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Sustainable Methodology Development using Renewable Feedstock: Dehydrative Mizoroki-Heck Reaction and the use of Cyrene™ as a Solvent in Chemical Synthesis

A Thesis Submitted to the University of Huddersfield in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

The University of Huddersfield

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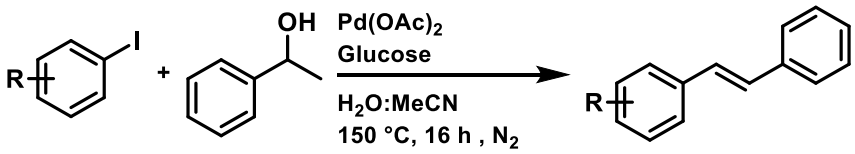
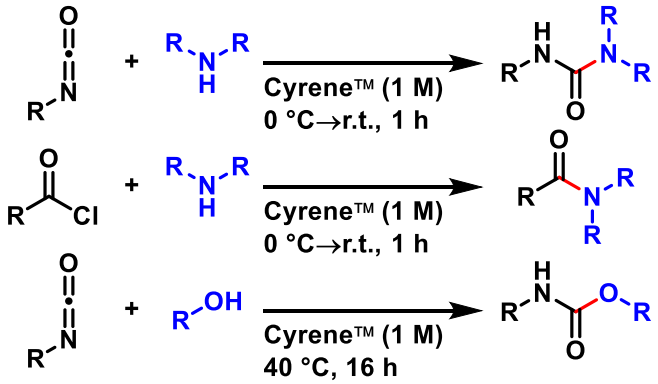
Abstract

The work presented in this thesis regards: 1) the development of a base free dehydrative cross-coupling process, utilising palladium(0) nanoparticles formed *in situ* under acidic conditions, 2) the development of synthetic protocols using the bio-available solvent Cyrene™ as a replacement dipolar aprotic solvent and 3) the use of Cyrene™ as a chiral scaffold.

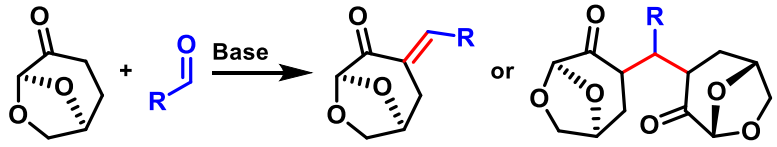
1) The use of sugars for the *in situ* formation of palladium nanoparticles has been previously developed in the Camp group. Building upon this work, a base free Mizoroki-Heck cross-coupling process for the synthesis of substituted stilbenes was developed and optimised, whereby glucose performed a dual role: stabilisation of the palladium(0) nanoparticles and regeneration of the active catalyst species. Due to the base free nature of this process, the reaction mixture becomes acidic. Relatively few protocols have been developed in which the feedstock of the Mizoroki-Heck reaction has changed from the standard alkene substrates. Typically, alkenes are reacted with aryl or alkyl halides in order to cross-couple and form a new C-C bond. Herein, a dehydrative method for the *in situ* formation of styrene and tandem cross-coupling process in a base free, H_2O/MeCN solvent system has been developed, taking advantage of the acidic nature of the reaction mixture. After optimisation, the steric, electronic and substrate scope of the reaction conditions were investigated. The molar efficiency (Mol. E%) was calculated and evaluated against similar methods for the synthesis of substituted stilbenes.



2) The need for a green replacement dipolar aprotic solvents has become crucial due to the placement of *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidine (NMP) on the REACH list of restricted chemicals. In recent years, the chemical Cyrene™ has been investigated as a bio-available replacement for the dipolar aprotic solvents. The synthesis of ureas, amides and carbamates in Cyrene™ was developed and optimised from either isocyanates or acid chlorides with amines or alcohols. The synthesis of carbamates was monitored by *in situ* ^{19}F NMR to determine the rate of the reaction in several solvents including Cyrene™. Additionally the large scale reaction, recycling of solvent and reuse was successfully performed.



3) Chiral scaffolds are useful tools as they allow the synthesis of several compounds of similar structure. The use of Cyrene™ as a chiral scaffold was investigated by several academic groups including the Camp group. Aldol condensation reactions were performed on Cyrene™ with a variety of aryl aldehydes in the presence of a strong base. Nine examples of condensation products were synthesised in very poor to moderate yields. X-ray crystallography was used to confirm the structure of the compounds synthesised. Interestingly, a bis-addition product was detected in one of the Aldol examples, efforts to synthesise this along with generality afforded two of these dimers as sole products.



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List of Abbreviations

Abbreviation	Meaning
δ	Chemical shift
Δ	Heat
Ac	Acetyl
APPI	Atmospheric Pressure Photoionisation
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br. s	Broad Singlet
Cat.	Catalyst
cm^{-1}	Wavenumbers
d	Doublet
dba	Dibenzylideneacteone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarisation Transfer
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMI	Dimethyl Isosorbide
DMSO	Dimethyl Sulfoxide
EI	Electron Ionisation
Eq.	Equation
equiv.	Equivalents
ESI	Electrospray Ionisation
GCMS	Gas Chromatography Mass Spectrometry
GSK	GlaxoSmithKline
GVL	γ-Valerolactone
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-Oxide hexafluorophosphate
HMBC	Heteroatom Multiple Bond Coherence (Spectroscopy)
HRMS	High Resolution Mass Spectrometry
IR	Infrared (Spectroscopy)
J	Coupling Constant
LGO	Levoglucosenone
m	Multiplet
m.p.	Melting Point
2-MeTHF	2-Methyltetrahydrofuran
Mol. E%	Molar Efficiency
MW	Microwave
m/z	Mass to Charge Ratio
NMP	*N*-Methylpyrrolidin-2-one
NMR	Nuclear Magnetic Resonance
NP	Nanoparticles
ppm	Parts Per Million
q	Quartet

Abbreviation	Meaning
quin	Quintet
r.t.	Room Temperature
s	Singlet
sept	Septet
sext	Sextet
S_N	Nucleophilic Substitution Reaction
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
THF	Tetrahydrofuran
TMG	Tetramethylguanidine
TOF	Time of Flight

