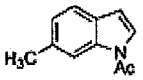
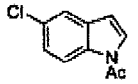
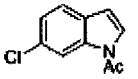
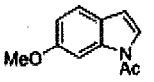
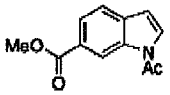
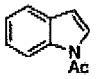
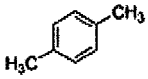
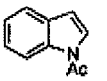
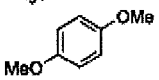
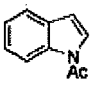
Catalyst load - check definition

Additional examples of reactions with substituted indoles and benzenes are included in Table 2. Thermal heating was used in reactions with chloro-substituted indoles (entries 3 and 4) because small amounts of hydrodechlorination were observed under microwave heating, which hampered product isolation.

– effects of MAOS

further substrate scope studies

Table 2: Scope of the palladium-catalyzed indole-benzene cross-coupling. $Pd(TFA)_2$ (indicated amount), $Cu(OAc)_2$(3 equivalents), 3-nitropyridine (1 equivalent to Pd), CsOPiv (40 mol %), and the *N*-acetylindole were added to a microwave vessel. The arene (~30 equivalents) and pivalic acid were then added, which was followed by microwave heating. Percent conversion and the **1**:**2**:**3** ratio values were determined by GC-MS. Values in the percent yield **1**column denote isolated yield. The asterisks denote that samples were heated thermally in a Schlenk tube. nd - not determined.

Entry	Indole	Arene	T (°C)	Mol % Pd	% Conv.	1:2:3	% Yield 1
1			140	10	100	11.2: 1: 0.4	84
2			140	10	100	10: 1: 0.6	81
3			110*	10	83	6.5: 1: 0	63
4			110*	10	81	5.7: 1: 0	61
5			140	10	100	10.5: 1: 0.3	74
6			140	20	80	2.8: 1: 0	54
7			140	20	nd	10.4: 1: 0.4	45
8			140	20	72	6.7: 1: 0	52
9			140	20	nd	9.9: 1: 0	42

Insufficient data exist at present to allow a detailed mechanistic discussion. Although superior reactivity is observed for indoles bearing electron-donating groups, no clear trends have yet emerged with respect to the benzene component. This relative reactivity is also observed in competition studies (see the supporting online material for further details). Nonetheless, these results clearly demonstrate that the dichotomous catalytic behavior required at each of the two metallation steps can be achieved. This knowledge should prompt the investigation and development of a broad range of other palladium-catalyzed oxidative cross-coupling reactions with different substrates.

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Figures

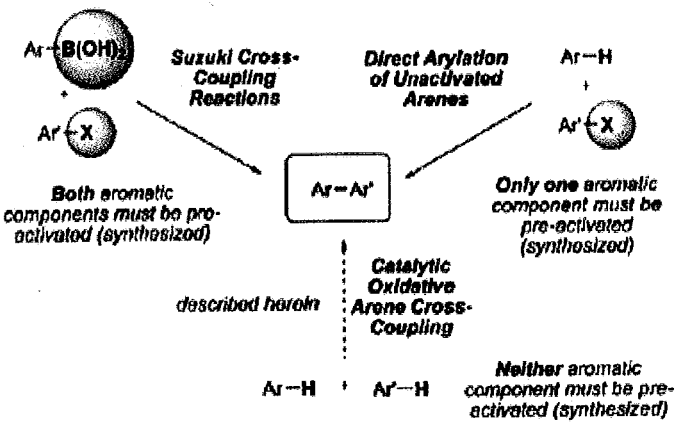
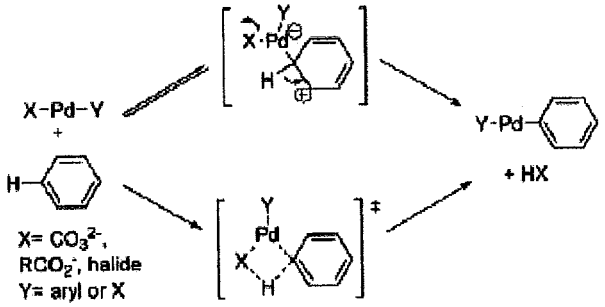
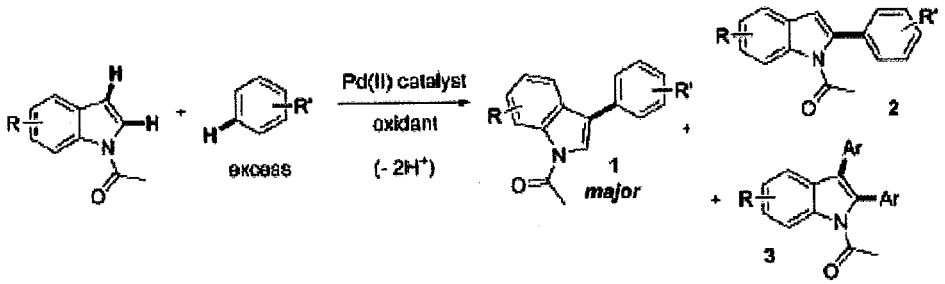


Fig. 1. Methods for the preparation of biaryl molecules. X is a halide or sulfonate.

Fig. 2. Mechanisms of arene palladation. The electrophilic aromatic metallation pathway (**top**) and concerted proton transfer–metallation pathway (**bottom**) are shown.





Scheme 1.

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Design of highly active heterogeneous palladium catalysts for the activation of aryl chlorides in Heck reactions

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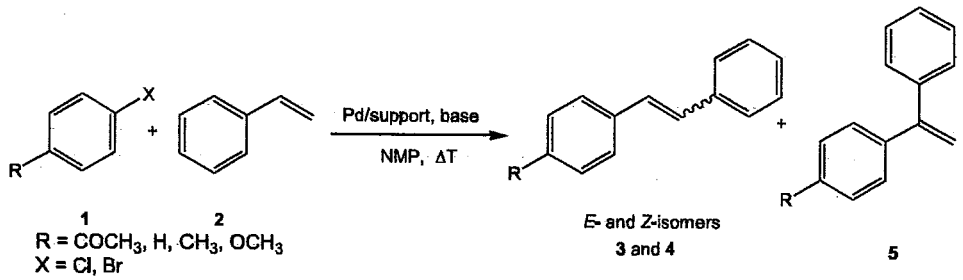
Abstract—In situ generation of highly active palladium species by intermediate dissolution of Pd from solid supported catalysts has been demonstrated to be a very successful approach for the activation of aryl chlorides in Heck reactions. The new 'heterogeneous' Pd catalysts act as reservoir for molecular Pd species with unsaturated coordination sphere in solution. Crucial Pd leaching and re-deposition onto the support can be controlled by optimization of reaction conditions and by the properties of the catalysts. Pd is re-deposited onto the support at the end of the reaction. The catalysts, palladium supported on activated carbon, on various metal oxides or fluorides and Pd complexes in zeolites, are easy to prepare, though the preparation conditions are crucial. The catalysts convert all aryl bromides completely within minutes (TON 100,000). Aryl chlorides (even deactivated ones) are converted with high yields, within 2–6 h. The catalysts belong to the most active ones in Heck reactions at all (including best homogeneous systems) and fulfill all relevant requirements for practical applications in laboratory and industry.

1. Introduction

CC coupling reactions like Heck reactions (Scheme 1) are of growing interest for organic synthesis and fine chemical industry.[1] Advantages of this reaction are a broad availability of aryl bromides and chlorides and the tolerance of a wide variety of functional groups. The Heck reaction is typically catalyzed by Pd complexes in solution. Expensive, and often sensitive ligands are necessary to activate Pd and to stabilize it against agglomeration and the formation of Pd black. Accordingly, there have been many efforts to develop new homogeneous systems in the last years.[1]

In addition, several heterogeneous Pd catalysts have been developed in order to overcome typical problems in homogeneous catalysis. The most frequent motivation given is: recovery, recycling, and reuse of the catalyst. However, one of the main and (in our opinion) most important differences between reported homogeneous and heterogeneous systems is the clearly lower activity of the latter catalysts, often being orders of magnitudes lower than that of soluble Pd complexes. This is reflected by the model systems investigated. Typical reports on heterogeneous catalysts focus on aryl iodides and activated aryl bromides as substrates. Reports on the successful activation of



Scheme 1. Heck reaction.

Keywords: CC coupling; Heck reaction; Heterogeneous catalysis; Palladium.
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bromobenzene and in particular of aryl chlorides are very seldom. Most of the reported catalysts that successfully activated aryl chlorides like Pd on activated carbon[2] and layered double hydroxides,[3] Pd complexes bound to polymer matrices[4] or immobilized in porous materials[5] exhibit relevant limitations: they need very long reaction times (several days) or high Pd concentrations for acceptable conversions; restriction on strongly activated aryl chlorides, high selectivity to undesired side products (dehalogenation of the aryl chloride) or a rather complex synthesis of the catalyst itself, which makes it too expensive for possible applications may also be severe problems. Very recently, we have reported that the in situ generation of dissolved Pd species from solid catalysts can be a new and very efficient approach for the activation of aryl chlorides in Heck reactions.[6] Those investigations force of course the discussion on the mechanism of the (heterogeneous) Heck reaction.[7]

While the homogeneous mechanism of the Heck reaction is widely accepted several proposals for the heterogeneous cycle have been made. Several authors suggested a direct interaction between reactants and palladium surface atoms either of supported particles or of colloids in solution as the initial step in the catalytic cycle.[7,8] Shmidt et al.[9] and Arai et al.[10] observed leaching of Pd from the support and claimed these dissolved species to be the active ones. Both performed kinetic investigations on reactions with aryl iodides that indicated a correlation between leaching and reaction rate. In recent years several additional experiments also with non-activated aryl bromides have been reported.[2a,6,7,11] Most of them strongly support this pseudo-homogeneous reaction mechanism and showed that very small amounts of Pd are sufficient for activation of aryl bromides. This interpretation corresponds well with reports of Reetz and de Vries, who achieved similar high activities using 'ligand free' Pd acetate.[12]

With solid catalysts these 'ligand free' active species are generated by dissolution of Pd from the solid. In particular, the determination of the Pd concentration in solution and its correlation with the rate of the Heck reaction were found to be very useful tools for corresponding conclusions.[6,11a] From these observations, the question arose if the control of this leaching process is possible with the aim to speed up the reaction and, which catalyst properties and reaction conditions are the best for the activation of the attractive aryl chlorides by a solid catalyst. This work presents our efforts to elucidate the mechanism of the heterogeneously catalyzed Heck reaction with aryl chlorides. Based on mechanistic insights we optimized heterogeneous Pd catalysts and reaction conditions. As a consequence efficient activation of aryl chlorides became possible by catalysts that are cheap and easily prepared.

2. Results and discussion

2.1. Catalyst preparation

The heterogeneous catalysts presented in this work were specifically prepared to achieve a high dispersion of Pd in oxidation state +II.[11a,13] This has been described and explained to be crucial for high activity and selectivity in Heck reactions of bromobenzene. In order to vary the Pd leaching and re-deposition equilibriums various preparation methods, precipitation of $Pd(OH)_2$ onto different supports, sol-gel techniques and incorporation of Pd(II) complexes into zeolite pores, were used.[14]

2.2. Catalytic activity

The optimized Pd/support catalysts exceed the activity of all heterogeneous catalysts for Heck reactions known so far by at least one order of magnitude. TON of more than 100,000 and TOF up to 39,000 h^{-1} can be achieved with Pd concentrations of less than 0.001 mol% in the Heck reaction of bromobenzene and styrene under standard conditions (NMP, NaOAc, 140 °C, argon atmosphere; Table 1). Comparison of the various support materials did not reveal significant support influences in the reactions. In fact, the high Pd(II) dispersion is found to be crucial also for the present investigations.

Applying exactly the same conditions in the reaction of 4-chloroacetophenone and styrene no conversion is observed. The addition of tetra-*n*-butylammoniumbromide (TBAB) and higher temperature (160 °C) lead to 65% conversion. Addition of TBAB probably prevents Pd agglomeration at this elevated temperature and Br^- can act as a supporting ligand for 'naked' Pd atoms (i.e., the system is now no longer 'ligand free'). Further improvements can be achieved by substitution of the base. While NaOAc leads only to 65% conversion, complete conversion occurs within 2 h using $Ca(OH)_2$ (Fig. 1, Table 2). TON of 10,000–20,000 and TOF of 5000–10,000 h^{-1} are obtained

Table 1. Heck coupling of bromobenzene and styrene

Entry	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield 3 (%)	TON[a]	TOF (h^{-1})[b]
1	Pd/TiO_2[c]	0.0011	95	86	87,000	22,000[d]
2	Pd/Al_2O_3[c]	0.0009	96	87	107,000	27,000[d]
3	Pd/TiO_2[c]	0.001	78	71	78,000	39,000
4	Pd/Al_2O_3[e]	0.01	99	94	10,000	5000
5	Pd/AlF_3[e]	0.009	99	93	11,000	5500
6	Pd/MgF_2[e]	0.009	99	93	11,000	5500

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 2 h.
[a] Moles of aryl halide converted/moles of Pd.
[b] TON/h.
[c] Prepared by precipitation of $Pd(OH)_2$ on support.
[d] 4 h reaction time.
[e] Prepared by sol–gel method.

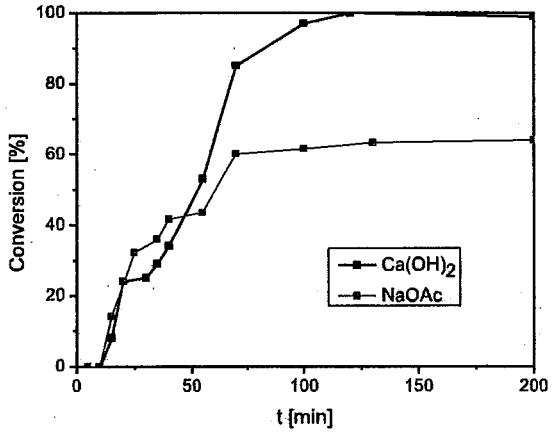

Figure 1. Kinetic investigations: influence of the base on the Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol base, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al_2O_3 catalyst, 160 °C.

achieved with different other supports, if specific redox conditions were adjusted in the system (Table 2, entries 4–9). Pd re-oxidation by oxygen and/or the support plays a crucial role too. In oxygen atmosphere higher yields could be achieved than in argon atmosphere (Table 2, entries 10, 11). This may be explained by partial re-oxidation of Pd to Pd(II) (lower concentration of Pd(0)) thus preventing Pd agglomeration (Pd black formation).

The use of Pd/NaY and a careful choice of reaction parameters allow the activation and conversion even of deactivated aryl chlorides, like 4-chlorotoluene and 4-chloroanisole, in Heck reactions (Table 2, entries 12, 13). Note, that the selectivity to the Heck products is 100% in all cases and that the problematic dehalogenation which is often found for reactions of aryl chlorides did not occur. We explain this by the controlled prevention of Pd particle formation in the present system (assuming that dehalogenation occurs according to a truly heterogeneous surface mechanism).

Table 2. Heck coupling of aryl chlorides and styrene

Entry	Aryl halide	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield **3** (%)
1	4-Chloroacetophenone[a]	Pd/Al_2O_3[b]	0.01	98	90
2	4-Chloroacetophenone[a]	Pd/Al_2O_3[c]	0.01	87	83
3	4-Chloroacetophenone[a]	Pd/NaY[d]	0.005	99	95
4	Chlorobenzene	Pd/Al_2O_3[b]	0.1	45	40[e]
5	Chlorobenzene	Pd/AlF_3[b]	0.1	36	32[e]
6	Chlorobenzene	Pd/Al_2O_3[c]	0.1	33	30[e]
7	Chlorobenzene	Pd/C[f]	0.1	33	32[e]
8	Chlorobenzene	$Pd/Ce/Al_2O_3$[c]	0.1	54	51[e]
9	Chlorobenzene	Pd/CeO_2[b]	0.1	54	51[e]
10	Chlorobenzene	Pd/NaY	0.05	49	45
11	Chlorobenzene	Pd/NaY	0.05	85	83[e]
12	4-Chlorotoluene	Pd/NaY	0.05	40	36[e]
13	4-Chloroanisole	Pd/NaY	0.05	21	19[e]

Conditions: 10 mmol aryl halide, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, argon atmosphere, 6 h.
[a] 2 h reaction time.
[b] Prepared by precipitation of $Pd(OH)_2$ on support.
[c] Prepared by sol–gel method.
[d] Without TBAB.
[e] O_2 atmosphere.
[f] E105 CA/W, Degussa AG.

with different catalysts. In the case of Pd/NaY addition of TBAB can be even renounced.

Kinetic investigations showed that the concentration of the molecular Pd species in solution correlates with the reaction course (Fig. 2). The highly active Pd species are generated in situ. Pd is dissolved from the support, stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction (after consumption of the aryl chloride).

The conversion of non-activated aryl chlorides like chlorobenzene occurs only satisfactorily if TBAB is added (independent of the support). The best results were achieved with Pd incorporated into the cages of a zeolite (Pd/NaY). Using this catalyst 85% conversion and a yield of 83% of *E*-stilbene were obtained in the Heck reaction of chlorobenzene and styrene within 6 h (TON = 1400, Table 2). This system is particularly suitable to avoid agglomeration of Pd probably by diffusion control. Good results could also be

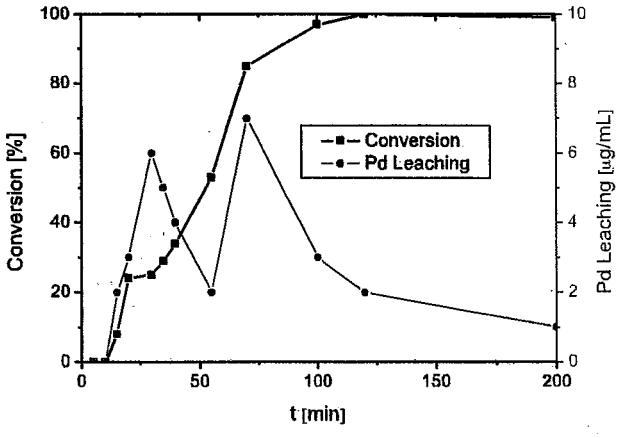

Figure 2. Kinetic investigations and Pd leaching: Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al_2O_3 catalyst, 160 °C.