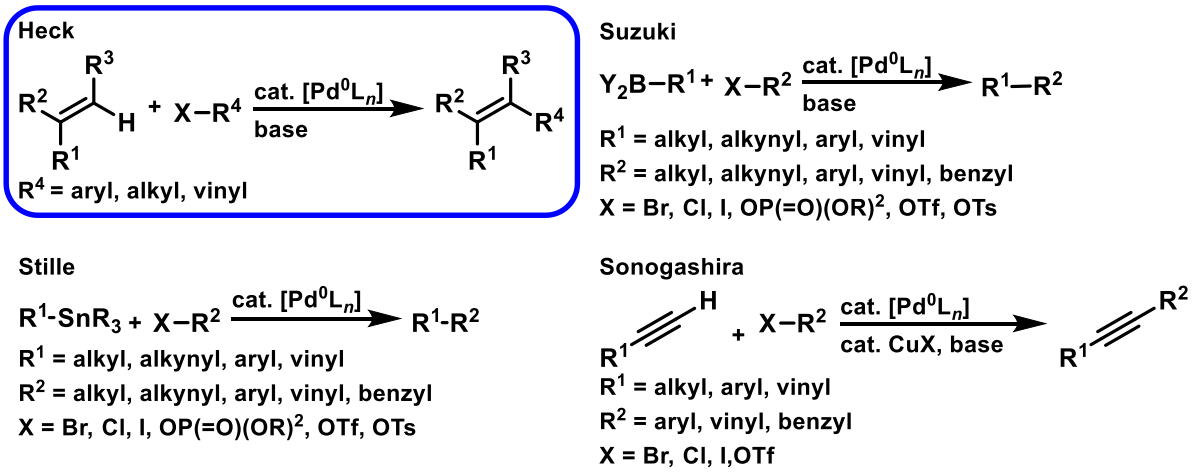
Chapter 1

Development of an acidic, dehydrative Mizoroki-Heck cross-couple methodology

Chapter 1: Development of an acidic, Dehydrative Mizoroki-Heck cross-coupling methodology - Sugar powered catalysis

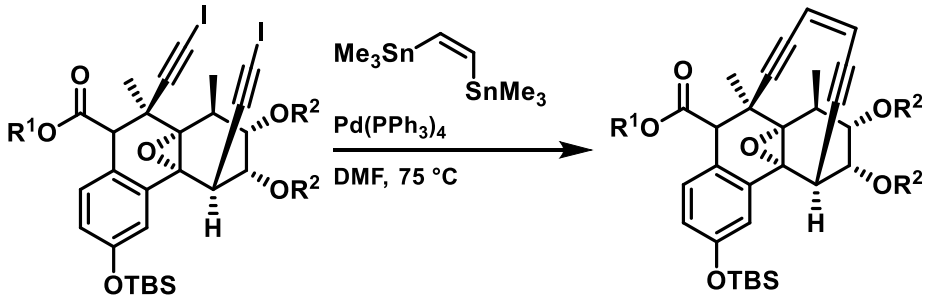
1.1 Introduction

Palladium-catalysed cross-coupling reactions have been extensively researched since their initial discovery in the early 1970's[1-6]. During the development of these reactions new and better ways to selectively couple carbon atoms not only to other carbon atoms, but also to heteroatoms such as nitrogen, oxygen and phosphorus have been developed. The importance of these reactions lead to Richard Heck, Ei-ichi Negishi and Akira Suzuki being awarded the Nobel Prize in chemistry in 2010 for their work that laid the foundation for many invaluable processes used daily in academic research and industry[7]. The most common palladium catalysed cross-coupling reactions that use palladium(0) as the catalytic species are the Stille, Suzuki, Sonogashira and Heck, reactions (Scheme 1.1)[8].



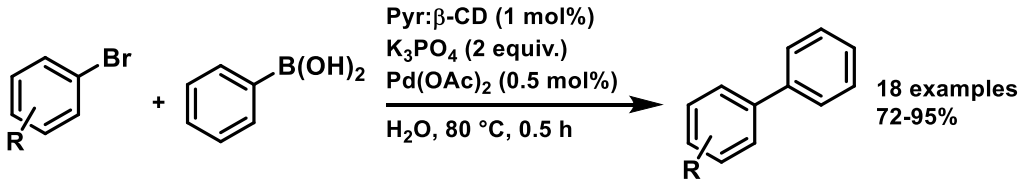
Scheme 1.1

The Stille reaction utilises organostannane compounds and has been the centre of some key steps where macrocycles have been "stitched" together. For example, Danishefsky *et al*. synthesised an important intermediate towards the synthesis of dynemicin A using a Stille reaction (Scheme 1.2)[9]. The reason why the Stille reaction was used in this synthesis was because the Sonogashira conditions attempted for the same ring closing step were unsuccessful and so a more powerful cross-coupling method was required. The toxicity of organostannane compounds is well known and causes problems if it leeches into the desired product, so alternative C-C bond forming methods were developed.



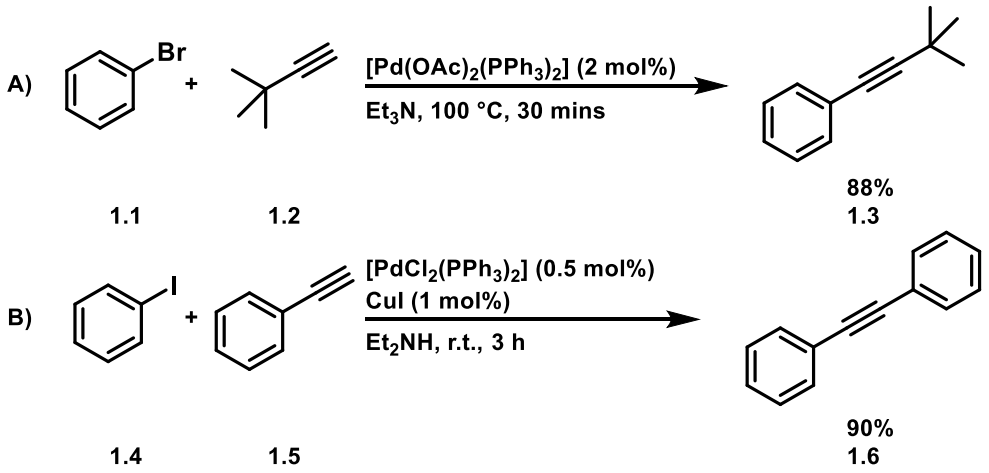
Scheme 1.2

The Suzuki-Miyaura reaction is a powerful tool for the synthesis of C-C bonds between 2 aromatic compounds.[10] Investigations of this reaction have led to many advances in the conditions of the reaction including the metal catalyst and solvents used. Many examples of palladium, nickel and gold have been developed. Pyridinium modified β-cyclodextrin (Pyr: β-CD) has been shown to be a good ligand for the palladium catalysed Suzuki-Miyaura reaction by Pitchumani and Khan[11]. The reaction, which takes place in water in the presence of K_3PO_4 at 80 °C for 30 mins, has increased efficiency due to the benificial interactions of the ionic supramolecular ligand with the water soluble boronic acids and hydrophobic aryl halides, therefore reducing the formation of homocoupled by-products (Scheme 1.3). 18 examples were prepared with a range of functionalities with very good to excellent yields.