2.3. Pd leaching as a function of reaction time

The progress of the reaction and the Pd content in solution were monitored for different substrates (4-chloroacetophenone, chlorobenzene) and catalysts (Pd/Al_2O_3, Pd/NaY zeolite, Figs. 2 and 3). In all cases the active Pd species are generated by dissolution from the support. They are stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction. For chlorobenzene and Pd/NaY zeolite catalysts Pd is dissolved (concentration reaches maximum after 20 min) and the conversion of chlorobenzene starts. The Pd content in solution decreases with the degree of aryl chloride consumed. The Pd concentrations in solution and the course of the reaction depend on catalyst, substrate, temperature, base, solvent, and additives. The maximum absolute amount of Pd in solution is higher for the optimized reaction system and chlorobenzene compared to 4-chloroacetophenone. Obviously the lower concentration in the latter case (controlled by the chosen reaction parameters) is not sufficient to activate the less reactive chlorobenzene. Even small divergences of the Pd content in solution correlated with fluctuations in the reaction course (Fig. 3). The divergences of the Pd concentration in solution may be due to the experimental procedure (disturbances/interruptions by the withdrawal of samples from the reaction mixture) or due to differences in the single reaction vessels (see Section 4). Note, that also the zeolite system shows leaching of Pd into bulk solution during the reaction. Obviously, the reaction takes place outside the zeolite pores. Pd leaves the pore system, catalyzes the Heck reaction and diffuses back into the pores (equilibrium).

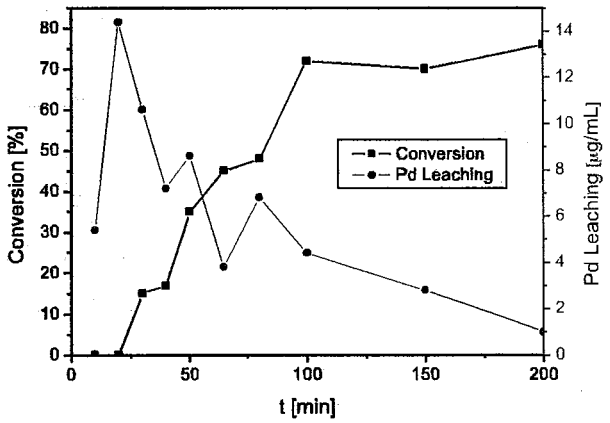

Figure 3. Kinetic investigations and Pd leaching: Heck coupling of chlorobenzene with styrene. Reaction conditions: 10 mmol chlorobenzene, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, 0.05 mol% Pd/NaY catalyst, 160 °C, O_2 atmosphere.

2.4. Catalyst recycling and reuse

The catalysts were recyclable several times. This is illustrated by the reaction of bromobenzene and styrene. Only a slight decrease in activity emerges in the second run (86% conversion). In the third run, still 69% conversion is achieved (Table 3). The decrease is caused by a partial reduction of Pd(II) to Pd(0) and a lower Pd dispersion after re-deposition. In contrast to observations with activated aryl bromides made by de Vries et al.,[15] reactivation of the catalyst by I_2 or Br_2 was not possible.

Table 3. Heck coupling of bromobenzene and styrene–catalyst recycling experiments

Entry	Run	Conversion (%)	Yield **3** (%)
1	1	98	90
2	2	86	80
3	3	69	62

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 140 °C, 6 h, 0.2 mol% Pd/Al_2O_3.

3. Conclusions

Pd supported on various oxides, fluorides and activated carbon and incorporated into zeolites can be an extremely active and selective catalyst for Heck reactions. The catalytic systems combine extremely high activity, short reaction times, and high selectivity in Heck reactions of aryl bromides and chlorides with the advantages of easy and complete Pd separation and recovery. The activity is comparable to the very best homogeneous catalyst systems. The heterogeneous catalysts are stable against air and moisture, no inert atmosphere and no expensive ligands are necessary. They are easy to prepare, the preparation conditions are crucial (high dispersion and +II oxidation state of Pd, certain water content, no thermal treatment or pre-reduction). Pd complexes ($[Pd(NH_3)_4]^{2+}$) incorporated into the pore system of zeolites (NaY) represent the best catalytic performances. Side reactions (dehalogenation) and Pd black formation can be excluded.

The development of these simple catalysts was possible by enlightenment of the reaction mechanism and corresponding careful optimization as well as choice of reaction parameters and catalyst properties. The highly active Pd species are generated in situ by intermediate dissolution of Pd from the solid support. The 'heterogeneous' Pd catalysts act as a reservoir for coordinative unsaturated molecular Pd species in solution. Pd is re-deposited onto the support at the end of the reaction. These processes are crucial and immanent components of the catalytic cycle, which obviously also involves heterogeneous reactions (oxidative addition of aryl halide to surface palladium atoms initializing dissolution). The Pd amount in solution correlates with the reaction rate and is strongly influenced by the reaction conditions. Solvent, temperature, substrates, base, additives, and atmosphere must be adjusted carefully. Experiments monitoring the Pd concentration in solution as a function of reaction rate were the most valuable tools for corresponding mechanistic studies. Pd leaching is a precondition for high activity and selectivity of heterogeneous catalysts in Heck reactions.

4. Experimental

4.1. General procedure for catalysis experiments

Reactions were performed in sealed pressure tubes after 5 min of purging with argon. Educts and solvents were used non-dried.

Filtered samples were extracted with water/CH_2Cl_2 and dried over $MgSO_4$. Products were identified by GC/MS. Conversions and yields were quantified by GLC using diethylene glycol dibutylether as internal standard ($\Delta_{rel} = \pm 5\%$).

4.2. Typical reaction conditions for Heck reactions with bromobenzene

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, about 0.001 mol% Pd/support, 10 mL NMP (1-methyl-2-pyrrolidone), $T = 140$ °C, 2–4 h.

4.3. Typical reaction conditions for Heck reactions with aryl chlorides

10 mmol aryl chloride, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 0.01–0.1 mol% Pd/support, 10 mL NMP, $T = 160$ °C, 2–6 h.

4.4. Typical reaction procedure for kinetic investigations

Sixteen identical experiments were performed in 16 pressure tubes as described above. At defined times the reactions were quenched. For Pd leaching 5 mL of the filtered sample were evaporated. Pd content of the residue was analyzed by flame AAS.

4.5. Recycling experiments

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 0.2 mol% Pd/Al_2O_3, 10 mL NMP, $T = 140$ °C, $t = 6$ h. After the reaction was finished, the catalyst was washed three times with CH_2Cl_2 and re-used.

Acknowledgements

The authors thank M. Barth and his co-workers for palladium analyses.

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First Draft

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How can palladium catalysts increase efficiency in the syntheses of aromatic compounds?

By

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Introduction

The quote is not very relevant and is perhaps a little clichéd

Deleted: *"Synthetic objectives are seldom if ever taken by chance ... the successful outcome of a synthesis ... provides a test of unparalleled rigor of the predictive capacity of the science"*¶
A R Todd (1907-1997)

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A successful organic synthesis demands the creative application of computational and theoretical techniques in order to identify a molecular framework with a structure well-suited to the desired function, and to then map out a synthetic route which may arrive at the target[1]. Putting together a complex molecule relies on having a library of efficient core reactions at one's disposal; frequently it is compounds exhibiting aromatic motifs that prove to be the core reagents of greatest value. Aromatic compounds are characterised by their delocalised system of pi-electrons, a well-defined geometric structure, relatively high levels of photochemical, thermal and chemical inertness as well as good potential for selective functionalisation[2]. It is therefore no surprise that compounds displaying an aromatic nucleus are ubiquitous in modern synthetic chemistry and are biosynthesised by organisms in every taxonomic kingdom. This is an area of chemistry that has been thoroughly investigated, but of course, many avenues remain unexplored. Here, we will focus on the palladium-catalysed synthesis of compounds exhibiting aromaticity – palladium is extremely versatile and highlights the tremendous power of a transition metal-mediated approach to constructing organic molecules. The combination of a well-behaved and structurally malleable compound class with a synthetic methodology that gives rise to highly selective routes provides us with an ideal territory to search for more efficient strategies in synthesis.

It is necessary but certainly not sufficient to merely identify and synthesise a target compound, the next and arguably more important stage is to refine the efficiency of the synthetic procedure. An efficient reaction scheme may be defined as one which produces a unit quantity of a target compound with the minimum input of resources. Evaluating synthetic efficiency is difficult: industrial chemists and research chemists have markedly different objectives and thus place emphasis on different aspects of efficiency. Industrial chemists will regularly choose reactions requiring cheap and readily available reagents whilst simultaneously attempting to maximise yield, minimise the number of steps, ease product isolation and purification, and reduce energy and time input. These objectives are self-explanatory and quite clearly can be grouped together as a set of economic considerations intended to improve cost effectiveness. Academic research in organic synthesis may share some of these goals, but the key difference is an emphasis on finding new reactions with inherent properties that are of interest – optimising a reaction to improve profitability is not the objective. Selectivity and atom economy are two examples of properties that confer greater efficiency; it will become evident that these properties also have economic repercussions and so will be of interest to industry, provided that it is feasible for the procedure to be scaled-up.

To achieve good atom economy is to maximise the proportion (by mass) of the reactants that end up in the final product and minimise waste as a consequence. Quantitatively this may be defined as the ratio of the molecular mass of the desired product to the sum of the molecular masses of all the products. Atom economy is an intrinsic feature of a reaction; this is in contrast to yield, which can be manipulated by altering reaction conditions and recycling the reaction mixture.

Selectivity is another reaction property that must be understood in order to appreciate the utility of organopalladium chemistry in achieving an efficient synthesis. The first division of selectivity to consider is chemoselectivity: this is the ability to ensure a reaction is effected only at the intended functional group(s); it is often the case that many potentially reactive groups will be present and these must be prevented from taking part in side reactions. Similarly, regioselectivity is the extent to which a compound reacts to give the desired structural isomer. In an unsymmetrical species, this necessitates the preference of one direction of bond breaking and formation over another, and in instances where several identical functional groups are present, there must be discrimination between different chemical environments[3]. Lastly we come to stereoselectivity; this facet of a synthesis is encompassed in the degree of diastereoselctivity and/or enantioselectivity. These concern the degree to which a single diastereoisomer or enantiomer is produced, achieving the latter objective is difficult due to the identical chemical and physical properties exhibited by chiral molecules; it is the subject of the field of asymmetric synthesis[3]. Quantitative assessment of the level of stereoselectivity is given by the enantiomeric or diastereomeric excess, this is calculated by determining the absolute value of the difference between the mole fraction of the desired stereoisomer and the sum of the mole fractions of the unwanted stereoisomers, it is normally expressed as a percentage[4]. Optical purity is also routinely used to quantify enantioselecitivty – it is the ratio of the specific rotation of the sample to the specific rotation of the pure desired enantiomer. Some authors use the term "specificity" to refer to 100% selectivity – this indicates that the reaction mechanism has a strict stereochemical requirement.

Realising these synthetic objectives is made possible thanks to a range methods, however, here we discuss a single family of techniques, that is, those reactions that involve the use palladium to mediate or catalyse reactions at the heart of preparative procedures. As we have seen, efficiency is very broad term encompassing many issues - overall "efficiency" is thus a trade-off between each of the competing factors. For example, consider a very slow reaction which demands expensive reagents, but which offers 100% atom economy and high yield. Clearly, the input of capital and time is high whilst the quantity of reagents required have been minimised – it is the net impact which must be considered. The net impact need not be considered solely in economic terms; it will transpire that the discussion regularly alludes to the terminology of green chemistry and indeed the consequence of improving efficiency is frequently a reduction in environmental impact. Transition elements frequently enable the attainment of efficiency in several of the aforementioned categories simultaneously. The extent to which the catalytic properties of palladium can be exploited in order to address the issue of efficiency, and hence bring great benefits to the chemical industry, will be considered by exploring a series of reactions that clearly illustrate that advantages and disadvantages of palladium-based synthesis.

Biaryl Synthesis

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Suzuki and Negishi Coupling

Palladium (Pd) catalysis can be used to great advantage in coupling reactions, that is, reactions leading to the amalgamation of organic fragments via carbon-carbon or carbon-heteroatom bond formation. Molecules consisting of two directly bonded aryl groups (biaryls) are indisputably among the most important compounds that can be produced in coupling reactions. Biaryl substructures are widespread in medicinal products, such as the antibiotic vancomycin and the potent antileukaemic agent stegnacin, as well as engineering materials including liquid crystals, molecular wires, and conducting polymers such as poly-p-phenylene[5, 6]. Moreover, aryl-aryl bond forming reactions are vital to the modern synthetic approach known as convergent synthesis in which several molecular fragments are assembled separately before being finally coupled in order

to assemble the target[7]. Sartans (angiotensin II receptor antagonists) are an important class of antihypertensive drugs that are synthesised using a Pd-based convergent strategy[8]. This class of drugs will also prove to be a good example of how syntheses already exploiting palladium chemistry can be further enhanced thanks to new advances.

Consideration of a typical nickel (Ni) catalysed Negishi coupling will serve as a useful case study to briefly survey the advantages of palladium over other transition elements. Figure 1.1 below shows a simple two-step synthesis of 2-phenylbenzaldehyde that I have designed; it is based on a similar procedure noted by Cepanec[5]. The reaction scheme affords the product with an overall yield of 82% within a 5.5h period. We can attribute the need for two steps to the fact that a protecting group (in this case, a cyclohexylimino group) is required to avoid complexation between the nickel species and the carbonyl. Deprotection (step two) introduces a further problem; the nickel complex is attacked by the acid (oxidative addition of the acid to the Ni(0)) and so the complex must either be continually replaced or an extraction step must be added to remove the catalyst[9]. The nickel complex is also relatively difficult to work with, it must be kept at 2°C and contact with oxygen should be minimised, Sigma Aldrich also confirm that the compound is hazardous – a faceshield and full-face particle respirator should be worn when using the substance[10]. Lastly, an unfortunate consequence of the reaction conditions is that the arylzinc reagent will undergo a homocoupling, this side reaction cannot be avoided and so an excess of the arylzinc compound must be added[5].

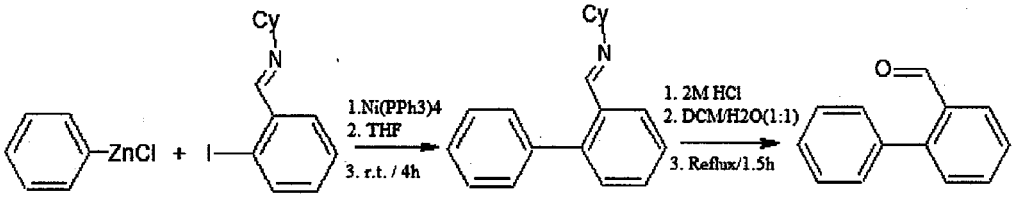

Figure 1.1: Scheme one – a Negishi coupling

Thimmaiah and Fang reveal that an innovative Suzuki-Miyaura coupling will afford the same product[11]. Not only is the yield much greater at 99%, but the $Pd_2(dba)_3$ confers complete chemoselectivity enabling the reaction to proceed in the absence of a carbonyl protecting group[11]. The number of steps is instantly halved, which leads to a reduction in the amount of apparatus and solvent used, and the synthesis is also much more rapid (four hours per batch is saved), however this is also due to the greater rate of reaction in the second scheme. Industry is likely to be deterred from using the second procedure as a result of the need for a specialised ligand (see figure 1.3) that is not widely produced and is thus costly, however, in association with the Pd-complex the ligand is only required in catalytic amounts as the substance is neither consumed in the reaction, nor chemically altered by the chosen reaction conditions. Moreover, the ligand activates the Pd-complex more strongly than conventional ligands: the reaction proceeds at a faster rate, in milder conditions, and in the presence of a smaller quantity of the expensive Pd compound[11]. The discoverers of the new class of ligands argue that the ligands are easy to prepare and make possible a variety of reactions that have previously been impossible, for example, they report the synthesis of the novel compound 2,6-dimethyl-2-phenyl-1,10-biphenyl[11]. For this reason, the ligands will be of interest to research groups.

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Other ligands, many readily available, can also enhance the reaction (though rate and yield are not enhanced as significantly) and crucially, ligand-free Suzuki cross-couplings have been documented. From the perspective of industry, both schemes could be made more appealing by reducing the amount of the expensive catalyst (catalyst loading) required, the first reaction is effective with a load of 1-5 Mol % while the second procedure was optimised at 1.5 Mol %[11].