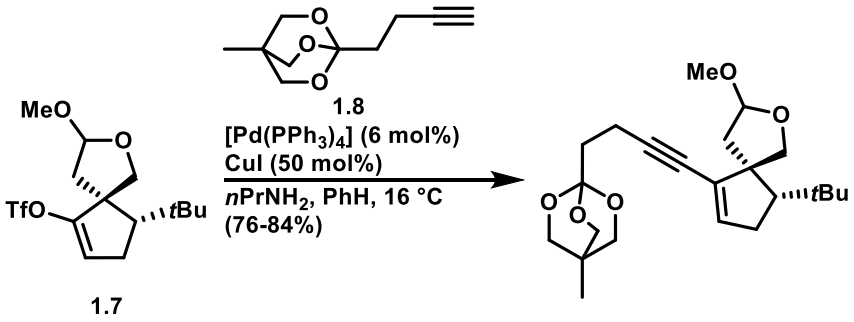
Scheme 1.3

The conditions of the Sonogashira reaction are relatively mild compared with those reported by Heck in 1975[12]. Heck reacted bromobenzene **1.1** with 3,3-dimethyl-1-butyne **1.2** at 100 °C with only a palladium catalyst and basic amine to afford coupled product (3,3-dimethylbut-1-yn-1-yl)benzene **1.3** (Scheme 1.4A)[13]. In contrast, the conditions Sonogashira developed between iodobenzene **1.4** and ethynylbenzene **1.5**, which allowed the reaction to proceed at room temperature to afford the desired cross-coupled product 1,2-diphenylethyne **1.6** (Scheme 1.4B)[14]. This was possible by the addition of a copper-halide in catalytic amounts where the copper-mediated transmetallation of the alkyne proceeds prior to the alkyne addition to the palladium species.



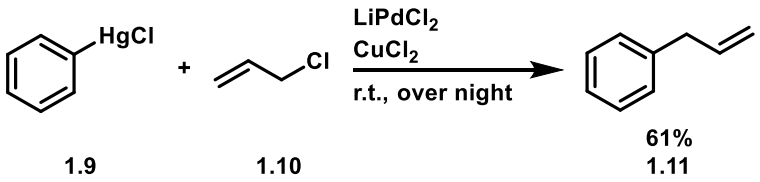
Scheme 1.4

Corey *et al*. used the Sonogashira reaction to couple cyclopentene fragment **1.7** to a trioxabicyclooctane alkyne **1.8** during their synthesis of (±)-ginkgolide B in 1988 (Scheme 1.5)[15]. In the coupling step a triflate group is used as a pseudohalide and couples to the unprotected alkyne with ease at reduced temperatures, utilising the cuprous conditions developed by Sonogashira.



Scheme 1.5

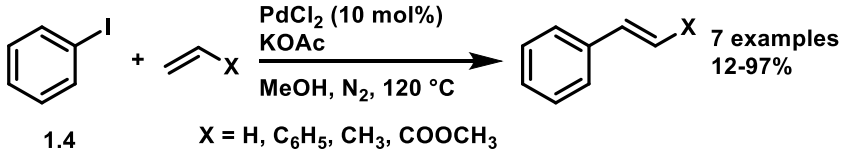
In 1968 Heck found that the reaction between prefunctionalised organic compounds, such as organomercurial benzene, would also undergo cross-coupling reactions with alkenes. Initial conditions developed by Heck couple phenylmercury chloride **1.9** and 3-chloro-1-butene **1.10** in the presence of lithium palladium chloride and copper chloride to make allylbenzene **1.11** (Scheme 1.6)[16].



Scheme 1.6

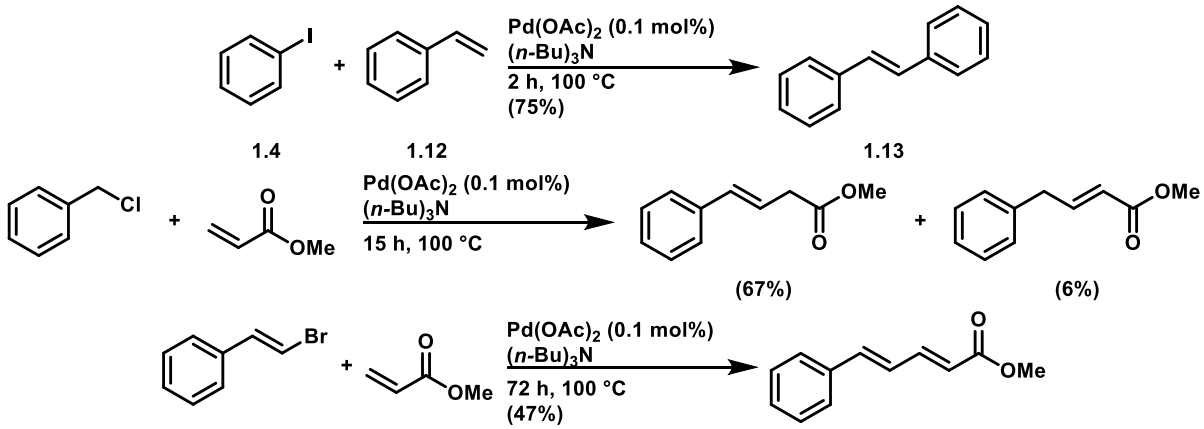
With the need to find less toxic reagents still able to undergo the reaction process it was found that oxidative addition with an aryl halide substrate would also provide the desired product. Mizoroki

showed that the coupling reaction between iodobenzene **1.4** and an olefin could proceed using catalytic amounts of palladium(II) dichloride in the presence of potassium acetate (Scheme 1.7)[17].



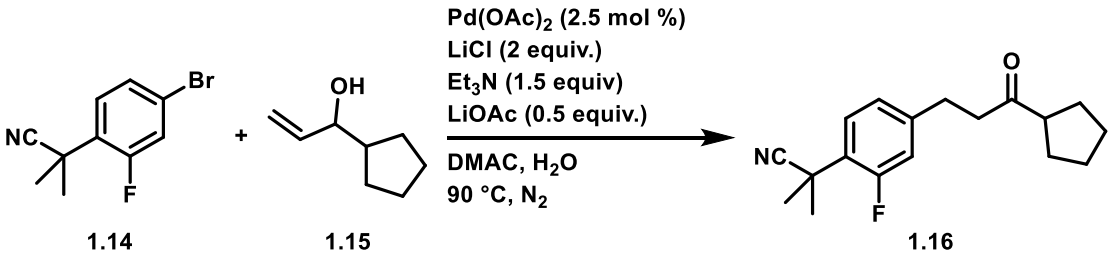
Scheme 1.7

Heck reported that similar reactions would occur when using palladium derived from $Pd(OAc)_2$ and would proceed readily at 100 °C, where iodobenzene **1.4** would cross-couple with styrene **1.12** to form stilbene **1.13** in good yield (Scheme 1.8)[18]. It was also stated that the reactions could proceed at atmospheric pressures in open vials contrary to Mizoroki's use of sealed reaction vessels. Aryl halide, benzyl halide and styryl halide compounds were found to react in these conditions. Iodo-compounds were found to be the most reactive with bromobenzene reacting slowly even at 150 °C.



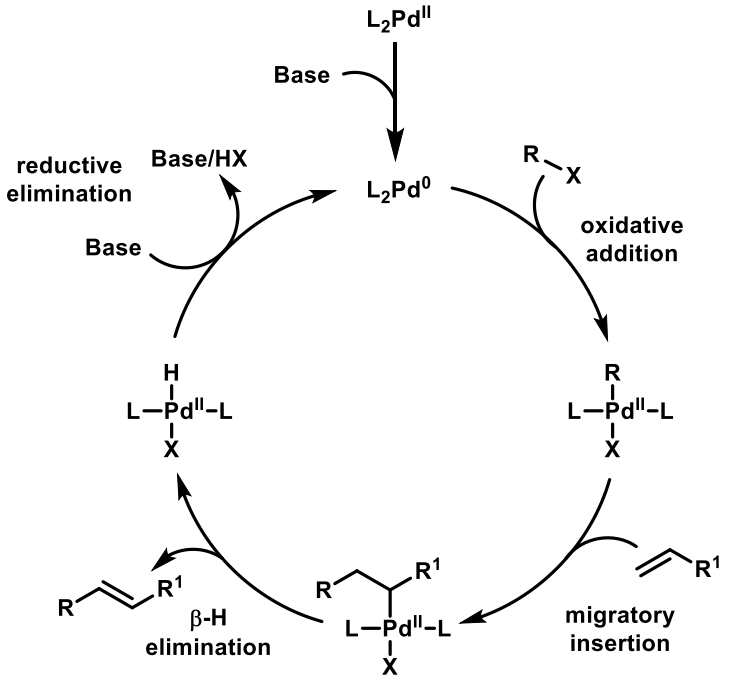
Scheme 1.8

In 2006, Pfizer used the Heck reaction in the synthetic process towards a hepatitis C polymerase inhibitor in a convergent approach after the initial synthetic route was deemed unsuitable for large-scale manufacture (Scheme 1.9)[19]. Bromoarene **1.14** was coupled with allylalcohol **1.15** in the presence of $Pd(OAc)_2$, LiCl, Et_3N and LiOAc to form ketone **1.16**. In this step it was found that chloride additives acted as ligands and the use of ligating bases provided enhanced reactivity with lower catalytic loading. Further modification to the reaction was required as a rapid increase in temperature was observed and therefore it was beneficial to increase the reaction time. Furthermore, portion wise addition of the catalyst and base into the reaction mixture provided sufficient temperature control, thus allowing the reaction to proceed smoothly on a 40 kg scale.



Scheme 1.9

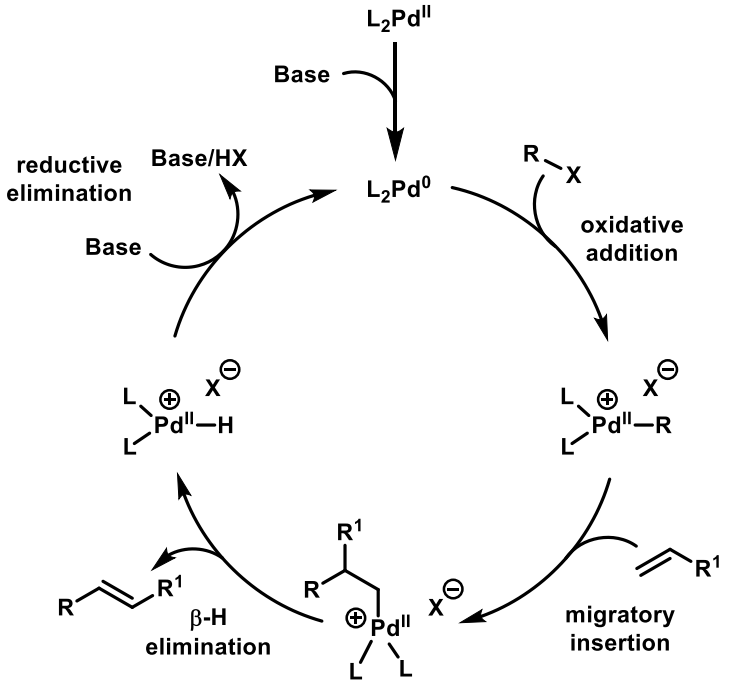
There are two main pathways by which the Heck reaction is proposed to proceed[20]. The first of which, the neutral pathway, starts with the oxidative addition of an aryl-halide to a Pd^0 species. Coordination of the Pd^{II} species to the alkene bond leads to insertion of the palladium in the α-position. β-Hydride elimination affords the cross-coupled product before reductive elimination of H-X by base regenerates the Pd^0 active catalytic species (Scheme 1.10). Based on this neutral mechanism the use of base in the Heck reaction is essential to regenerate the catalyst however the base is required in stoichiometric quantities and therefore generates additional waste in the reaction. As well as the waste from the base, the ligands bound to the palladium are usually phosphine based and are added to the reaction mixture to increase the effectiveness of the catalyst or make the catalyst more selective[21]. Although the use of phosphine ligands has many benefits some of these compounds are quite toxic and must be handled with care and should not be exposed to the environment.



Scheme 1.10

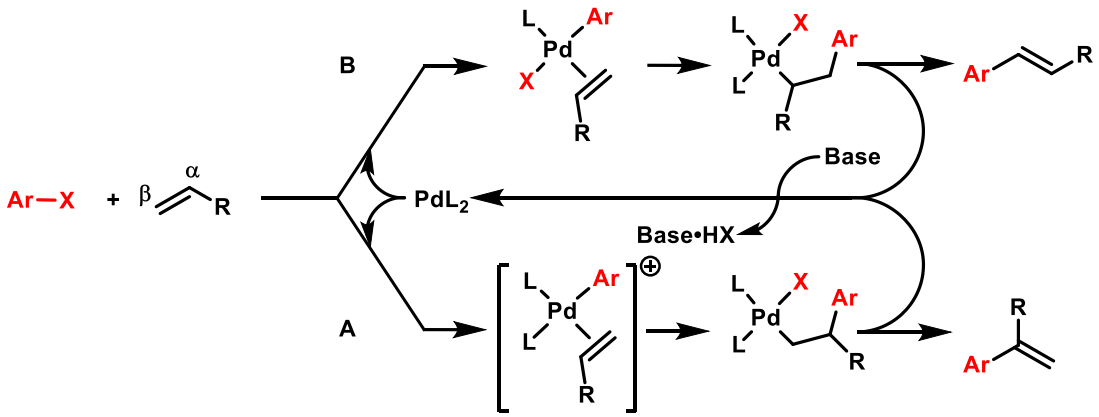
It has also been proposed that the Heck reaction can proceed via a cationic palladium species (Scheme 1.11)[20]. Initially the mechanism proceeds in the same way as the neutral pathway however

it differs in that the halide is abstracted from the palladium complex. The cationic route comes about by the creation of metal salts formed *in situ*, which act to stabilise the halide in solution. It is this cationic palladium species which leads to branched chain isomer formation (*cf.* Scheme 1.12).



Scheme 1.11

The neutral pathway features a dissociation of a neutral ligand from the palladium(II) species (pathway **B**, Scheme 1.12), whereas the ionic pathway features a dissociation of a halide anion instead[22]. It is this electronic difference that leads to the cross-coupling reaction resulting in the linear or the branched chain isomer (pathway **A**, Scheme 1.12). When the alkene associates to the palladium(II) species in the ionic pathway, the double bond is polarised leading to a positively charged α carbon, rendering it more susceptible to attack from the migrating aryl moiety on the palladium catalyst.