Excessive catalyst loads are inefficient in two respects, firstly they unnecessarily increase the cost of the reaction and secondly, the high concentration encourages catalyst particle agglomeration leading to cluster formation, the clusters precipitate out as palladium black – this is uneconomical as it is not a catalytically active species. Astonishingly, the problems associated with the reaction scheme, that is, the use of an exotic ligand and also the need for a relatively high catalyst loading could potentially be overcome concomitantly. The technique in question is the use of so-called "homeopathic" conditions. Predictably, catalyst loading is greatly reduced (to approximately 0.02Mol %), the ligand is excluded, and the reaction is run in ambient conditions[12]. High yields were obtained (up to 95%) though they varied with substrates and were on the whole lower than scheme two [12]. Potential exists to lower catalyst concentrations even further, a 0.0025 Mol % loading was successfully employed to obtain 4-acetylbiphenyl in an 85% isolated yield[12]. Both highly-activating ligands and the opposing technique of homeopathic conditions are clearly worthy of further work; they promise to greatly influence the synthesis of biaryls for both industrial and research purposes.

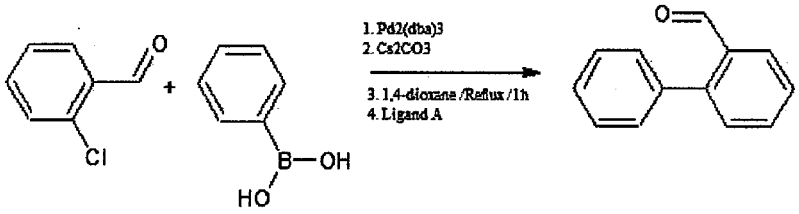

Figure 1.2: Scheme two

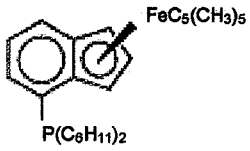

Figure 1.3: The structure of ligand A (a benzoferrocenyl dicyclohexyl phosphine derivative called 4-(Dicyclohexylphosphino)indenyl-pentamethylcyclopentadienyliron)

The simplicity and enormous potential of the Suzuki coupling is emphasised by the fact that a simple example of one is now carried out as a practical at the University of Oxford by second and third year undergraduates – this is testament to the increasing accessibility of organopalladium chemistry to chemists[13]. Use in the setting of a teaching laboratory also confirms that Pd-species are in general safe to handle, markedly so in comparison to Ni-complexes – this is convenient as no special protective gear is required. Scheme two also produces less waste than scheme one due to the absence of competing reactions (no homocoupling is observed in either the scheme recorded in figure 1.2 or the homeopathic procedure). However, the atom economies of both the methods discussed so far are not optimum, by-products from the desired reactions are produced in stoichiometric quantities. Nonetheless, the Suzuki method still offers superior efficiency over the Negishi reaction in this respect, as the by-products are all inorganic facilitating extraction from the reaction mixture.

Reactions yielding biaryls without invoking the power of transition element catalysis are rare, the sole common example is the Gomberg-Bachmann-Hey (GBH) reaction; this reaction instead exploits diazonium salts[14]. Admittedly, the GBH method allows a wide range of biaryls to be produced, but the chemoselectivity is low and subsequently yields rarely exceed 40%. This is a result of the fact that a plethora of side reactions occur; the aryl radicals generated will undergo polymerisation, reduction to the parent arene, and azo coupling to give brightly coloured

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compounds in cases where the arene to be arylated is activated by an electron-donating group. One would therefore assume that this reaction is of no use in modern synthetic routes owing to its poor efficiency, however, many syntheses have continued to use the GBH reaction and its variants, for instance, a Suzuki coupling strategy to synthesise the NSAID diflunisal in a single step was only developed in October 2009[15]. Previously, a three-step procedure involving a GBH reaction between the diazonium salt of 2,4-difluoroaniline and anisole, followed by ether hydrolysis and Kolbe-Schmidt carboxylation, had been favoured[16].

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One-Pot Synthesis

Now with an idea of some of the generic benefits we can exploit by using Pd-based methods, it is possible to turn to a more technically demanding synthesis – a triaryl synthesis. Figure 1.4 (below) shows a completely regioselective one-pot double Suzuki coupling yielding a differentially substituted pyrrole[17]. By assembling a tripartite structure in a single reaction vessel, a target compound can be assembled in fewer reactions and purification steps, with fewer reagents, and with less apparatus. Motivation for the synthesis of these compounds stems predominantly from their use in herbicides; this particular structural motif is prevalent in the protox inhibitor class of herbicides[18]. Two major difficulties must be overcome in order to achieve success in this synthesis, the first is that two sequential coupling reactions must take place in the same reaction vessel, and secondly, both couplings must take place with high regioselectivity: one reagent must attack only. Owing to the relatively nascent nature of Pd-mediated synthesis, there is no sure-fire way of determining an ideal combination of solvent, ligand and base. A common strategy for choosing a suitable catalytic system is a high-throughput screening approach; this involves setting up different reaction conditions on a millilitre scale and allowing the reactions to take place in parallel. Yield and product characterisation are the most important points to consider – yield is in this instance an integral part of the synthetic efficiency as the reaction conditions have been fixed. Following analysis of this nature, it was found that running the reaction under the first three conditions highlighted in the scheme and in the absence of p-fluorophenyl boronic acid produced exclusive monocoupling in the 5-position, even an attempt at forced dicoupling with 24 hours of vigorous reflux was unsuccessful. The next hurdle was to substitute the other boronic acid into the 4-position. Initial attempts to do so involved adding a different, more active catalyst to the reaction mixture in combination with the species to be coupled. Despite the success of this strategy, it was found that even a cheaper strategy could be employed; a new catalyst could be synthesised in situ by addition of a phosphine ligand. A modest 58% yield was obtained. Numerically, this is disappointing, but if we take into account the fact that two regiospecific reactions have taken place without any work-up, isolation or purification in between and that two sequential monocoupling would enable the same product to be isolated in a mere 10% yield, then we can certainly claim that this is an impressive result.

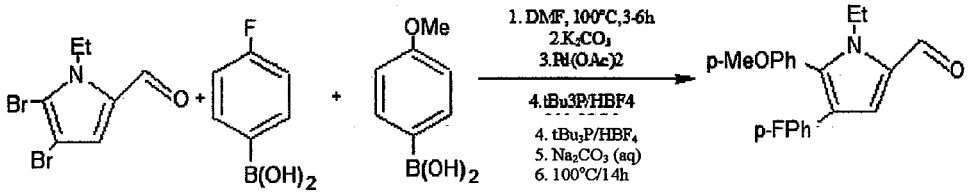

Figure 1.4: A synthesis of a substituted pyrrole to illustrate the "one-pot" concept

The strategy outlined here clearly has laid the foundations for the development of other related syntheses; this same dicoupling technique has been used to prepare substituted pyridines, thiophenes, and most recently, general unsymmetrical triaryls[19,20]. Whilst pyrroles are rarely useful, these latter protocols make the synthesis suitable to a range of applications including organic LEDs (OLEDs) and important pharmaceuticals such as Lipitor, a statin for cholesterol reduction, and Celebrex, an arthritis treatment[19]. What's more, a greatly improved isolation procedure utilising neutral alumina instead of silica has been developed; this has boosted yields to 97% for certain substrate combinations. Without doubt, palladium's scope for one-pot syntheses is of great value; the capacity to amalgamate reaction steps will cut costs in industrial routes whilst the fact that the technique can give rise to quickly converging schemes will almost certainly result in its exploitation by research labs in search of facile total syntheses of complicated natural products.

Heck Reactions: Arylation of Alkenes

The Heck, or Mizoroki-Heck, reaction can be defined as the Pd-catalysed coupling of an alkene and an sp^2 (aryl or alkenyl) halide or triflate[21]. The technique is extremely versatile, thus accommodating many substrates, countless variants exist, and a myriad of innovative efficiency-enhancing modifications have emerged. Heck reactions have proved to be fertile grounds for the development of asymmetric catalytic protocols. The striking ability of the reaction to achieve this is illustrated quite unequivocally in Overman's highly enantioselective synthesis of a series of spirooxoindoles exhibiting a single quaternary carbon centre, of which one example is shown below[22]. The most significant aspect of this success was the formation of both enantiomers at will, with very minor alterations to the reaction conditions. Another notable feature of the reaction is that it is an example of a desymmetrising Heck reaction as chirality has been introduced into a prochiral substrate; no enantiopure starting reagents are called for as is the case for a chiral pool synthesis. The first procedure in figure 2.1 (top) produced the S-isomer in an 81% yield and 71% enantiomeric excess (e.e.); after conducting the reaction with the addition of PMP, in the presence of DMA and in the absence of silver phosphate, but at the elevated temperature of 110°C, the R-isomer was obtained in 77% isolated yield and 66% e.e. [22]. It is this great sensitivity of the Heck reaction that confers its excellent versatility.

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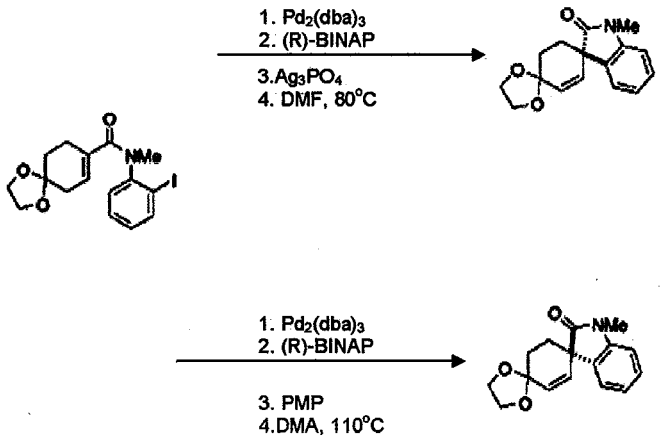

Figure 2.1: A reaction showing one of the first highly asymmetric intramolecular heck reactions

Whilst the yield and e.e. may not seem impressive when compared to more up-to-date asymmetric syntheses, this data should not overshadow the great ease of controlling the outcome of the synthesis. It is useful to compare the nature of the control over stereochemistry to that achieved by other strategies; first of all we shall consider enzyme-based methods. The enantioselective synthesis of cyanohydrins via biocatalysis with hydroxynitrile lyases is a procedure that has benefited from extensive research since 1908. However, until recently only the (R)-lyase was known, eventually advanced over-expression and cloning techniques have led to the discovery of the (S)-lyase which yields the other isomer[23]. So, even though each technique allows the acquisition of both isomers, the enzymatic route demands a long search for a naturally occurring mutant that achieves the goal (a 95 year long search in the case of the (S)-hydroxynitrilelyase); asymmetric heck reactions however have demonstrated control can be placed firmly in the hands of the researchers[24]. Our second comparison will be to methods based on artificial catalysts: either an organocatalyst or other transition-metal catalysts. These approaches tend to take advantage of either an asymmetric induction, in which a reagent, auxillary or catalyst is able to impart a particular stereochemistry onto the product by virtue of its own chirality, or a kinetic resolution in which one of the enantiomers undergoes a reaction much more rapidly in the presence of a chiral catalyst – the two different products can then be separated more easily.In the Heck reaction, contrary to these other asymmetric catalytic procedures, the enantioselectivity is not a result of the chiral ligand's (i.e. BINAP's) ability to accomplish an asymmetric induction at some point in the catalytic cycle. Instead, an almost alchemical manipulation of the solvent and additives in the reaction mixture has led to fine stereochemical control. As of 2010, the mechanistic interpretation is still under some dispute though it seems that silver phosphate's presence opens up rapid interconversion between the pro-(*R*) and pro-(*S*) intermediates that come into existence following initial oxidative addition[25]. Further work revealed more unusual occurrences. When high-purity Ag_3PO_4 was used, the R-product was the primary product. However, when a fractionally less pure Ag_3PO_4 was employed (or if the high-purity salt was first exposed to light), the S-product was the major product was obtained[25]. This points to the presence of a Ag(0) species perturbing the post-oxidative addition equilibrium. This exemplifies the fact that the reaction outcome can be controlled by attempting to understand the chemistry - we alluded to this in our discussion of enzymes above. Exploiting very simple procedures to synthesise enantiopure products is one of the synthetic breakthroughs offered by the Heck reaction. Enantioselective reactions can thus be effected without having to spend time either designing and attempting to synthesise intricate chiral ligands, or performing kinetic resolutions, which only serve to add more (low yielding) steps to the reaction scheme[26]. Nonetheless, determining the alteration that must be made to the reaction conditions in order to invert the stereoselectivity is not necessarily easy, in many instance trial and improvement is required due to a lack of understanding of the mechanistic chemistry.

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Mizoroki–Heck reactions continually resurface in the hunt for efficient syntheses. A recurring theme in research in this area is the use of a reaction set-up which promotes easy recycling of the catalyst to maximise catalyst usage and to save time. Supported palladium catalysts have realised this objective, and have additionally enhanced regioselectivity to unprecedented levels, owing to the steric hindrance of the catalyst at the catalyst-support interface. A recent technique used in the synthesis of a range of cinnamates appears to be an easy to implement and highly effective stategy. Supporting a $Pd(NH_3)_4Cl_2$ on silica (SiO_2) in a BMIM-PF_6 solvent system enabled Okubo and colleagues to diastereospecifically synthesise a set of alkyl cinnamates with at least 95% yield[27]. In particular, ethyl cinnamate, an important flavouring compound, was isolated in 100% yield after reflux for 1h[25]. The extent of leaching of the catalyst into the solvent did not exceed 0.24%

of the initial catalyst load; the investigation demonstrated six reuses of the catalyst with no loss of performance in the system – more work is necessary to reveal the upper limit to this statistic, but this procedure alone will already be of enormous interest to the flavour and fragrance industry[27].

The aforementioned technique of immobilisation (which is an example of heterogeneous catalysis - using a catalyst in a distinct phase to the reaction mixture) is currently eagerly investigated. Unfortunately, reduced reaction rate is often a side-effect of enforcing a heterogeneous catalyst – chemically, this is quite expected. If the system is truly biphasic with minimal leaching, one can only expect reaction to occur at the interface between the substrate and the catalyst surface whilst a homogenously catalysed reaction can take advantage of a catalyst dispersed uniformly throughout the reaction mixture. Two further strategies can be employed to attempt to counteract this: phase-transfer catalysis and a novel method discovered by Kleist based on dissolution and redeposition. Using a phase-transfer catalyst (PTC) is certainly not a concept unique to palladium chemistry, it is extensively put into practice to solve this problem in an array of synthetic applications. Only the Heck reaction has been extensively trialled for use with a PTC and the results show a marginal improvement in reaction rate. On a side note, using a PTC method in an aqueous medium does bring with it an advantage; water is a very cheap and environmentally friendly solvent. An especially useful strategy is binding the substrate to the liquid polymer PEG and conducting a standard homogeneous reaction procedure in an aqueous environment. In normal circumstances, the poor solubility of the Pd-catalyst would render the method useless but the PEG serves as a support and a PTC, thus enabling efficient reaction between the Pd-catalyst and the substrate when they come in to contact[28].

Whilst this is another technique to remember for the industrial chemist searching for green alternatives, it does not enable us to combine the benefits of a catalyst-support method and a fast reaction. For this objective, the only potential solution is to draft in the line of attack suggested by Kleist. Kinetic investigations confirm the expected result that an increased concentration of the leached Pd-catalyst in the solution leads to a greater rate of reaction, the insight of the Kohler lab was to capitalise on the rate increase obtained from a homogeneous catalyst whilst combining it with a catalyst support to aid recycling. Despite the paradoxical nature of this proposal, the objective was accomplished by designing a supported catalyst system that consists of a solid catalyst which is in equilibrium with a dispersed Pd-species in solution. Several systems were tried but incorporating the palladium into a zeolite cage was most effective[29]. During the reaction, Pd diffused from the zeolite pores to give reaction rates which exceeded any previous Pd-catalysed heterogeneous reaction by at least a factor of ten[29]. Following completion of the reaction, essentially all the Pd is re-deposited onto the support. Kleist et al. believe that the protocol meets all the "requirements for practical applications in laboratory and industry" and indeed, the concept of combining the benefits of homogeneous and heterogeneous catalysis whilst evading their problems has the potential to transform many procedures exploiting traditional Heck reactions.

Future Work

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Earlier we considered the advantages that can be reaped by employing Pd-catalysis in order to link aromatic structural subunits. The methods already discussed are very good, but they have an inherent drawback that places an upper bound on their efficiency. In all of the reactions discussed above, the coupling partners had to be activated, typically by a halogen on one species and an electropositive group such as boronic acid (which must be further activated by a base) on the other – these additional groups are absent in the product and inevitably form by-products. If these reactions could take place without preactivation, then the process would become much more atom economic, as waste products owing their existence to the preactivating groups would no longer be

present. For this reaction to succeed the catalyst must not lead to the formation of homocoupled products, as this would offset any increase in the efficiency of the process. In order to induce this selective cross-coupling, the catalyst must initially react with the first arene substrate, after which total inversion of selectivity must occur such that the Pd-complex will exclusively react with the other arene. Figure 3.1 below outlines how this selectivity could take place within the framework of a simplified yet feasible catalytic cycle.

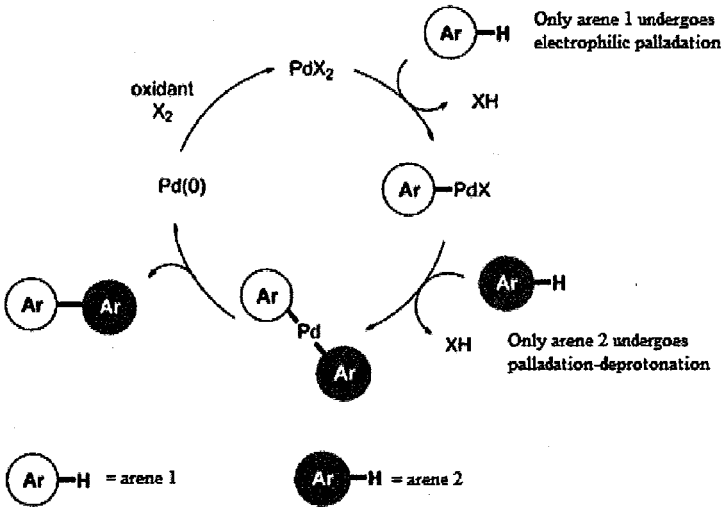

Figure 3.1 (above): A possible direct arylation cycle (adapted from the Fagnou and Stuart publication)[30].

Stuart and Fagnou have reported the first example of a direct arylation[30]. Facilitation of the selectivity inversion was achieved by provoking two different mechanisms: an aromatic electrophillic palladation followed by a concerted palladation-deprotonation; this was the sequence proposed in the cycle above. Their study has revealed successful couplings between N-acetylindoles and simple substituted benzenes. Figure 3.2 below demonstrates one such reaction. Although the arylindoles are not a widely synthesised class of compounds, they are frequently found in natural products – an example is the diazonamide A, a secondary metabolite of an ascidian that functions as an anticancer agent at nanomolar concentrations – the compound is of interest to medicinal chemists for this reason[31].

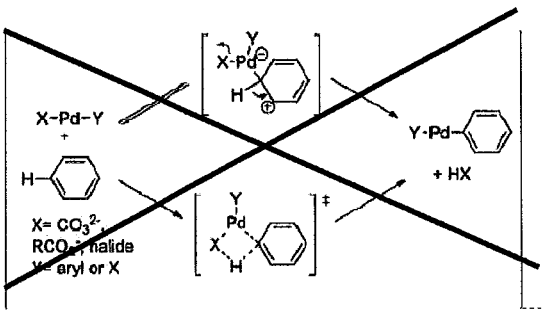

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Figure 3.2: The electrophilic metallation mechanism (top) and concerted proton transfer-metallation below.

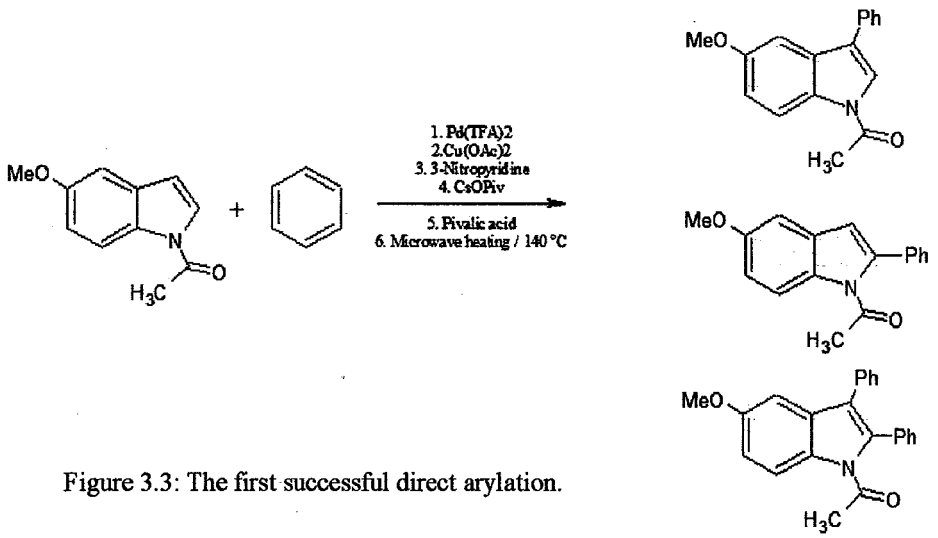

Figure 3.3: The first successful direct arylation.

Further work is much needed for this methodology to make its way into industrial synthetic routes. The catalytic system is suitable for only a small group of substrates, which suggests a series of extensive substrate scope studies should be carried out, and furthermore, the mechanistic efficiency is diminished by the high catalyst loading required (10 mol %) and the requirement for a copper (II) acetate oxidant in stoichiometric quantities. Arguably the most important goal for research in this area is to develop a pathway that incorporates an oxidative concluding step in the cycle, this would enable the oxidant to be removed and the catalyst loading to fall. In addition, to warrant a role in industry, the 84% yield must be improved and research should aim for complete regioselectivity – in this instance, the products were obtained in the ratio 11.2:1:0.4 (product 1:product 2:product 3) although this is high regioselectivity, regiospecificity is the next target. A feature of this reaction which need not change is the heating protocol – microwave irradiation was shown to reduce reaction time from 48h (achieved in an oil bath) to 5h. The result is testament to the synergy between microwave assisted organic synthesis (MAOS) and Pd-mediated reactions. Whilst microwave methods are not the focus of this review, they are relevant to the design of efficient synthetic procedures; volume 266 of the "Topics in Current Chemistry" series provides an excellent account of the increasingly important role of this family of techniques.

Above, we established how synthetic efficiency can be greatly ameliorated by the use of the aptly named "one-pot" concept. The idea can be taken a step further: it would be even more efficient if we could trigger a second reaction without having to introduce a new catalyst or modify the existing catalyst following initiation. Carrying out a sequence of two or more discrete reactions, in which subsequent transformations occur at functionalities altered in former steps, is known as a cascade or domino reaction[25]. Domino reactions are simultaneously environmentally sound and elegant in nature. In terms of the principles of green chemistry, the reaction ticks several boxes, among the useful features are the minimisation of solvent and reagent quantities, the reduction in the time and thus energy input required, and the high atom economies achieved. Researchers seeking new domino processes are finding the library of Pd-catalysed reactions to be the most fruitful place to look – this is because Pd has the

unique ability to catalyse a variety of bond-forming reactions; C-C, C-O and C-N being the most useful. The other vital characteristic of Pd that we encountered at the start was its high chemoselectivity, for domino reactions this is vital as it enables functionalisation in the absence of protecting groups.

A breathtaking synthesis of okaramine N, an insecticidal alkaloid, argues a compelling case for the importance of domino reactions[31]. Retrosynthetic analysis was used to plan the synthesis, the result of which was the prediction that eight steps would be required, starting from a tetracyclic intermediate synthesised in two-steps with a reductive N-alkylation in the presence of $NaBH_4$ and a Schiff base, followed by an acylation[32]. Furthermore, the intention was to exploit the modern Fujiwara–Moritani modification to the Heck reaction; hence facilitating certain heck reactions without halogenation of the aromatic substrate – this achieves a synthetic goal analogous to the direct biaryl synthesis. However, the first five steps were achieved with a single reaction: an intramolecular cyclisation cascade reaction that is almost unrecognisable as a Heck reaction. The cascade has been outlined below to reveal the distinct nature of each of the transformations and to partially elucidate the mechanism. A notable feature of the cascade is that several steps are unexpected yet are still able to proceed with almost total regioselectivity. First of all, the presence of two indole groups suggests that a competing mode of ring closure will operate to give an undesired 7-membered ring. Instead, only the intended indole (the N-unprotected indole) cyclises via a 7-exo-trig 1,2-insertion with almost complete chemoselectivity to give a 7-membered ring. Whilst the feasibility of this mode of ring closure is predicted by Baldwin's rules, consideration of the product reveals that an 8-membered must be generated; fortunately a spontaneous ring expansion in step four rectifies the problem[33]. Following the initial ring formation, β-hydride elimination is the expected step due to the presence of seven optimally located hydrogen atoms. Nonetheless, the reaction again diverges from the anticipated result by heterolytic fragmentation into a tertiary carbocation. Upon termination of this domino reaction, preparation of the target compound is achieved in three straightforward steps[33].

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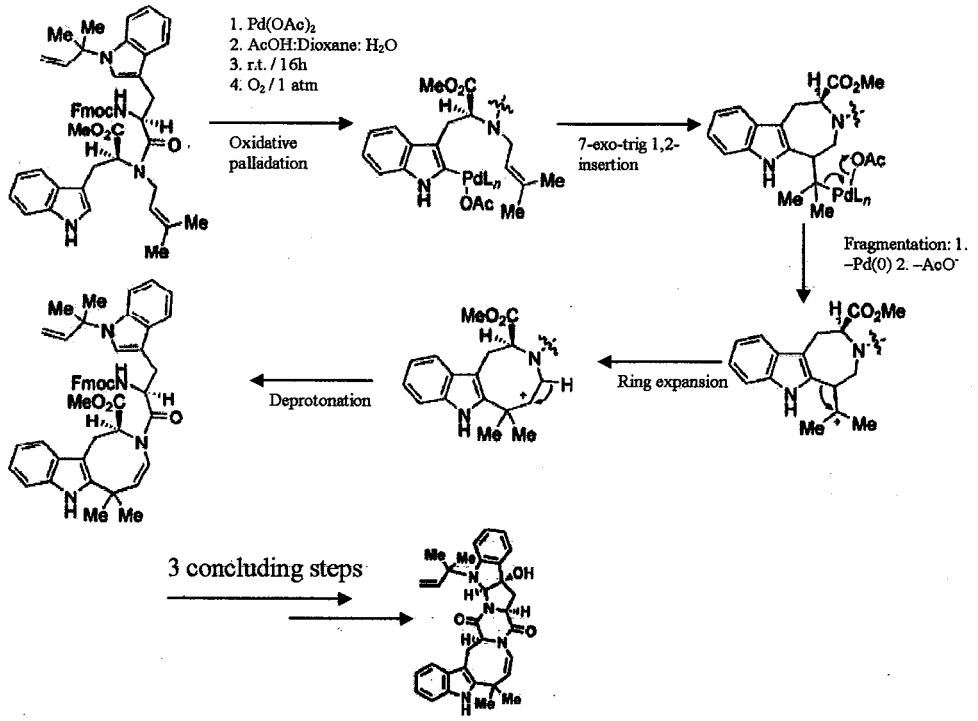

Figure 3.4: The total synthesis of okaramine.

It is a surprise that this synthesis was conceived given the unconventional route it follows, Baran et al. admit that they were "humbled by the large number of completely unforeseen roadblocks" – but of course this should have been expected given the low feasibility of the reaction[33]. Selecting the solvent system was among the most challenging of steps, but being a Heck reaction great sensitivity to reaction conditions is expected. Omitting acetic acid from the reaction mixture led to no reaction occurring whilst in the absence of water, 7-membered rings were formed exclusively (no ring expansion took place)[34]. A thorough understanding of the subtleties of domino reactions is necessary before the methodology can become a staple for industry, at the moment the design process is highly labour intensive due to the amount of good fortune and guesswork involved.

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Conclusions

In recent years, more and more palladium-derived compounds are being recognised as important catalysts in an eclectic assortment of syntheses including the production of industrial feedstock and fine chemicals as well as the assembly of large, intricate natural products. Through our examples we have shown that Pd catalysts enable: high selectivity, high yields, shorter synthetic routes, mild reaction conditions and low toxicity in addition to the tolerance of unprotected functional groups, oxygen, water, and acid. These traits are among the hallmarks of a green and commercially attractive synthesis – an efficient synthesis. Even in light of the great expense of palladium (see appendix B for more information on the price of palladium), the rapid appearance of palladium catalysed reactions in industry over the last 20 years emphasises the extent to which this major drawback is overshadowed.

Perhaps the most important, yet least documented, facet of palladium chemistry that we encountered above is what Fairlamb has aptly termed the "black-box". Research in this field regularly uncovers unexpected and unexplainable phenomena that promise to enhance the efficiency

of synthetic routes, for instance, the idea of homeopathic conditions has led to significantly reduced catalyst loadings in isolated cases, but only when this observation has been fully rationalised can we expect to see it become a standard procedure in the optimisation of reaction conditions. This same conclusion could be drawn from many of the novel protocols that we have investigated, but progress is already discernable in some key areas. Direct arylation without prefunctionalisation of the substrates promises to solve all issues of waste formation with a pathway offering maximum atom economy. Fagnou's untimely death has slowed progress in the field but his lab continue to report direct coupling strategies – it is only a matter of time before a large library of these direct reactions are available for widespread use. A key factor in the pace of this particular development is the concomitant mechanistic elucidation work that has been undertaken – this provides a theoretical base from which substrate and reagent combinations can be postulated. This work serves as an excellent template for research in Pd-mediated synthesis – firstly observing the "black-box" at work and then unpacking the mechanics of its action such that the techniques scope can be broadened.

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Palladium's role in synthetic chemistry is perhaps analogous to that of the stem cell in biology – it acts a progenitor from which a plethora of systems can be developed to catalyse a vast range of reactions, and what's more it may be the only viable catalyst for a given transformation (for example, the GBH reaction).

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More often than not, palladium catalysts exhibit the conventional characteristics of an efficient synthesis, furthermore, modifications to the system (for example, new ligands, solvents or additives) frequently lead to "black-box" phenomena that may enhance palladium's existing efficiency, and lastly, completing the triad of useful properties is palladium's versatility, it catalyses an enormous variety of reactions - a feature useful in its own right - but also vital to the success of one-pot and domino reactions, the most efficient of all reaction schemes. A more arresting concluding sentence would be better.

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Second Draft

OCR
RECOGNISING ACHIEVEMENT

Extended Project Qualification (Level 3)

How can palladium catalysts increase efficiency in the synthesis of aromatic compounds?

Supervisor:

Abstract

Modern synthetic chemists are continually striving to prepare compounds more efficiently, and one method that they are invoking routinely is the use of a palladium catalyst. Palladium is currently an important catalyst in many commercial syntheses due to the large number of high yielding and highly selective pathways it mediates. However, de novo palladium catalytic systems are more esoteric – but crucially, offer marked improvements in efficiency. The often unusual behaviour of palladium has made it the catalyst of choice for those in search of novel, efficient synthetic routes. Coupling reactions of aromatic compounds have been identified as the subset of organic synthesis that is best placed to benefit from the advantages of palladium, and so they will be our focus here. Reactions of this nature are vital to the development of convergent synthetic routes in industry and also to research labs pursuing total synthesis, which necessitate the assembly of complex molecules consisting of multiple substructures. Here we present the palladium-based procedures that have already led to efficient strategies, with particular regard to biaryl synthesis and Heck reactions, and additionally review current research that promises to shape the next generation of palladium-based methodologies.

Introduction

A successful organic synthesis demands the creative application of computational and theoretical techniques in order to firstly identify a molecular framework with a structure well-suited to the desired function, and to then map out a synthetic route which may arrive at the target[1]. Putting together a complex molecule relies on having a library of efficient core reactions at one's disposal; frequently it is compounds exhibiting aromatic motifs that prove to be the core reagents of greatest value. Aromatic compounds are characterised by their delocalised system of pi-electrons, a well-defined geometric structure, relatively high levels of photochemical, thermal and chemical inertness as well as good potential for selective functionalisation[2]. It is therefore no surprise that compounds displaying an aromatic nucleus are ubiquitous in modern synthetic chemistry and are biosynthesised by organisms in every taxonomic kingdom. This is an area of chemistry that has been thoroughly investigated, but of course, many avenues remain unexplored. Here, we will focus on the palladium-catalysed synthesis of compounds exhibiting aromaticity – palladium is extremely versatile and highlights the tremendous power of a transition metal-mediated approach to constructing organic molecules. The combination of a well-behaved and structurally malleable compound class with a synthetic methodology that gives rise to highly selective routes provides us with an ideal territory to search for more efficient strategies in synthesis.

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It is necessary but certainly not sufficient to merely identify and synthesise a target compound, the next and arguably more important stage is to refine the efficiency of the synthetic procedure. An efficient reaction scheme may be defined as one which produces a unit quantity of a target compound with the minimum input of resources. Evaluating synthetic efficiency is difficult: industrial chemists and research chemists have markedly different objectives and thus place emphasis on different aspects of efficiency. Industrial chemists will regularly choose reactions requiring cheap and readily available reagents whilst simultaneously attempting to maximise yield, minimise the number of steps, ease product isolation and purification, and reduce energy and time input. These objectives are self-explanatory and quite clearly can be grouped together as a set of economic considerations intended to improve cost effectiveness. Academic research in organic synthesis may share some of these goals, but the key difference is an emphasis on finding new reactions with inherent properties that are of interest – optimising a reaction to improve profitability is not the objective. Selectivity and atom economy are two examples of properties that confer greater efficiency; it will become evident that these properties

also have economic repercussions and so will be of interest to industry, provided that it is feasible for the procedure to be scaled-up.

To achieve good atom economy is to maximise the proportion (by mass) of the reactants that end up in the final product and minimise waste as a consequence. Quantitatively this may be defined as the ratio of the molecular mass of the desired product to the sum of the molecular masses of all the products. Atom economy is an intrinsic feature of a reaction; this is in contrast to yield, which can be manipulated by altering reaction conditions and recycling the reaction mixture.

Selectivity is another reaction property that must be understood in order to appreciate the utility of organopalladium chemistry in achieving an efficient synthesis. The first division of selectivity to consider is chemoselectivity: this is the ability to ensure a reaction is effected only at the intended functional group(s); it is often the case that many potentially reactive groups will be present and these must be prevented from taking part in side reactions. Similarly, regioselectivity is the extent to which a compound reacts to give the desired structural isomer. In an unsymmetrical species, this necessitates the preference of one direction of bond breaking and formation over another, and in instances where several identical functional groups are present, there must be discrimination between different chemical environments[3]. Lastly we come to stereoselectivity; this facet of a synthesis is encompassed in the degree of diastereoselctivity and/or enantioselectivity. These concern the degree to which a single diastereoisomer or enantiomer is produced, achieving the latter objective is difficult due to the identical chemical and physical properties exhibited by chiral molecules; it is the subject of the field of asymmetric synthesis[3]. Quantitative assessment of the level of stereoselectivity is given by the enantiomeric or diastereomeric excess, this is calculated by determining the absolute value of the difference between the mole fraction of the desired stereoisomer and the sum of the mole fractions of the unwanted stereoisomers, it is normally expressed as a percentage[4]. Optical purity is also routinely used to quantify enantioselecitivty – it is the ratio of the specific rotation of the sample to the specific rotation of the pure desired enantiomer. Some authors use the term "specificity" to refer to 100% selectivity – this indicates that the reaction mechanism has a strict stereochemical requirement.