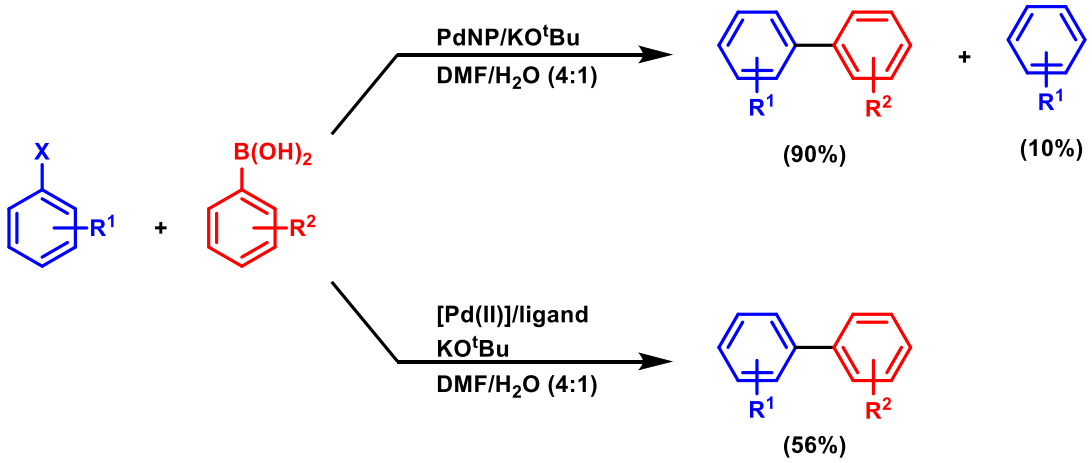
Scheme 1.12

1.1.1 Nanoparticle Catalysis

The two main types of catalysis are heterogeneous catalysis and homogeneous catalysis[23]. The two types differ in the phase in which the catalysis takes place where homogenous catalysis occurs in the same phase as the reaction components and heterogeneous catalysis is where the catalyst is in a different phase to the reaction components[24]. Heterogeneous catalysts are the best for reducing the metal leeching due to it being in a different phase than the reaction however they suffer from reduced activities as the active sites are only on the surface as in supported metal catalysts like those found in car exhausts. Homogeneous catalysts are in the same phase of the reaction and so there is a larger quantity of active sites available for the reactions to proceed, however, as these catalysts are usually dissolved in the solvent, removal from the product can be difficult to perform and so has low recyclability[25].

Nanoparticle catalysis provides a good mid-point between these two types of catalysis where the size of each particle allows for lots of active sites as in homogeneous catalysis while providing the recyclability of heterogeneous catalysis due to its ease of separation[26].

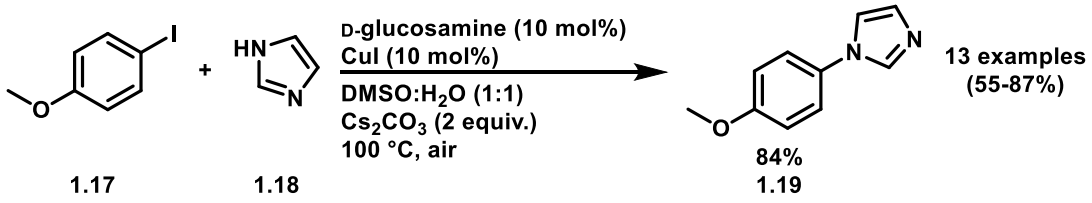
With nanoparticle catalysis becoming a well-researched field in catalytic chemistry more uses have been found in a range of reaction types. Recently it has been shown that PdNPs are able to catalyse the Suzuki reaction to give a higher yield than Pd(II)-ligand complexes (Scheme 1.13)[27]. In this case arylhalides were reacted with arylboronic acids to afford the desired biphenyls in 90% yield with the remaining 10% recovered as the dehalogenated phenyl. Using the Pd(II)-ligand complex only produced the desired biphenyl in 56% yield, however these conditions did not produce the dehalogenated phenyl as the nanoparticles did.



Scheme 1.13

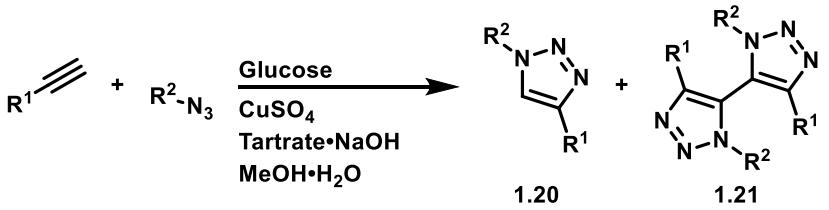
1.1.2 Use of monosaccharides in metal-catalysed coupling reactions

Metal catalysed reactions are essential for organic chemists in the synthesis of important chemicals. In order to reduce the expense and cost to the environment of these reactions monosaccharides have been added to metal catalysed reactions[28]. Addition of monosaccharides to metal catalysed reactions can serve many purposes. Using monosaccharides as ligands for metals is one of the most common uses of monosaccharides in metal catalysed reactions. For example, Zhang and co-workers developed and efficient copper catalysed C-X coupling reaction in the presence of D-glucosamine[29]. In this work it was found that D-glucosamine afforded the best yield over other monosaccharides chosen as green ligands for this reaction. Optimisation of the reaction conditions using 4-iodoanisole **1.17** and imidazole **1.18** as model substrates, resulted in ideal conditions which allowed the synthesis of 13 examples in 55-87% yields including aryl imidazole **1.19** in 84% (Scheme 1.14). These conditions were also used to synthesise an intermediate compound for Nilotinib, an anti-cancer drug, as a single regioisomer in 81% yield.



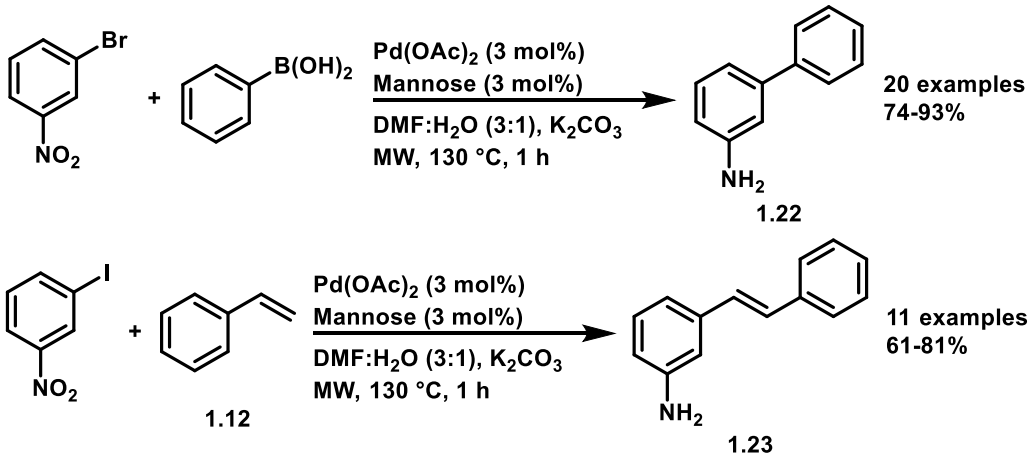
Scheme 1.14

In efforts to find green alternatives to bases like triethylamine it has been found that reducing sugars have the ability to reduce metal precatalysts as shown by Curvas-Yañez *et al*. who demonstrated that copper-catalysed alkyne-azide cycloaddition reactions, otherwise known as click reactions, would proceed using glucose as the reducing agent[30]. As a model study, benzyl azide was reacted with phenylacetylene at room temperature with glucose, tartrate-NaOH and $CuSO_4$ solution (Scheme 1.15). The concentration of glucose was found to be important, 0.25 molar equivalents was found to be ideal, with more or less affording lower yields. After 2 hours, 2 compounds were isolated from the reaction, triazole **1.20** and bistriazole **1.21**, similar results have been seen in previous studies of this nature[31], however when the reaction time was extended to 24 h only the triazole was isolated. Overall, 10 triazoles were synthesised in good to excellent yields. Interestingly, it was found that 3 triazoles synthesised only afforded the bistriazole in poor to moderate yields.