Realising these synthetic objectives is made possible thanks to a range methods, however, here we discuss a single family of techniques, that is, those reactions that involve the use palladium to mediate or catalyse reactions at the heart of preparative procedures. As we have seen, efficiency is very broad term encompassing many issues - overall "efficiency" is thus a trade-off between each of the competing factors. For example, consider a very slow reaction which demands expensive reagents, but which offers 100% atom economy and high yield. Clearly, the input of capital and time is high whilst the quantity of reagents required have been minimised – it is the net impact which must be considered. The net impact need not be considered solely in economic terms; it will transpire that the discussion regularly alludes to the terminology of green chemistry and indeed the consequence of improving efficiency is frequently a reduction in environmental impact. Transition elements frequently enable the attainment of efficiency in several of the aforementioned categories simultaneously. The extent to which the catalytic properties of palladium can be exploited in order to address the issue of efficiency, and hence bring great benefits to the chemical industry, will be considered by exploring reactions that clearly illustrate the advantages and disadvantages of palladium-based synthesis.

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Biaryl Synthesis

Suzuki and Negishi Coupling

Palladium (Pd) catalysis can be used to great advantage in coupling reactions, that is, reactions leading to the amalgamation of organic fragments via carbon-carbon or carbon-heteroatom bond formation. Molecules consisting of two directly bonded aryl groups (biaryls) are indisputably among the most important compounds that can be produced in coupling reactions. Biaryl substructures are widespread in medicinal products, such as the antibiotic vancomycin and the potent antileukaemic

agent stegnacin, as well as engineering materials including liquid crystals, molecular wires, and conducting polymers such as poly-p-phenylene[5, 6]. Moreover, aryl-aryl bond forming reactions are vital to the modern synthetic approach known as convergent synthesis in which several molecular fragments are assembled separately before being finally coupled in order to assemble the target[7]. Sartans (angiotensin II receptor antagonists) are an important class of antihypertensive drugs that are synthesised using a Pd-based convergent strategy[8]. This class of drugs is also an example of how syntheses already exploiting palladium chemistry can be further enhanced thanks to new advances.

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Comparing a typical nickel (Ni) catalysed Negishi coupling to the palladium catalysed Suzuki coupling will serve as a useful case study to briefly survey the ways in which efficiency can be enhanced by employing a palladium catalyst in place of a different transition metal. Figure 1.1 below shows a simple two-step synthesis of 2-phenylbenzaldehyde that I have designed; it is based on a similar procedure noted by Cepanec[5]. The reaction scheme affords the product with an overall yield of 82% within a 5.5h period. We can attribute the need for two steps to the fact that a protecting group (in this case, a cyclohexylimino group) is required to avoid complexation between the nickel species and the carbonyl. Deprotection (step two) introduces a further problem; the nickel complex is attacked by the acid (oxidative addition of the acid to the Ni(0)) and so the complex must either be continually replaced or an extraction step must be added to remove the catalyst[9]. The nickel complex is also relatively difficult to work with, it must be kept at 2°C and contact with oxygen should be minimised, Sigma Aldrich also confirm that the compound is hazardous – a faceshield and full-face particle respirator should be worn when using the substance[10]. Lastly, an unfortunate consequence of the reaction conditions is that the arylzinc reagent will undergo a homocoupling, this side reaction cannot be avoided and so an excess of the arylzinc compound must be added[5].

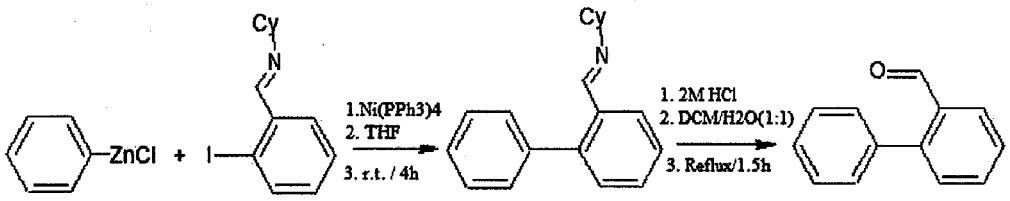

Figure 1.1: Scheme one – an example of a nickel-catalysed Negishi Coupling

Thimmaiah and Fang reveal that an innovative Suzuki-Miyaura coupling will afford the same product[11]. Not only is the yield much greater at 99%, but the $Pd_2(dba)_3$ confers complete chemoselectivity enabling the reaction to proceed in the absence of a carbonyl protecting group[11]. The number of steps is instantly halved, which leads to a reduction in the amount of apparatus and solvent used, and the synthesis is also much more rapid (four hours per batch is saved), however this is also due to the greater rate of reaction in the second scheme. Industry is likely to be deterred from using the second procedure as a result of the need for a specialised ligand (see figure 1.3) that is not widely produced and is thus costly, however, in association with the Pd-complex the ligand is only required in catalytic amounts as the substance is neither consumed in the reaction, nor chemically altered by the chosen reaction conditions. Moreover, the ligand activates the Pd-complex more strongly than conventional ligands: the reaction proceeds at a faster rate, in milder conditions, and in the presence of a smaller quantity of the expensive Pd compound[11]. The discoverers of the new class of ligands argue that the ligands are easy to prepare and make possible a variety of reactions that have previously been impossible, for example, they report the synthesis of the novel compound 2,6-dimethyl-2-phenyl-1,10-biphenyl[11]. For this reason, the ligands will be of interest to research groups.

Other ligands, many readily available, can also enhance the reaction (though rate and yield are not enhanced as significantly) and crucially, ligand-free Suzuki cross-couplings have been

documented. From the perspective of industry, both schemes could be made more appealing by reducing the amount of the expensive catalyst (catalyst loading) required, the first reaction is effective with a load of 1-5 Mol % while the second procedure was optimised at 1.5 Mol %[11]. Excessive catalyst loads are inefficient in two respects, firstly they unnecessarily increase the cost of the reaction and secondly, the high concentration encourages catalyst particle agglomeration leading to cluster formation, the clusters precipitate out as palladium black – this is uneconomical as it is not a catalytically active species. Astonishingly, the problems associated with the reaction scheme, that is, the use of an exotic ligand and also the need for a relatively high catalyst loading could potentially be overcome concomitantly. The technique in question is the use of so-called "homeopathic" conditions. Predictably, catalyst loading is greatly reduced (to approximately 0.02Mol %), the ligand is excluded, and the reaction is run in ambient conditions[12]. High yields were obtained (up to 95%) though they varied with substrates and were on the whole lower than scheme two [12]. Potential exists to lower catalyst concentrations even further, a 0.0025 Mol % loading was successfully employed to obtain 4-acetylbiphenyl in an 85% isolated yield[12]. Both highly-activating ligands and the opposing technique of homeopathic conditions are clearly worthy of further work; they promise to greatly improve the efficiency with which biaryls are synthesised for both industrial and research purposes.

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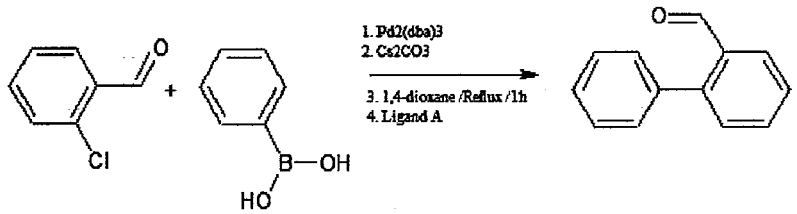

Figure 1.2: Scheme two

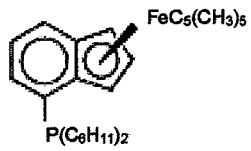

Figure 1.3: The structure of ligand A (a benzoferrocenyl dicyclohexyl phosphine derivative called 4-(Dicyclohexylphosphino)indenyl-pentamethylcyclopentadienyliron)

The simplicity and enormous potential of the Suzuki coupling is emphasised by the fact that a simple example of one is now carried out as a practical at the University of Oxford by second and third year undergraduates – this is testament to the increasing accessibility of organopalladium chemistry to chemists[13]. Use in the setting of a teaching laboratory also confirms that Pd-species are in general safe to handle, markedly so in comparison to Ni-complexes – this is convenient as no special protective gear is required. Scheme two also produces less waste than scheme one due to the absence of competing reactions (no homocoupling is observed in either the scheme recorded in figure 1.2 or the homeopathic procedure). However, the atom economies of both the methods discussed so far are not optimum; by-products from the desired reactions are produced in stoichiometric quantities. Nonetheless, the Suzuki method still offers superior efficiency over the Negishi reaction in this respect, as the by-products are all inorganic facilitating extraction from the reaction mixture.

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Reactions yielding biaryls without invoking the power of transition element catalysis are rare, the sole common example is the Gomberg-Bachmann-Hey (GBH) reaction; this reaction instead exploits diazonium salts[14]. Admittedly, the GBH method allows a wide range of biaryls to be produced, but the chemoselectivity is low and subsequently yields rarely exceed 40%. This is a result

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of the fact that a plethora of side reactions occur; the aryl radicals generated will undergo polymerisation, reduction to the parent arene, and azo coupling to give brightly coloured compounds in cases where the arene to be arylated is activated by an electron-donating group. One would therefore assume that this reaction is of no use in modern synthetic routes owing to its poor efficiency, however, many syntheses have continued to use the GBH reaction and its variants, for instance, a Suzuki coupling strategy to synthesise the NSAID diflunisal in a single step was only developed in October 2009[15]. Previously, a three-step procedure involving a GBH reaction between the diazonium salt of 2,4-difluoroaniline and anisole, followed by ether hydrolysis and Kolbe-Schmidt carboxylation, had been favoured[16].

One-Pot Synthesis

Now with an idea of some of the generic benefits we can exploit by using Pd-based methods, it is possible to turn to a more technically demanding synthesis – a triaryl synthesis. Figure 1.4 (below) shows a completely regioselective one-pot double Suzuki coupling yielding a differentially substituted pyrrole[17]. By assembling a tripartite structure in a single reaction vessel, a target compound can be assembled in fewer reactions and purification steps, with fewer reagents, and with less apparatus. Motivation for the synthesis of these compounds stems predominantly from their use in herbicides; this particular structural motif is prevalent in the protox inhibitor class of herbicides[18]. Two major difficulties must be overcome in order to achieve success in this synthesis, the first is that two sequential coupling reactions must take place in the same reaction vessel, and secondly, both couplings must take place with high regioselectivity: one reagent must attack only. Owing to the relatively nascent nature of Pd-mediated synthesis, there is no sure-fire way of determining an ideal combination of solvent, ligand and base. A common strategy for choosing a suitable catalytic system is a high-throughput screening approach; this involves setting up different reaction conditions on a millilitre scale and allowing the reactions to take place in parallel. Yield and product characterisation are the most important points to consider – yield is in this instance an integral part of the synthetic efficiency as the reaction conditions have been fixed. Following analysis of this nature, it was found that running the reaction under the first three conditions highlighted in the scheme and in the absence of p-fluorophenyl boronic acid produced exclusive monocoupling in the 5-position, even an attempt at forced dicoupling with 24 hours of vigorous reflux was unsuccessful. The next hurdle was to substitute the other boronic acid into the 4-position. Initial attempts to do so involved adding a different, more active catalyst to the reaction mixture in combination with the species to be coupled. Despite the success of this strategy, it was found that even a cheaper strategy could be employed; a new catalyst could be synthesised in situ by addition of a phosphine ligand. A modest 58% yield was obtained. Numerically, this is disappointing, but if we take into account the fact that two regiospecific reactions have taken place without any work-up, isolation or purification in between and that two sequential monocoupling would enable the same product to be isolated in a mere 10% yield, then we can certainly claim that this is an impressive result.

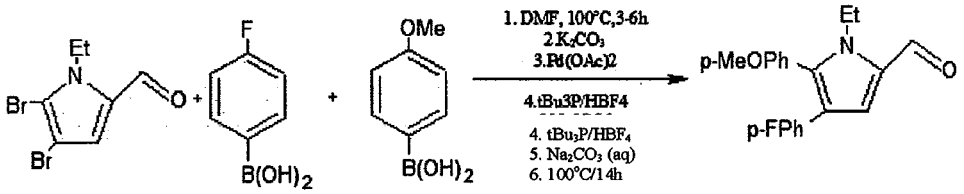

Figure 1.4: A synthesis of a substituted pyrrole to illustrate the "one-pot" concept

The strategy outlined here clearly has laid the foundations for the development of other related syntheses; this same dicoupling technique has been used to prepare substituted pyridines, thiophenes, and most recently, general unsymmetrical triaryls[19,20]. Whilst pyrroles are rarely useful, these latter protocols make the synthesis suitable to a range of applications including organic LEDs (OLEDs) and important pharmaceuticals such as Lipitor, a statin for cholesterol reduction, and Celebrex, an arthritis treatment[19]. What's more, a greatly improved isolation procedure utilising neutral alumina instead of silica has been developed; this has boosted yields to 97% for certain substrate combinations. Without doubt, palladium's scope for one-pot syntheses is of great value; the capacity to amalgamate reaction steps will cut costs in industrial routes whilst the fact that the technique can give rise to quickly converging schemes will almost certainly result in its exploitation by research labs in search of facile total syntheses of complicated natural products.

Heck Reactions: Arylation of Alkenes

Asymmetric catalysis

The Heck, or Mizoroki-Heck, reaction can be defined as the Pd-catalysed coupling of an alkene and an sp^2 (aryl or alkenyl) halide or triflate[21]. The technique is extremely versatile, thus accommodating many substrates, countless variants exist, and a myriad of innovative efficiency-enhancing modifications have emerged. Heck reactions have proved to be fertile grounds for the development of asymmetric catalytic protocols. The striking ability of the reaction to achieve this is illustrated quite unequivocally in Overman's highly enantioselective synthesis of a series of spirooxoindoles exhibiting a single quaternary carbon centre, of which one example is shown below[22]. The most significant aspect of this success was the formation of both enantiomers at will, with very minor alterations to the reaction conditions. Another notable feature of the reaction is that it is an example of a desymmetrising Heck reaction as chirality has been introduced into a prochiral substrate; no enantiopure starting reagents are called for as is the case for a chiral pool synthesis. The first procedure in figure 2.1 (top) produced the S-isomer in an 81% yield and 71% enantiomeric excess (e.e.); after conducting the reaction with the addition of PMP, in the presence of DMA and in the absence of silver phosphate, but at the elevated temperature of 110°C, the R-isomer was obtained in 77% isolated yield and 66% e.e. [22]. It is this great sensitivity of the Heck reaction that confers its excellent versatility.

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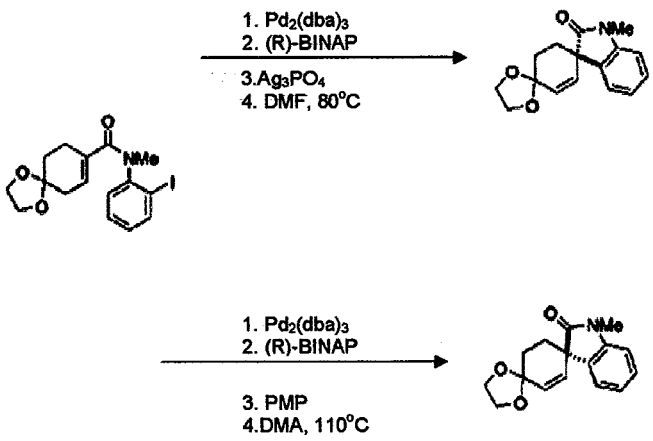

Figure 2.1: A reaction showing one of the first highly asymmetric intramolecular heck reactions

Whilst the yield and e.e. may not seem impressive when compared to more up-to-date asymmetric syntheses, this data should not overshadow the great ease of controlling the outcome of the synthesis. It is useful to compare the nature of the control over stereochemistry to that achieved by other strategies; first of all we shall consider enzyme-based methods. The enantioselective synthesis of cyanohydrins via biocatalysis with hydroxynitrile lyases is a procedure that has benefited from research since 1908. However, until recently only the (R)-lyase was known, eventually advanced over-expression and cloning techniques have led to the discovery of the (S)-lyase which yields the other isomer[23]. So, even though each technique allows the acquisition of both isomers, the enzymatic route demands a long search for a naturally occurring mutant that achieves the goal (a 95 year long search in the case of the (S)-hydroxynitrilelyase, admittedly research was not continuously taking place, only a few researches dabbled in the field); asymmetric heck reactions however have demonstrated control can be placed firmly in the hands of the researchers[24]. Our second comparison will be to methods based on artificial catalysts: either an organocatalyst or other transition-metal catalysts. These approaches tend to take advantage of either an asymmetric induction, in which a reagent, auxiliary or catalyst is able to impart a particular stereochemistry onto the product by virtue of its own chirality, or a kinetic resolution in which one of the enantiomers undergoes a reaction much more rapidly in the presence of a chiral catalyst – the two different products can then be separated more easily. In the Heck reaction, contrary to these other asymmetric catalytic procedures, the enantioselectivity is not a result of the chiral ligand's (i.e. BINAP's) ability to accomplish an asymmetric induction at some point in the catalytic cycle. Instead, an almost alchemical manipulation of the solvent and additives in the reaction mixture has led to fine stereochemical control. As of 2010, the mechanistic interpretation is still under some dispute though it seems that silver phosphate's presence opens up rapid interconversion between the pro-(*R*) and pro-(*S*) intermediates that come into existence following initial oxidative addition[25]. Further work revealed more unusual occurrences. When high-purity Ag_3PO_4 was used, the product the R-product was the primary product. However, when a fractionally less pure Ag_3PO_4 was employed (or if the high-purity salt was first exposed to light), the S-product was the major product was obtained[25]. This points to the presence of a Ag(0) species perturbing the post-oxidative addition equilibrium. This exemplifies the fact that the reaction outcome can be controlled by attempting to understand the chemistry - we alluded to this in our discussion of enzymes above. Exploiting very simple procedures to synthesise enantiopure products is one of the synthetic breakthroughs offered by the Heck reaction. Enantioselective reactions can thus be effected without having to spend time either designing and attempting to synthesise intricate chiral ligands, or performing kinetic resolutions, which only serve to add more (low yielding) steps to the reaction scheme[26]. Nonetheless, determining the alteration that must be made to the reaction conditions in order to invert the stereoselectivity is not necessarily easy, in many instance trial and improvement is required due to a lack of understanding of the mechanistic chemistry.

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Comment [D7]: Replace this with a technical term

Supported Catalysts

Mizoroki–Heck reactions continually resurface in the hunt for efficient syntheses. A recurring theme in research in this area is the use of a reaction set-up which promotes easy recycling of the catalyst to maximise catalyst usage and to save time. Supported palladium catalysts have realised this objective, and have additionally enhanced regioselectivity to unprecedented levels, owing to the steric hindrance of the catalyst at the catalyst-support interface. A recent technique used in the synthesis of a range of cinnamates appears to be an easy to implement and highly effective stategy. Supporting a $Pd(NH_3)_4Cl_2$ on silica (SiO_2) in a BMIM-PF_6 solvent system enabled Okubo and colleagues to diastereospecifically synthesise a set of alkyl cinnamates with at least 95% yield[27]. In particular, ethyl cinnamate, an important flavouring compound, was isolated in 100% yield after reflux for 1h[25]. The extent of leaching of the catalyst into the solvent did not exceed 0.24% of the initial catalyst load; the investigation demonstrated six reuses of the catalyst with no loss of performance in the system – more

work is necessary to reveal the upper limit to this statistic, but this procedure alone will already be of enormous interest to the flavour and fragrance industry[27].

The aforementioned technique of immobilisation (which is an example of heterogeneous catalysis - using a catalyst in a distinct phase to the reaction mixture) is currently eagerly investigated. Unfortunately, reduced reaction rate is often a side-effect of enforcing a heterogeneous catalyst – chemically, this is quite expected. If the system is truly biphasic with minimal leaching, one can only expect reaction to occur at the interface between the substrate and the catalyst surface whilst a homogenously catalysed reaction can take advantage of a catalyst dispersed uniformly throughout the reaction mixture. Two further strategies can be employed to attempt to counteract this: phase-transfer catalysis and a novel method discovered by Kleist based on dissolution and redeposition. Using a phase-transfer catalyst (PTC) is certainly not a concept unique to palladium chemistry, it is extensively put into practice to solve this problem in an array of synthetic applications. Only the Heck reaction has been extensively trialled for use with a PTC and the results show a marginal improvement in reaction rate. On a side note, using a PTC method in an aqueous medium does bring with it an advantage; water is a very cheap and environmentally friendly solvent. An especially useful strategy is binding the substrate to the liquid polymer PEG and conducting a standard homogeneous reaction procedure in an aqueous environment. In normal circumstances, the poor solubility of the Pd-catalyst would render the method useless but the PEG serves as a support and a PTC, thus enabling efficient reaction between the Pd-catalyst and the substrate when they come in to contact[28].

Whilst this is another technique to remember for the industrial chemist searching for green alternatives, it does not enable us to combine the benefits of a catalyst-support method and a fast reaction. For this objective, the only potential solution is to draft in the line of attack suggested by Kleist. Kinetic investigations confirm the expected result that an increased concentration of the leached Pd-catalyst in the solution leads to a greater rate of reaction, the insight of the Kohler lab was to capitalise on the rate increase obtained from a homogeneous catalyst whilst combining it with a catalyst support to aid recycling. Despite the paradoxical nature of this proposal, the objective was accomplished by designing a supported catalyst system that consists of a solid catalyst which is in equilibrium with a dispersed Pd-species in solution. Several systems were tried but incorporating the palladium into a zeolite cage was most effective[29]. During the reaction, Pd diffused from the zeolite pores to give reaction rates which exceeded any previous Pd-catalysed heterogeneous reaction by at least a factor of ten[29]. Following completion of the reaction, essentially all the Pd is re-deposited onto the support. Kleist et al. believe that the protocol meets all the "requirements for practical applications in laboratory and industry" and indeed, the concept of combining the benefits of homogeneous and heterogeneous catalysis whilst evading their problems has the potential to transform many procedures exploiting traditional Heck reactions.

Future Work

Direct Arylation

Earlier we considered the advantages that can be reaped by employing Pd-catalysis in order to link aromatic structural subunits. The methods already discussed are very good, but they have an inherent drawback that places an upper bound on their efficiency. In all of the reactions discussed above, the coupling partners had to be activated, typically by a halogen on one species and an electropositive group such as boronic acid (which must be further activated by a base) on the other – these additional groups are absent in the product and inevitably form by-products. If these reactions could take place without preactivation, then the process would become much more atom economic, as waste products owing their existence to the preactivating groups would no longer be present. For this reaction to succeed the catalyst must not lead to the formation of homocoupled products, as this would offset any increase in the efficiency of the process. In order to induce this selective cross-

coupling, the catalyst must initially react with the first arene substrate, after which total inversion of selectivity must occur such that the Pd-complex will exclusively react with the other arene. Figure 3.1 below outlines how this selectivity could take place within the framework of a simplified yet feasible catalytic cycle.

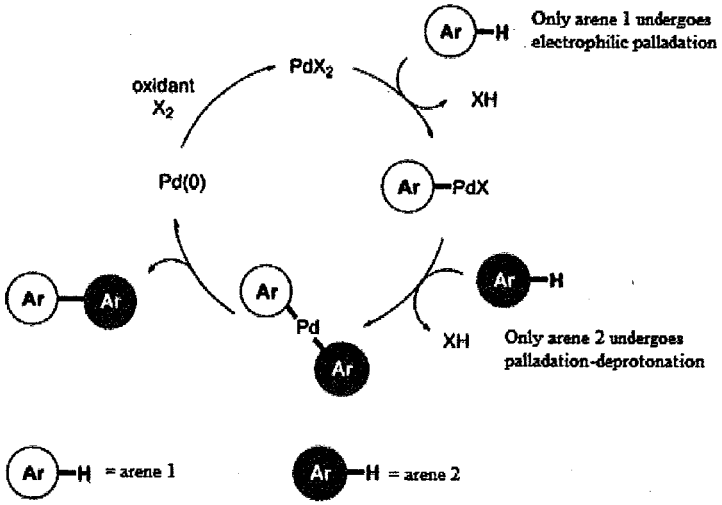

Figure 3.1 (above): A possible direct arylation cycle (adapted from the Fagnou and Stuart publication)[30].

Stuart and Fagnou have reported the first example of a direct arylation[30]. Facilitation of the selectivity inversion was achieved by provoking two different mechanisms: an aromatic electrophillic palladation followed by a concerted palladation-deprotonation; this was the sequence proposed in the cycle above. Their study has revealed successful couplings between N-acetylindoles and simple substituted benzenes. Figure 3.2 below demonstrates one such reaction. Although the arylindoles are not a widely synthesised class of compounds, they are frequently found in natural products – an example is the diazonamide A, a secondary metabolite of an ascidian that functions as an anticancer agent at nanomolar concentrations – the compound is of interest to medicinal chemists for this reason[31].

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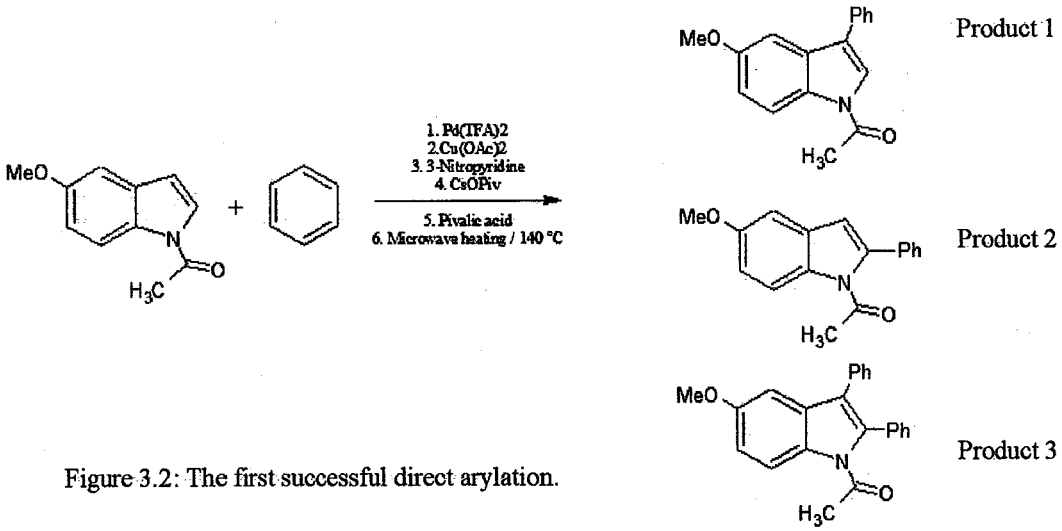

Figure 3.2: The first successful direct arylation.

Further work is much needed before this methodology can make its way into industrial synthetic routes – but the increasing number of publications in this field suggests its emergence is imminent[31]. The catalytic system is suitable for only a small group of substrates, which suggests a series of extensive substrate scope studies should be carried out, and furthermore, the mechanistic efficiency is diminished by the high catalyst loading required (10 mol %) and the requirement for a copper (II) acetate oxidant in stoichiometric quantities. Arguably the most important goal for research in this area is to develop a pathway that incorporates an oxidative concluding step in the cycle, this would enable the oxidant to be removed and the catalyst loading to fall. In addition, to warrant a role in industry, the 84% yield must be improved and research should aim for complete regioselectivity – in this instance, the products were obtained in the ratio 11.2:1:0.4 (product 1:product 2:product 3) although this is high regioselectivity, regiospecificity is the next target. A feature of this reaction which need not change is the heating protocol – microwave irradiation was shown to reduce reaction time from 48h (achieved in an oil bath) to 5h. The result is testament to the synergy between microwave assisted organic synthesis (MAOS) and Pd-mediated reactions. Arguably the most useful instance of this phenomenon is a Buchwald-Hartwig amination of aryl chlorides reported by Diels et al. in which reaction times were reduced from 1 day to 10 minutes – the procedure is directly applicable to a range of syntheses including the natural product lavendamycin and raloxifene[32]. Whilst microwave methods are not the focus of this review, they are relevant to the design of efficient synthetic procedures; volume 266 of the "Topics in Current Chemistry" series provides an excellent account of the increasingly important role of this family of techniques.

Comment [D9]: Try to find out what substrate studies are planned

Comment [D10]: Include an explanation of why this current system is unsuitable

Comment [D11]: I should attempt to find some 2009-2010 research relating to direct arylation

Domino Reactions

Above, we established how synthetic efficiency can be greatly ameliorated by the use of the aptly named "one-pot" concept. The idea can be taken a step further: it would be even more efficient if we could trigger a second reaction without having to introduce a new catalyst or modify the existing catalyst following initiation. Carrying out a sequence of two or more discrete reactions, in which subsequent transformations occur at functionalities altered in former steps, is known as a cascade or domino reaction[25]. Domino reactions are simultaneously environmentally sound and elegant in nature. In terms of the principles of green chemistry, the reaction ticks several boxes, among the useful features are the minimisation of solvent and reagent quantities, the reduction in the time and thus energy input required, and the high atom economies achieved. Researchers seeking new domino processes are finding the library of Pd-catalysed reactions to be the most fruitful place to look – this is because Pd has the unique ability to catalyse a variety of bond-forming reactions; C-C, C-O and C-N being the most useful. The other vital

Comment [D12]: Consider including the 12 principles of green chemistry in the appendix

characteristic of Pd that we encountered at the start was its high chemoselectivity, for domino reactions this is vital as it enables functionalisation in the absence of protecting groups.

A breathtaking synthesis of okaramine N, an insecticidal alkaloid, argues a compelling case for the importance of domino reactions[33]. Retrosynthetic analysis was used to plan the synthesis, the result of which was the prediction that eight steps would be required, starting from a tetracyclic intermediate synthesised in two-steps with a reductive N-alkylation in the presence of $NaBH_4$ and a Schiff base, followed by an acylation[34]. Furthermore, the intention was to exploit the modern Fujiwara–Moritani modification to the Heck reaction; hence facilitating certain heck reactions without halogenation of the aromatic substrate – this achieves a synthetic goal analogous to the direct biaryl synthesis. However, the first five steps were achieved with a single reaction: an intramolecular cyclisation cascade reaction that is almost unrecognisable as a Heck reaction. The cascade has been outlined below to reveal the distinct nature of each of the transformations and to partially elucidate the mechanism. A notable feature of the cascade is that several steps are unexpected yet are still able to proceed with almost total regioselectivity. First of all, the presence of two indole groups suggests that a competing mode of ring closure will operate to give a 7-membered ring formed from the wrong indole. Instead, only the intended indole (the N-unprotected indole) cyclises via a 7-exo-trig 1,2-insertion with almost complete chemoselectivity to give a 7-membered ring. Whilst the feasibility of this mode of ring closure is predicted by Baldwin's rules, consideration of the product reveals that an 8-membered must be generated; fortunately a spontaneous ring expansion in step four rectifies the problem[35]. Following the initial ring formation, β-hydride elimination is the expected step due to the presence of seven optimally located hydrogen atoms. Nonetheless, the reaction again diverges from the anticipated result by heterolytic fragmentation into a tertiary carbocation. Upon termination of this domino reaction, preparation of the target compound is achieved in three straightforward steps[35].

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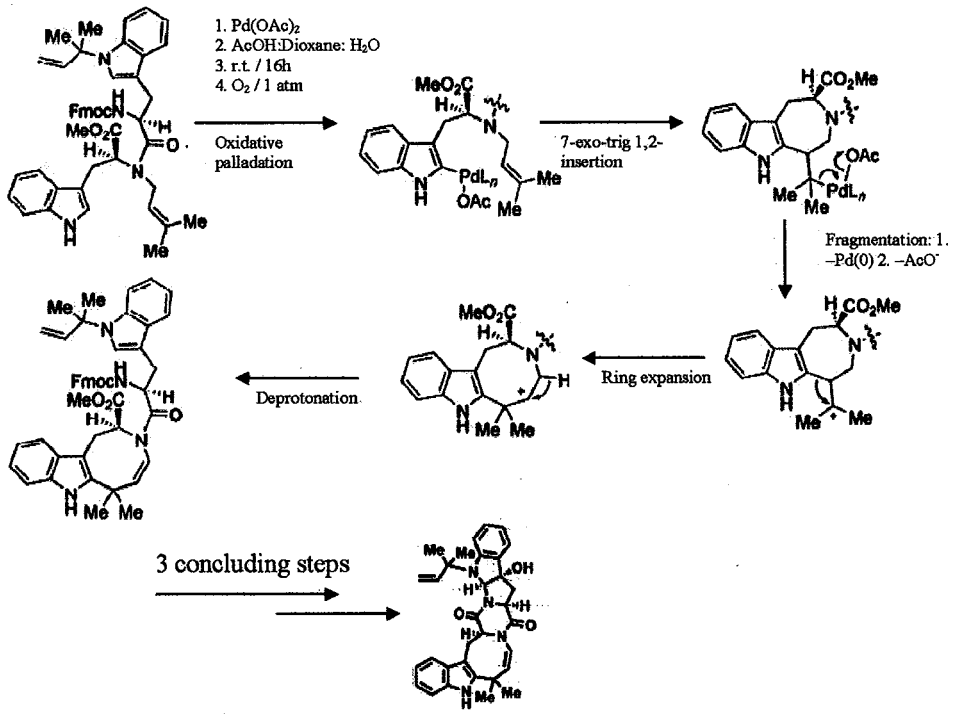

Figure 3.3: The total synthesis of okaramine.

It is a surprise that this synthesis was conceived given the unconventional route it follows, Baran et al. admit that they were "humbled by the large number of completely unforeseen roadblocks" – but of course this should have been expected given the low feasibility of the reaction[35]. Selecting the solvent system was among the most challenging of steps, but being a Heck reaction great sensitivity to reaction conditions is expected. Omitting acetic acid from the reaction mixture led to no reaction occurring whilst in the absence of water, 7-membered rings were formed exclusively (no ring expansion took place)[36]. A thorough understanding of the subtleties of domino reactions is necessary before the methodology can become a staple for industry, at the moment the design process is highly labour intensive due to the amount of good fortune and guesswork involved.

Conclusions

In recent years, more and more palladium-derived compounds are being recognised as important catalysts in an eclectic assortment of syntheses including the production of industrial feedstock and fine chemicals as well as the assembly of large, intricate natural products. Through our examples we have shown that Pd catalysts enable: high selectivity, high yields, shorter synthetic routes, mild reaction conditions and low toxicity in addition to the tolerance of unprotected functional groups, oxygen, water, and acid. These traits are among the hallmarks of a green and commercially attractive synthesis – an efficient synthesis. Even in light of the great expense of palladium, the rapid appearance of palladium catalysed reactions in industry over the last 20 years emphasises the extent to which this major drawback is overshadowed.