Scheme 1.15

Recently *D*-mannose has been shown to have a role in the one-pot tandem protocol for the synthesis of aminobiphenyl **1.22** and aminostilbene **1.23** compounds (Scheme 1.16). Jian *et al*. developed this tandem protocol for both Suzuki reactions and Heck reactions and were able to show the generality of the prep by synthesising many aminobiphenyl and aminostilbene compounds[32]. It was found that the reaction proceeded first by the fast cross-coupling reaction followed by slow reduction and so by stopping the reaction early nitrobiphenyls and nitrostilbenes could be isolated. It is thought that the role of $_D$-mannose in this reaction acts as a ligand, stabilising the palladium species enabling the fast cross-coupling reaction to take place as well as a source of hydrogen, used to reduce the nitro moiety.

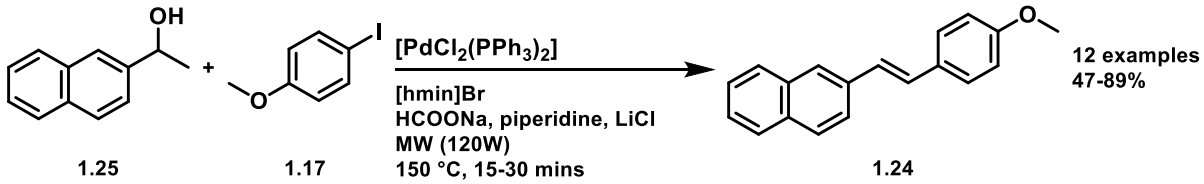


Scheme 1.16

1.1.3 *In situ* formation of styrene in cross-coupling reactions

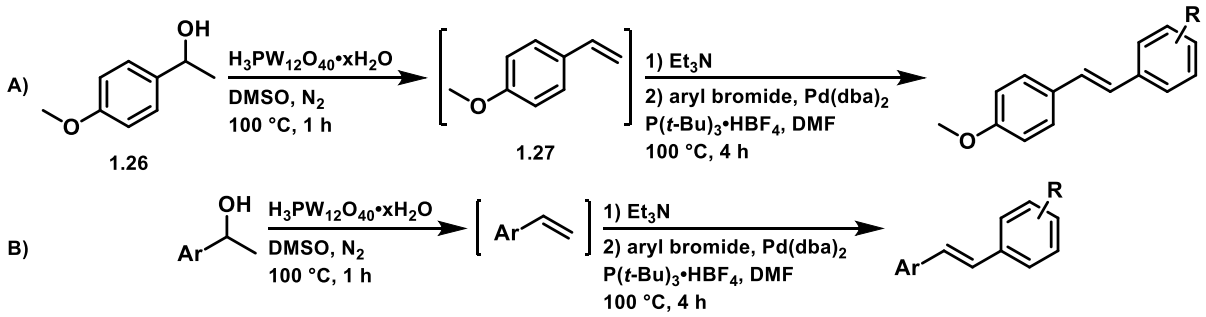
While the Mizoroki-Heck reaction has become a mainstay in chemical synthesis two aspects of the reaction have had limited investigations; the use of exogenous base to recycle the catalyst recycling and the use of styrene type alkenes as the main feedstock of the reaction[33, 34]. Dehydration of secondary alcohols to alkene derivatives has not been investigated much for tandem Mizoroki-Heck reactions, this is due to the opposite nature of the reaction conditions necessary for each step to proceed. Heck reactions typically need basic conditions in order to recycle the metal catalyst, while the dehydrative process of secondary alcohols to alkenes requires acidic conditions. This renders this methodology moot as neither reaction can take place in the same medium.

Ionic liquids have been used as solvent for the Heck reaction in recent years and a tandem dehydrative cross-coupling process was developed by Sinha *et al*. whereby the cross-coupled product (*E*)-2-(4-methoxystyryl)naphthalene **1.24** was prepared from 4-iodoanilsole **1.17** and the *in situ* formed 1-vinylnaphthalene by dehydration of 1-(naphthalene-2-yl)ethan-1-ol **1.25** (Scheme 1.17)[35]. It was found that a combination of HCOONa and piperidine acting as bases provided the best yields and reduced the time required in the microwave from 40 mins to 15 mins.



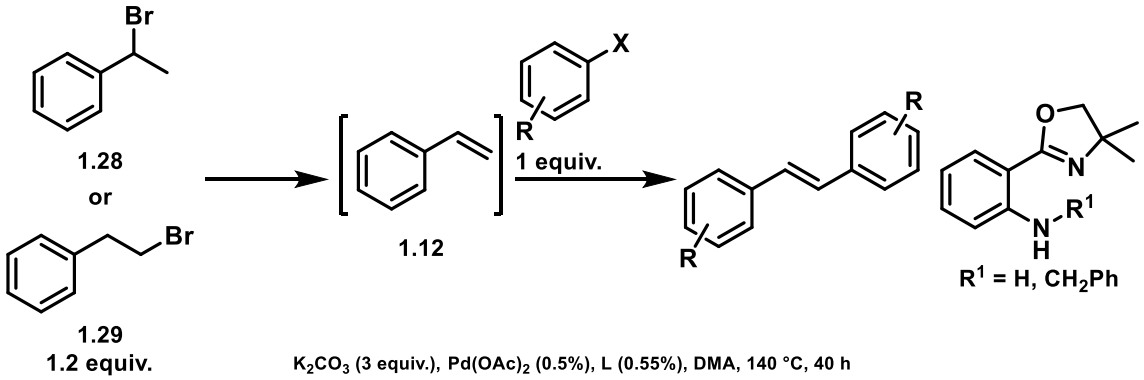
Scheme 1.17

Another example of using alcohols as precursor alkenes was shown by Xiao *et al.* where the alcohol, such as 1-(4-methoxyphenyl)ethan-1-ol **1.26**, was first treated with a catalytic amount of a heteropolyacid, such as $H_3PW_{12}O_{40}$, in DMSO for 1 h at 100 °C (Scheme 1.18)[36]. This resulted in efficient and selective production of alkene **1.27**. Addition of excess base followed by aryl halide, palladium catalyst and a phosphine ligand in DMF with 4 h of heating resulted in the desired coupled product in high yields. They were able to demonstrate good substrate scope for both the haloarene, 12 examples 66-85% (Scheme 1.18A) and the alcohol, 12 examples 51-91% (Scheme 1.18B).