Comment [D15]: Add some information about the price of palladium to the appendix

Perhaps the most important, yet least documented, facet of palladium chemistry that we encountered above is what Fairlamb has aptly termed the "black-box". Research in this field regularly uncovers unexpected and unexplainable phenomena that promise to enhance the efficiency of synthetic routes, for instance, the idea of homeopathic conditions has led to significantly reduced catalyst loadings in isolated cases, but only when this observation has been fully rationalised can we expect to see it become a standard procedure in the optimisation of reaction conditions. This same conclusion could be drawn from many of the novel protocols that we have investigated, but progress is already discernable in some key areas. Direct arylation without prefunctionalisation of the substrates promises to solve all issues of waste formation with a pathway offering maximum atom economy. Fagnou's recent death has slowed progress in the field but his lab continue to report direct coupling strategies – it is only a matter of time before a large library of these direct reactions are available for widespread use. A key factor in the pace of this particular development is the concomitant mechanistic elucidation work that has been undertaken – this provides a theoretical base from which substrate and reagent combinations can be postulated. This work serves as an excellent template for research in Pd-mediated synthesis – firstly observing the "black-box" at work and then unpacking the mechanics of its action such that the techniques scope can be broadened.

Palladium's role in synthetic chemistry is perhaps analogous to that of the stem cell in biology – it acts a progenitor from which a plethora of systems can be developed to catalyse a vast range of reactions, and what's more it may be the only viable catalyst for a given transformation.

More often than not, palladium catalysts exhibit the traditional characteristics of an efficient synthesis (high atom economy, yield, and selectivity). Furthermore, modifications to the system (for example, new ligands, solvents or additives) frequently lead to "black-box" phenomena that may enhance palladium's existing efficiency, and lastly, completing the triad of useful properties is palladium's versatility, it catalyses an enormous variety of reactions - a feature useful in its own right - but also vital to the success of one-pot and domino reactions, the most efficient of all reaction schemes[37]. With increasing pressure on chemists to design syntheses that are more environmentally sound and more economical, palladium catalysts will almost certainly feature ever more prominently in 21st century synthetic endeavours.

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Field Code Changed

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Appendix A: List of Abbreviations

Ac	Acetyl
BINAP	2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMIM-PF_6	1-Butyl-3-methylimidazolium hexafluorophosphate
Cy	Cyclohexylamino
dba	Dibenzylideneacetone
DCM	Dichloromethane
DMA	Dimethylacetamide
DMF	Dimethylformamide
Et	Ethyl
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
Me	Methyl
OPiv	Pivalate (2,2-dimethylpropanoate)
p-	Para-
PMP	1,2,2,6,6-pentamethylpiperidine
r.t.	Room temperature
tBu	Tertiary-butyl
TFA	Trifluoroacetate
THF	Tetrahydrofuran

An OCR Extended Project
Review Presentation

How can palladium catalysts increase efficiency in the synthesis of aromatic compounds?

Starting the Project

- Format: dissertation vs. investigation
- Topic: efficiency in synthesis
- From topic to title:

1. Synthetic efficiency → 1. Synthetic efficiency, 2. Transition-metal catalysis → 1. Synthetic efficiency, 2. Palladium catalysis, 3. Aromatic compounds

→ **Final Title**

Planning and Preparation

- Development of a timeline
- Objectives and skills were considered:
- 1. Scientific writing
  2. Project management
  3. Research skills
- Relevant resources were identified:
- 1. Books and journals
  2. Specialist software

Research

- Problem: ATHENS access
- Solution: a compromise (walk-in user agreement)
- Logical use of resources:

1. Books → 2. Review articles → 3. Letters and research articles

Time

The Dissertation

- Understanding synthetic efficiency
- Why palladium?
- **Biaryl synthesis**
- **Heck reactions**
- Latest research and future work

Efficiency in Synthesis

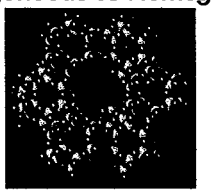
- Minimisation of resource usage
- Reaction parameters: Atom economy, selectivity, yield and rate
- Economic considerations: Number of steps, purification and isolation, capital input and time input.

Biaryl Synthesis

- Recurring benefits of Pd: protecting groups, side reactions, selectivity, and no feasible alternatives
- Phenomena:
- Homeopathic conditions
- One-pot synthesis

Heck Reactions

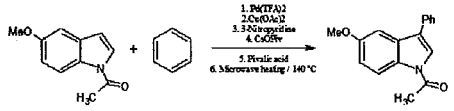
- Asymmetric synthesis and desymmetrisation
- Super-additive effects
- Heterogeneous vs Homogeneous



Faujasite – a zeolite

Latest Research

- Direct arylation



- Domino (or "cascade") reactions – see whiteboard

Conclusions

- Classical efficiency parameters
- Green chemistry
- Promising synthetic strategies
- "Black box" behaviour
- Future work

A parallel microreactor

Evaluation

- Long-term time management
- Research techniques
- Scientific writing: conventions and style
- Personal development: university and career
- Improvements

Acknowledgements

Thank you to:

- Dr A J Bullard
- Mr A M Robson
- Mr I G Judd

Audience Feedback

Was the presentation delivered effectively?

Yes. The complex and intricate subject matter was presented succinctly and concisely. The presentation used a well balanced mix of PowerPoint, actual development of diagrams on a whiteboard and speech.

How well were questions dealt with?

The topic was new to me and the presentation quickly engaged my interest. Questions were dealt with concisely and effectively. [redacted] was able to provide answers beyond the limits of the presentation.

Overall, was the content engaging?

Yes. Enjoyable and stimulating – I was left with a desire to find out more.

Name: BERNARD PIKE

Signature: BPike 28 April 2010

Audience Feedback

Was the presentation delivered effectively?

Yes. Having been intrigued by the glimpses I had previously had of Dan's work, I felt extremely satisfied after the presentation with the development in my understanding of the use of palladium as a catalyst. The spoken and visual aspects of the presentation were seamlessly interlinked: Dan had obviously practised the synchronisation of his professionally-prepared powerpoint presentation with his speaking, with the result that the ideas flowed coherently and I was able to grasp his difficult topic. The use of eye contact was very good, but perhaps more gesture could have been used – nevertheless, we were generally totally enthralled!

How well were questions dealt with?

Dan responded assuredly and thoroughly to questions regarding both the project's progress and the technical aspects of the chemistry of his project. He came into his element while rapidly formulating clear, considered answers: it was evident that he enjoyed the chemistry as much as he has enjoyed doing this project. Dan was able to handle my specialist questions as assertively as queries from the teachers in the audience who did not have a background in chemistry – those teachers might in fact also have benefitted from handouts to cement the new ideas in their minds.

Overall, was the content engaging?

Very much so. I found many of the facts about palladium catalysis very interesting, particularly the ideas of homeopathic catalysts and the latest supported catalysts. It was surprisingly enjoyable to hear about Dan's similar experiences to me in effectively planning, effecting, reviewing and evaluating his project.

Name: ADAM WRIGHT

23/04/10

Signature: AWright

Evaluation document for the Extended Project

Introduction

Organic chemistry, in particular the theoretical aspects such as reaction mechanisms and linear free energy relationships, has been an interest of mine for quite a long time. However, after having spent a week observing and assisting in some fascinating synthetic chemistry at the University of Oxford, and in addition, conducting a synthesis of the analgesic Lidocaine at the University of Reading, I began to develop a particular interest in the theory and practice of organic synthesis. Dr John Baum, Senior Technician at the University of Reading is a former medicinal chemist – he fondly recounted an experience in which he developed a modification to a synthetic route that offered a 0.5% improvement in the yield and was subsequently regarded as a "hero". It is examples such as this which indicated to me the importance of developing efficient syntheses – an aspect of chemistry that is rarely encountered in standard undergraduate textbooks. When I first came across the "Extended Project" in July 2009, it seemed natural that I should write a dissertation relating to these experiences in some way.

Following discussions with my chemistry teacher, and another pupil who was also keen to do a chemistry-related extended project, we thought that it would be enjoyable to conduct a practical investigation in which we determine the activation energies for some of the classic reactions encountered at A2 level. Despite the fact that the topic was not directly related to my initial idea, I decided to maintain both ideas as possibilities for the project. The basis of the investigation was the fact that the activation energy of reaction is a useful parameter as it is related to the rate constant of the reaction via the Arrhenius equation: $k=Ae^{-Ea/RT}$; catalysts are employed to lower activation energies in order to increase the rate of reaction. Activation energy data is very difficult to find – both on the internet and in print. Subsequently, it was suggested that we could aim to publish our findings in the journal Education in Chemistry. We hoped to carry out the work at Reading University in September; unfortunately we had chosen a time at which the staff were very busy and so supervision would have been problematic and it would also have been very difficult as lab space is limited during term time. Consequently, the idea of a practical was quickly discarded and I returned to the idea of a dissertation.

The first task with which I was faced was the formulation of my project title; I was aware immediately that a discussion of efficiency in synthesis would encompass a very wide range of chemical concepts and that 5000 words would enable only a superficial reference to each aspect of the discipline. Furthermore, I needed to develop a title that was clearly focussed before any research could be conducted. After looking through "March's Advanced Organic Chemistry" for inspiration, I came across some examples of transition metal catalysis being employed to generate excellent yields and achieve high selectivity. Catalysis was one of the general concepts for efficient synthesis that Ryoshi refers to in the aforementioned Nature article, and in addition, I was already acquainted with the basics of organometallic chemistry. This provided me with sufficient stimuli to produce my first working title: "How can transition metal catalysis be used to improve the efficiency of organic syntheses". After a discussion with my supervisor, Dr Bullard, it was agreed that the title was suitable – nonetheless I did not want to launch into extensive research yet, as I had raised the issue that the scope may still be too broad to adequately cover in a dissertation of about 5000 words. This was reiterated by my supervisor who also emphasised the importance of conducting thorough background reading before undertaking a project. At this point I was certain that my dissertation topic would not change, and that the only foreseeable alteration to my working title was an increase in specificity. Thus, I decided it was time to draw up a plan for the whole project, with projected time-scales for each activity.

Planning

A technique that is often useful for planning is critical path analysis, a method referenced in the specification, however, I decided against the use of this type of plan because I felt that it would unnecessarily complicate the planning phase in the context of my project. Writing a scientific dissertation is linear and sequential in nature, and hence does not necessarily require tasks to be completed simultaneously. I decided to base my deadlines for each task on a system in which I divided the months into 3 blocks: early, mid and late. My intention was to complete each task in the sequence dictated by my plan. This was useful as it was gave me enough flexibility to account for tasks which took less or more time than I expected, but still provided me with dates to work towards such that I could assess the extent to which I was on track to finish the project on time.

In hindsight, I feel that the simple and clear plan I produced enabled me to quickly realise the goals of my project and it certainly gave me a good framework for writing the dissertation.

Research

Due to the fact that transition metal mediated synthesis is an area benefiting from extensive current research, I expected from the outset that a sizeable proportion of my sources would be from primary research documented in journal articles. In order to better understand the research articles, my supervisor suggested that I start by reading some of the review articles to get up to speed with the key developments and principles in the field. This initial work directly led to the development of my final title, two articles in particular (references 8 and 33 in my dissertation bibliography) suggested that it was palladium that offered the greatest versatility in organic synthesis. Having read these articles I began to use Google Scholar to search for articles relating to palladium catalysis. It quickly became clear that palladium based reactions not only outnumbered those of other transition metals, but were undoubtedly under the most investigation for use in synthesis. When I was certain that palladium-based reactions would provide all the material I need to write my dissertation, I altered my working title.

As recorded in the "outcome" column of my plan, I was unable to download the articles at home. Instead, I had to use one of the university library's computers. Obtaining articles in this way was slow, and at times frustrating – each time I needed to access a different journal I had to locate a member of staff such that they could log me in. Fortunately, this was a problem I foresaw and so I took some steps to reduce the number of visits I would have to make to gather all my research material. At home, after locating interesting articles using Google Scholar, I looked through the journals to which the university had subscribed and ensured that I would be able to access the article. Initially, I used basic keyword searches such as "palladium catalyst", later adding phrases related to efficiency such as "selectivity" and "atomy economy". In addition, I began to use the Boolean operators "AND" and "OR" as well the asterisk (known as a wildcard symbol) to build more intricate searches. By reading the abstracts I was able to quickly identify those that directly related to my project title. It was also useful to search for the authors of some of the articles that I had identified – it was often the case that authors had published other useful articles. One of the authors I came across, Keith Fagnou, was leading a research team dealing with the use of palladium in designing efficient syntheses – their primary goal was to design direct arylations (see the "future work" section of the dissertation for further information).

After having collected a large number of potentially useful articles, I was able to go to the university and save them to a USB flash drive. The process was less troublesome than I expected – by grouping the articles by journal, I could download them quite quickly, one after the other, only searching for a staff member to log me in when I needed to change to a different journal. Consequently, I only had to visit the library three times to access the E-journals.

Two more visits to the library were required in order to obtain all the photocopies from books that I wanted, as well as the photocopy of an article only available as a hardcopy. Following the completion of this, I was in position where I could closely read through each article and eliminate those that were least useful – I had downloaded many more than I intended to use; this was because I didn't want to waste time reading them at the library. By reading through them, I also began to think of potential subheadings for my dissertation such that I could group together similar concepts.

Source Evaluation

Whenever I used a new source, for example, a journal to which I had made no prior reference, I briefly evaluated it in order to ensure it was suitable for my purposes. In this section, I have typed up the notes that I made – the sources are firstly grouped by type, and are then arranged in order of appearance in my bibliography.

Books

1. Warren, S. *Organic Synthesis: The Disconnection Approach*, pp. xi-xii (Wiley, New York, 1982).
2. De Meijere, A., et al. *Carbon Rich Compounds I*, pp.47 (Springer Verlag, Berlin,1998).
3. Clayden, J., Greeves, N., Warren, S. & Wothers, P. *Organic Chemistry*, pp. 1313-1315 (Oxford Univ. Press, Oxford, 2001).
4. Carey,F.A., Sundberg, R.J. *Advanced Organic Chemistry: Structure and mechanisms*, pp.76 (Springer, New York, 2007).
5. Cepanec, I. *Synthesis of Biaryls*, pp. 2-3, 101-102 (Elsevier, New York, 2004).
6. Hall, D.G. *Boronic acids: preparation and applications in organic synthesis and medicine*, pp.124 (Wiley-VCH, Weinheim, 2005).
7. Rahman, A.U. *Studies in Natural Producs Chemistry Volume 35*, pp.399 (Elsevier, New York, 2008).
8. Hruby, V.J,Vardanyan, R. *Synthesis of essential drug*, pp.39-40 (Elsevier, Boston, 2006).
9. Tsuji, J. *Palladium Reagents and Catalysts: New perspectives for the 21st Century*, pp.109 (Wiley, New York, 2004).
10. Carreira, E.M., Kvaerno, L. *Classics in Stereoselective Synthesis*, pp.50 (Wiley, Weinheim, 2008).
11. Oestreich, M. *The Mizoroki-Heck Reaction*, pp. 442-444, 281(Wiley, Chichester, 2009).
12. Kozlowski, M.C., Walsh, J.C. *Fundamentals of asymmetric catalysis*, pp.232 (University Science Books, Sausalito, 2009).
13. Nicolaou, K.C., Snyder, S.A. *Classics in total synthesis II: more targets, strategies, methods*, pp.551-552,617 (Wiley, Weinheim, 2003).
14. Anslyn, E.V., Dougherty,D.A. *Modern Physical Organic Chemistry*, pp. 568 (University Science Books, Sausalito, 2005).

- All the books have been published by respected academic publishers; hence, I am prepared to trust the content as being factually correct.
- All the books are quite recent except for *"Organic Synthesis: The Disconnection Approach"* – since I only extracted trivially information from it for my introduction, it does not matter that the book is 28 years old.
- *Carbon Rich Compounds I* is from the "Topics in Current Chemistry" series whilst the recommendation is that it should be cited as a journal, the fact that I only used it for some very general information (as opposed to the research content), I have included it as a book.

Journals

1. **Innovations in Pharmaceutical Technology**
   - Aimed at the pharmaceutical industry – hence, the normal readership is critical and demanding; I would expect that the information is accurate.
   - The journal would be more accurately described as a magazine since it isn't peer-reviewed.
   - However, the only information that I have extracted from this article relates to the method of synthesis of sartans – this is simply a piece of factual information and not something that relies on a sound scientific method.
   - The article's authors has referenced the peer-reviewed journal "Hypertension Research" to obtain this information themselves.
   - Overall, this source has provided with a useful example that highlights one of my points and furthermore, it was interesting background reading.
2. **Russian Journal of Coordination Chemistry**
   - This is a peer-reviewed and highly respected journal (in Russia).
   - The only concern is that error or ambiguity could be introduced as a result of the translation from Russian to English.
   - I only needed to use content relating to a chemical reaction – thus there is unlikely to be a chance of misinterpretation as it is independent of language.
3. Tetrahedron
4. Advanced Synthesis & Catalysis
5. Journal of the American Chemical Society
   - One of the articles I have used was published in 1924 and so I should consider how useful this source is.
   - The age of the article is important in supporting the point I make in the dissertation – the only non-transition metal based means of producing a biaryl is a variation of this old-fashioned method. It has remained unchanged since this time – my 16th reference in the dissertation reports the use of the method for a pharmaceutical synthesis.
6. Central European Journal of Chemistry
7. Organic Letters
8. Pest Management Science
9. The Journal of Organic Chemistry
10. Tetrahedron Letters
11. Tetrahedron: Asymmetry
12. Chinese Chemical Letters
    - As with the Russian journal, there is the issue of errors or ambiguity be introduced due to the translation.
    - The concepts reported are briefly corroborated in a book, number 11 in my list, and so this provides sufficient justification in my opinion.
13. Science
14. Angewandte Chemie International Edition
15. Chemical Society Reviews

The journals with no comment below them are all internationally recognised peer-reviewed journals – they are reliable enough to be used by professional research scientists and so are definitely sufficient for my needs.