Scheme 1.18

Saiyed and Bedekar reported a one-pot synthesis of stilbenes in 2010 whereby the active alkene in the cross-coupling was generated *in situ*, by dehydrohalogenation or by Wittig reaction[33]. The formation of styrene **1.12** by dehydrohalogenation is performed under basic conditions and realising that the Mizoroki-Heck reaction requires basic conditions, a tandem dehydrohalogenation and cross-coupling was attempted. It was found that both (1-bromoethyl)benzene **1.28** and (2-bromoethyl)benzene **1.29** were suitable precursors for the *in situ* formation of styrene and cross-coupling with a variety of aryl halides (Scheme 1.19). Overall, 15 examples of stilbenes were synthesised using the tandem dehydrohalogenation/cross-coupling reaction conditions in good to excellent yields of 54-88%.

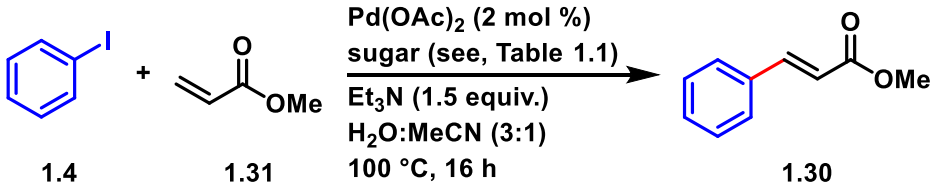


Scheme 1.19

1.1.4 Previous work in the Camp Group

In an attempt to develop greener methods for palladium-catalysed cross-coupling reactions the Camp group investigated the use of simple sugars to make nanoparticles for *in situ* formed catalysts for use in aqueous media[37, 38]. Investigations began to determine the viability of sugar derived nanoparticles as catalysts where simple sugars added to the reaction mixture allow the formation of metal nanoparticles for use in metal catalysed reactions. The Sonogashira, Suzuki-Miyaura and Mizoroki-Heck reactions were chosen to evaluate the use of the nanoparticles as the mechanisms for these reactions have been extensively studied and are therefore well known and widely understood; the reactions also allow the use of aqueous conditions which enabled the investigation into the recyclability of the reaction conditions.

To begin with the synthesis of methyl cinnamate **1.30** was studied by the reaction between iodobenzene **1.4** and methyl acrylate **1.31** in the presence of palladium(II) acetate [$Pd(OAc)_2$], triethylamine and a reducing sugar in a water:acetonitrile mix (3:1) at 100 °C was initially studied using four reducing sugars, fructose, cellulose and glucose (Scheme 1.20, Table 1.1). These sugars were selected as they have the potential to reduce palladium(II) to palladium(0)[38]. The reaction containing fructose (Scheme 1.20, Table 1.1, Entry 1), provided the lowest yield at only 2% despite fructose having the largest reducing potential of the sugars used and surprisingly hindered the reaction when compared to the reaction carried out in the absence of any sugar (Scheme 1.20, Table 1.1, Entry 5). The presence of cellulose and sucrose in the reaction mixture were beneficial to the reaction with yields of 21% and 58% (Scheme 1.20, Table 1.1, Entries 2 and 3) respectively. However, when the reaction was carried out using glucose as the reducing sugar, the desired product was isolated with nearly quantitative yield (Scheme 1.20, Table 1.1, Entry 4). It was found that the amount of glucose in the reaction was key to providing the best yield, when too much sugar was added it reduced the surface area of the palladium(0) nanoparticle catalyst slowing down the process, while not enough sugar increased the particle aggregation reducing surface area and causing deactivation of the catalyst (Scheme 1.20, Table 1.1, Entries 9-11). The addition of both triethylamine and $Pd(OAc)_2$ were found to be essential for the reaction to proceed (Scheme 1.20, Table 1.1, Entries 7 and 8). It was also found that preformed Pd^0 nanoparticles did not perform as well as the *in situ* formed nanoparticles yielding only 20% (Scheme 1.20, Table 1.1, Entry 12).



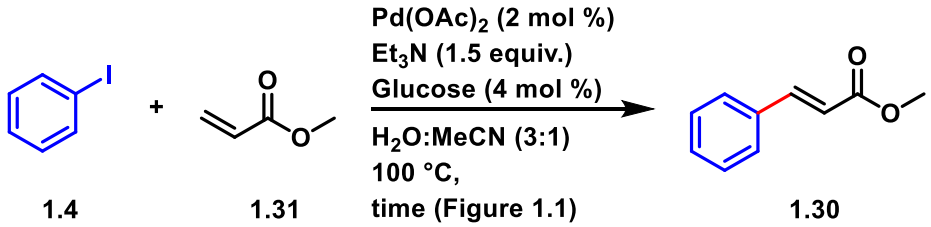
Scheme 1.20

Table 1.1 Sugar-derived palladium(0) nanoparticles as catalysts for the Mizoroki-Heck reaction[38]

Entry	Sugar	Pd/sugar ratio	Yield[a] (%)
1	Fructose	1 : 2	2
2	Cellulose	1 : 10[b]	21
3	Sucrose	1 : 2	58
4	Glucose	1 : 2	97
5	-	1 : 0	18
6[c]	-	1 : 0	12
7[c]	Glucose	1 : 2	6
8[c,d]	Glucose[e]	-	0
9	Glucose	1 : 1	70
10	Glucose	1 : 3.5	50
11	Glucose	1 : 4	42
12[f]	Glucose	1 : 2	20

[a] Isolated yield. [b] A 1 : 10 weight to weight ratio of palladium acetate to cellulose was used. [c] No Et_3N was added. [d] No palladium acetate was added. [e] 4 mol % glucose was added. [f] PdNP's were preformed and isolated.

The pH of the cross-coupling reaction was then monitored by setting up a series of reactions between iodobenzene **1.4** and methyl acrylate **1.31** under the standard conditions and stopping them at specific times (Scheme 1.21). Once the pH of the reaction mixtures was taken the reaction was worked up and purified to afford methyl cinnamate **1.30**. This allowed the comparison of pH, yield and time and indicated that as the reaction time progressed the pH decreased from the initial point at 11.7 to 2.66. Importantly it was also found that the yield of the reaction increased despite the reaction medium becoming more acidic with a maximum isolated yield of 97% at pH 2.66 (Figure 1.1).