Websites

1. http://www.sigmaaldrich.com
   - This is a major chemical supplier – their information needs to be up-to-date and accurate for legal reasons.

2. http://weblearn.ox.ac.uk
   - The University of Oxford is a prestigious institution and therefore inevitably provides accurate information to its students.
   - I have used the source to refer to a practical that is conducted as part of the Oxford Chemistry course – I can confirm the accuracy of the source from first hand experience, as I have witnessed the reaction in question taking place in the Dyson Perrins Laboratory, Oxford.

Mid-Term Review

There was only a short window of opportunity to conduct a mid-term review due to the imminence of examinations in January. However, the succinct notes that I produced following a discussion with my supervisor were useful as a means of reflecting on my performance. In the period before conducting a review, my progress had slowed but this did not cause me to fall behind schedule. My supervisor did not have any concerns and so encouraged me to continue working in the same way I had been before the review. The notes produced for the review are a reflection of my own thoughts and can be found in the Project Progression Record

Dissertation

I was able to make a confident start on the dissertation by using the natural groupings of the research articles and books to develop the subheadings, and then swiftly writing an introduction. The introduction was produced using my own creativity – I used references to tidy it up and provided clearer and more concise definitions, but the content barely changed following the first draft. The body of the dissertation was written with markedly less fluency than the introduction – stringing together complex ideas into meaningful comments was not easy. Furthermore, linking together different articles required high levels of understanding and interpretation. What felt like a slow rate of work turned out to be fast enough, as the first draft took about three weeks to produce. Significant redrafting took place within this first draft – arguably this could have been described as several drafts, but I only deemed it complete when it was of an acceptable quality and it was coherent in at least the majority of places. The EndNote free trial certainly saved me time; all my references were already formatted correctly and so I only needed to add the relevant superscripts as I wrote the text.

In my view, my decision to introduce a greater number of subheadings was the most major of my changes in subsequent drafts. Upon reading it through with the subheadings, I found that it was easier to read the text and it was also less visually formidable – very large blocks of text were no longer present.

I chose not to apply (with precision) the suggested one reference per 100 words rule – the main reason was that I felt I was contributing lots of my own analysis and content, and hence I was not plagiarising or simply copying out of the sources. Whenever I felt I had used an idea or concept from a source – I referenced it, and I believe that adding more citations would be superfluous.

Presentation

My own comments on the presentation can be found on the plan as well as in the Project Progression Record. It was a good experience to present to a small audience. The audience consisted of two members of staff (Dr B C Pike and Mr A M Robson) and two students – it was easier to make eye contact with each member of the audience and also to detect whether everyone was following what was being said. This produced a quiet and calm environment in which to deliver the presentation – this aided its success. Originally I had intended to present to only one member of staff, however, I later decided that it would be better to present to an audience with both a specialist and a non-specialist. This was because I would be able to receive comments on both technical and non-technical aspects of the presentation. The success of the presentation has been confirmed by the fact that I have been asked to deliver the presentation again, later in the year, to students intending to do an Extended Project next year. In addition to my own comments, I have included the PowerPoint slides on which my talk was based, and perhaps most importantly, the audience feedback forms – these provide the most objective evidence that I can produce.

There is still room for improvement in the way I deliver presentations – I feel that I can learn to present information, and also respond to questions, with greater concision. This will be important for conferences and symposia that I will be expected to attend later on in my career.

Final Evaluation

Completing the project has been an important means for me to assess the extent to which I enjoy immersing myself in scientific research. The process has consumed a lot of my time – but I do not regret it. For several years I have considered academic research as being a possible career, and so completing the project provided me with convincing evidence that this is something I would take pleasure in doing. I should also take care to remember that a lot of scientific research is concerned with conducting experiments; this is a feature that the Extended Project has not enabled me to practise. Fortunately, I have had the chance to complete some extended practical investigations in university laboratories and so, this is an aspect of science I have had chance to do more often. For this reason, it was therefore a good decision to write a dissertation and not do a kinetics practical – I have learned more from the writing of a dissertation than I would have from another practical. On a practical note, I also feel well prepared for starting a demanding Natural Sciences course in September – working to deadlines, speed reading, and properly referencing the work to avoid any accusations of plagiarism are all skills that I will be expected to use.

To conclude this portfolio I feel that it is appropriate to review some of the skills that I have developed during my time completing the Extended Project, and moreover, assess the outcome of the project, particularly with regard to its impact on my university studies and beyond. Below, I run through the main skills I believe I have developed directly as a result of the project:

(Screenshots will be included to illustrate the software where appropriate)

1. Use of the software "ChemSketch" to draw complex molecules and present synthetic routes.

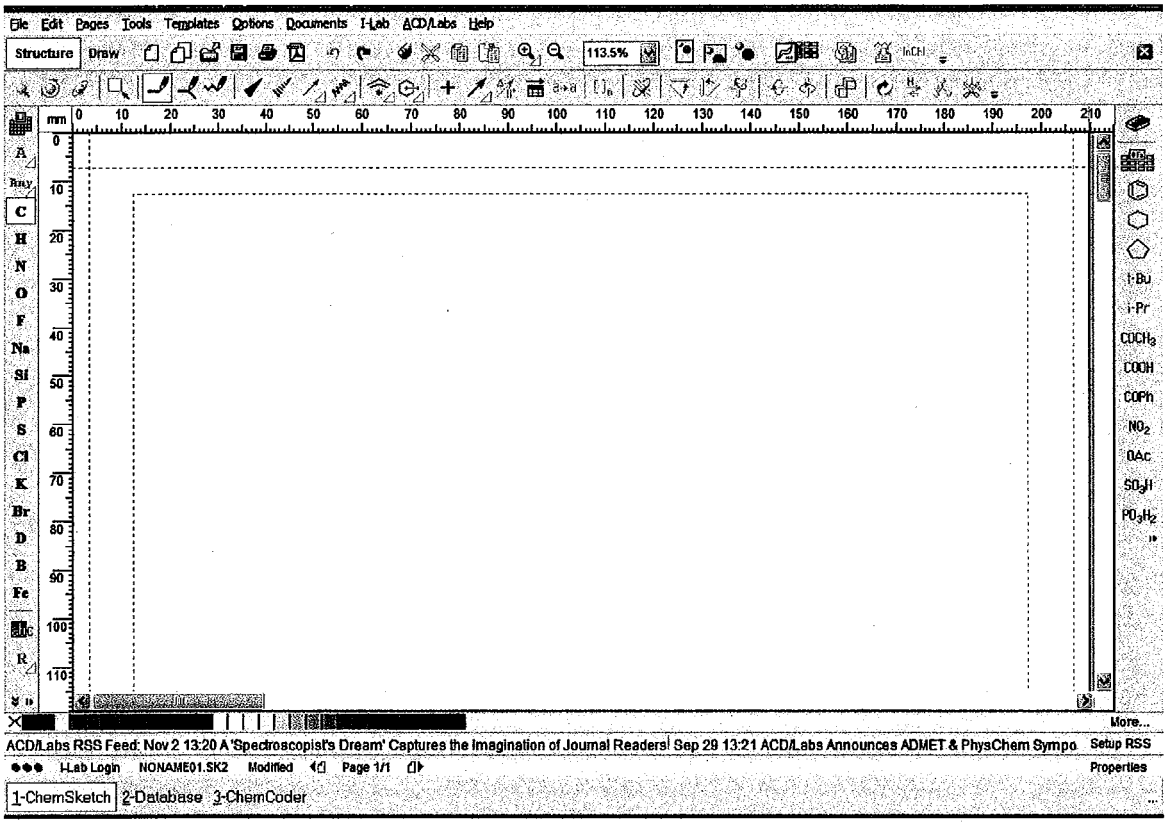
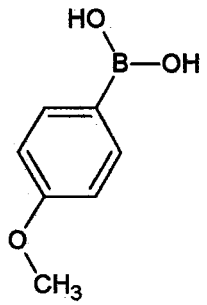


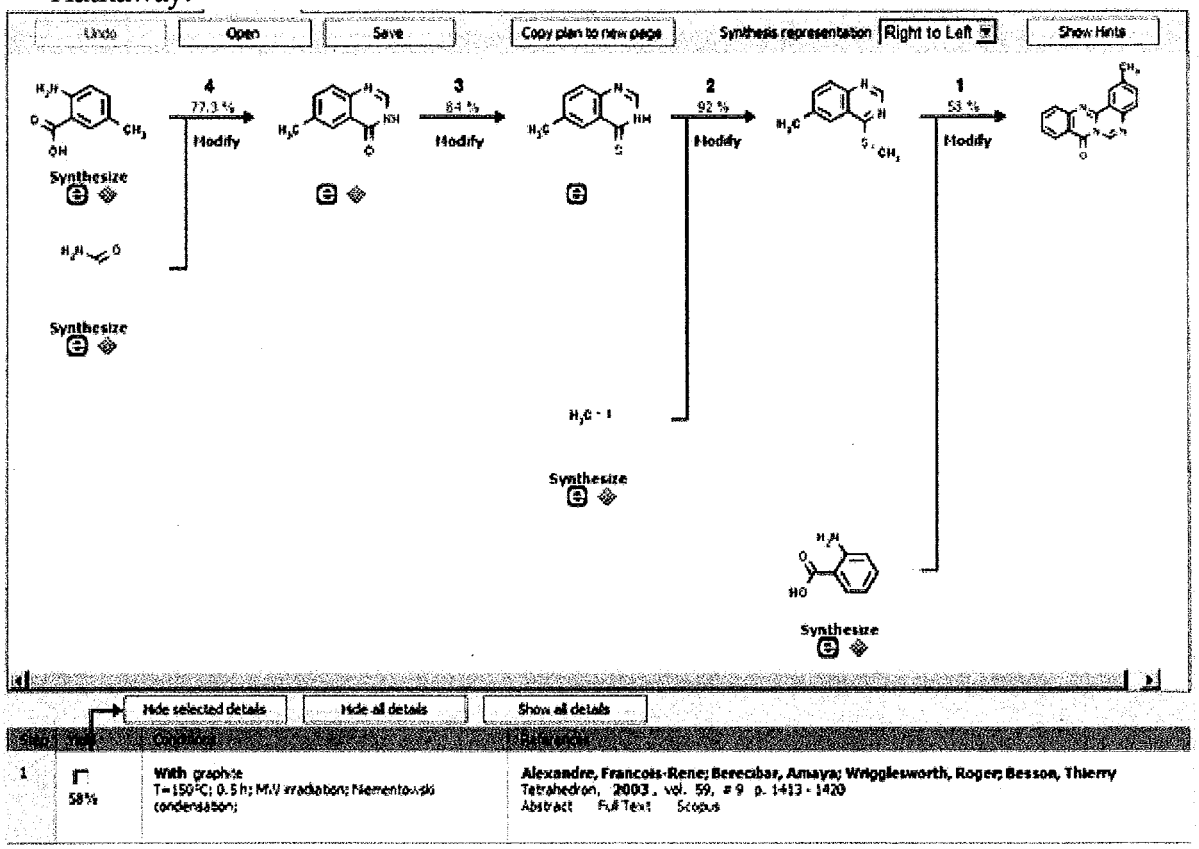
Figure 1: Here is a screenshot depicting the ChemSketch interface.

Despite its simplistic appearance the program offers powerful functionalities, for example, it supports the InChI notation. InChI, or the International Chemical Identifier, is a method of representing chemical structures in a format that is easily understandable by both computers and humans. I learnt how to deal with this notation to facilitate some of my structure drawing – instead of manually drawing the very large structures using the separate tools for the addition of atoms, bonds, or groups, I was able to determine an InChI code for at least the structure's framework. In some cases I could use the RSC's free database, http://www.chemspider.com/, to find InChI codes if I knew the systematic name for a compound. For instance, (4-methoxyphenyl)boronic acid was among the compounds I encountered – all I then needed to do was look it up on the RSC database from which I could obtain the InChI designation: InChI=1/C7H9BO3/c1-11-7-4-2-6(3-5-7)8(9)10/h2-5,9-10H,1H3. ChemSketch then enabled me to rapidly generate the displayed formula:

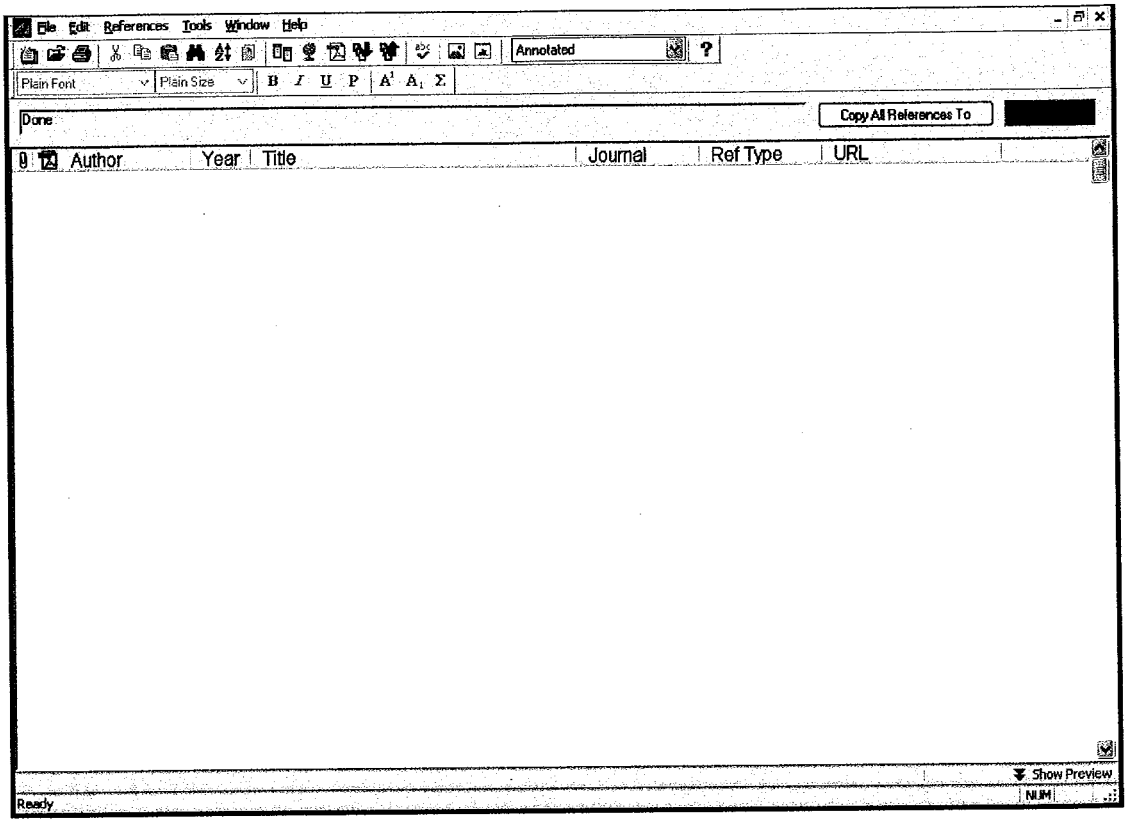


By using ChemSketch, I then had chemical structures in a format that was easy to manipulate, by adding additional chemical groups, or moving around several structures to create a synthetic route.

2. Use of the workflow tool "Reaxys" to plan and assess the viability of the syntheses that I later drew up on ChemSketch. Training was necessary in order to exploit this online tool most effectively and this was provided by the Chemistry Liaison Librarian, Mrs Helen Hathaway.



3. The use of EndNote to produce a bibliography of professional quality. I used the beginner and intermediate guides available at: www.reading.ac.uk/library/finding-info/endnote/lib-endnote-guides.aspx in order to teach myself how to use the software.



It enabled me to rapidly import a reference and then convert it to a format of my choice. I chose to use the convention adopted by Nature – a style supported by the software and also one which is precise and widespread in the scientific community. As predicted, the free trial expired before the completion of my project – since I had foreseen this I ensured I imported as many references as I could whilst I had access to the software; even if I was not sure that I would end up using the source. As I wrote the dissertation I simply deleted the irrelevant references, and manually added the few extra sources that I collected at a later date.

4. Conducting extensive research using both primary and secondary sources. – Chemistry is an experimental subject, and so new work in the field is dominated by reports of experimental investigations. By learning to use genuine research material at this early stage in my scientific career, I have confirmed an interest in the scientific method and additionally, have given myself a taste of academia.
5. Writing a dissertation in the style of a scientific review article – much could be improved in my dissertation. In particular, I could spend months fine tuning the stylistic aspects of the essay to enhance the flow of ideas. However, I will be able to develop this with essays on other topics in the future – I would risk becoming bored or frustrated if I spent a lot more time on this essay. Nevertheless, going through the motions of writing a science-based essay has reawakened my interest in writing freely on a topic – it will remain something that I enjoy doing in the future.
6. Presentation skills – all scientists will need to present their work, hence being able to design a simple and understandable presentation and speak with conviction about science is a fundamental skill.
7. Time management and planning – these skills will be vital at university where the work load will be significant.

These last 3 skills all come under the umbrella term of "transferable" skills – they will be useful to me regardless of the career I end up in – and so for this reason, the Extended Project is a useful educational tool and I would recommend it to all post-16 students.

CONTACT US

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Telephone 01223 553998

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