Scheme 1.21

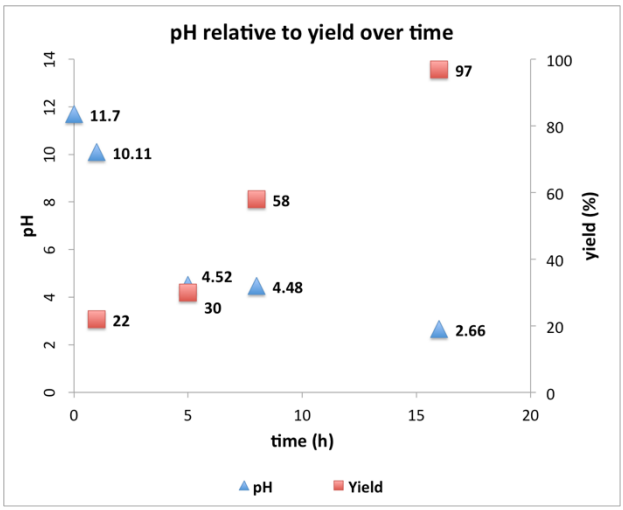
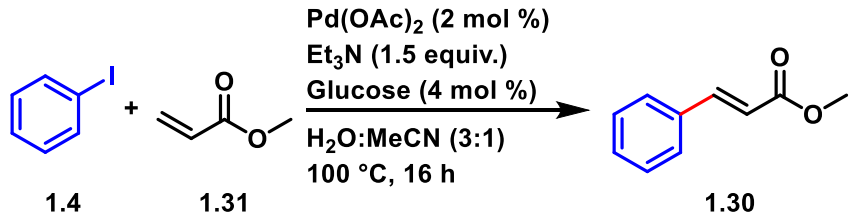


Figure 1.1: Graph showing the pH vs. time vs. yield of the PdNP mediated cross-coupling reaction

An important aspect of this research was to investigate the recyclability of the palladium catalyst and so the cross-coupling reaction between iodobenzene **1.4** and methyl acrylate **1.31** was investigated (Scheme 1.22, Table 1.2). Recycling of the sugar derived *in situ* formed palladium nanoparticle catalyst was achieved by utilising the hydrophilic nature of the catalyst. Upon reaction completion, diethyl ether was added to the mixture and subjected to centrifugation, this process allowed the palladium catalyst to stay in the aqueous phase of the mixture while allowing the organic product to collect in the organic phase and to be isolated. The organic layer was then dried and the solvent removed under reduced pressure. The resulting crude residue was purified by flash column chromatography. Iodobenzene **1.4**, methyl acrylate **1.31**, MeCN and Et_3N were then added to the aqueous layer containing the catalyst and the reaction carried out again. Initial results from the recycling process showed that excellent yields could be obtained from recycled catalyst, 92% from the first and second times reusing the catalyst (Scheme 1.22, Table 1.2, Entries 2 and 3). The isolated yield was found to drop slightly upon use of the 3rd recycled catalyst at 82% (Scheme 1.22, Table 1.2, Entry 4), however the isolated yield drops significantly upon more recycling, down to 61% after the 4th recycling of the catalyst (Scheme 1.22, Table 1.2, Entry 5).



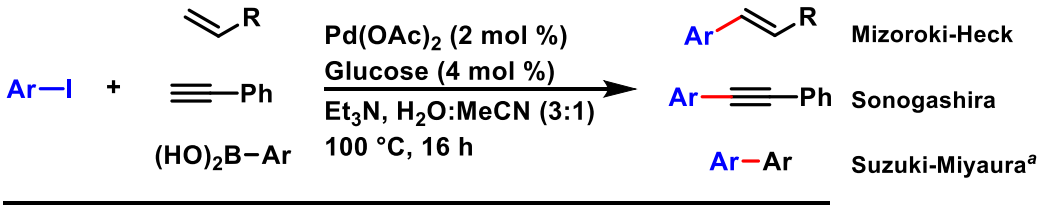
Scheme 1.22

Table 1.2: Recylability of the in situ *formed palladium nanoparticle catalysts*

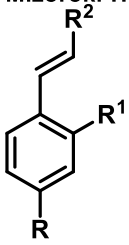
Entry	Pd/sugar ratio	Yield[b] (%)	Notes
1	1 : 2	97	
2[a]	-	92	1st recycle
3[a]	-	92	2nd recycle
4[a]	-	82	3rd recycle
5[a]	-	61	4th recycle

[a] Et_3N (1.5 equiv.) was added after each cycle, but no additional palladium or glucose. [b] Isolated yield

Following from this work the catalytic viability of the *in situ* formed palladium nanoparticles was explored in terms of reaction type and substrate scope and so the Sonogashira, Suzuki-Miyaura and the Mizoroki-Heck reaction were investigated (Scheme 1.23). Continuing with the Mizoroki-Heck reaction, 7 compounds were synthesised using the developed reactions conditions using a variety of substituted aryl iodides and alkenes with isolated yields of 47-100% (Scheme 1.23). It should be noted that acrylic acid can be tolerated in the reaction conditions, two reactions involving acrylic acid achieving an isolated yield of 100%. The catalytic viability of the sugar derived palladium nanoparticles in the Sonogashira reaction was investigated and it was found that the reaction proceeded as expected with moderate to excellent yields. As with the Sonogashira and Mizoroki-Heck reactions the palladium nanoparticles were catalytically active in the Suzuki-Miyaura reaction. Reactions of aryl iodides with phenyl boronic acid provided products in good to excellent yields. Using DMF as the solvent also supported the use of aryl bromides in this process.

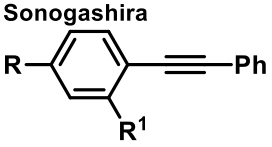


Mizoroki-Heck



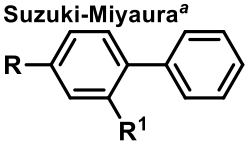
1, R = R^1 = H, R_2 = CO_2Me, 97%
2, R = R^1 = H, R_2 = CO_2H, 100%
3, R = R^2 = CO_2H, R^1 = H, 100%
4, R = H, R^1 = NH_2, R^2 = CO_2H, 93%
5, R = R^1 = H, R_2 = Ph, 90%
6, R = NO_2, R^1 = H, R^2 = Ph, 94%
7, R = CHO, R^1 = H, R^2 = CO_2Me, 47%

Sonogashira



1, R = R^1 = H, 95%
2, R = NO_2, R^1 = H, 60%
3, R = H, R^1 = NH_2, 44%

Suzuki-Miyaura[a]



1, R = R^1 = H, 98% (98%)[b]
2, R = NO_2, R^1 = H, 94%
3, R = H, R^1 = NH_2, 65%

[a] Ar-I (1.0 equiv.), $(HO)_2$B-Ph (1.5 equiv.), glucose (10 mol %), $Pd(OAc)_2$ (2 mol %), Cs_2CO_3 (2.0 equiv.), DMF:H_2O (10:1), 100 °C, 16 h. [b] Ph-Br (1.0 equiv.) was used

Scheme 1.23

1.2 Aims & objectives

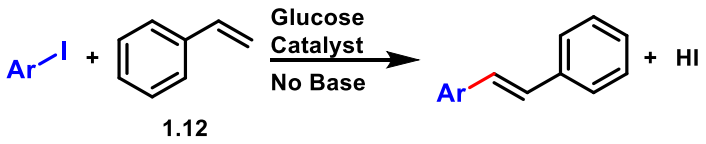
The aim of this research is to develop dehydrative palladium-catalysed cross-coupling reaction in which a simple sugar is used to reduce the pre-catalyst, stabilise the active catalyst and then regenerate the catalyst – sugar powered catalysis. This aim will be met by achieving the following goals:

1. Further development of a ligand free Mizoroki-Heck reaction in which the reducing sugar stabilises the active catalyst
2. Development of a Mizoroki-Heck protocol that is without the addition of an exogenous base in which the reducing sugar stabilises and regenerates the active catalyst
3. Development of a dehydrative palladium-catalysed cross-coupling reaction

1.3 Results and discussion

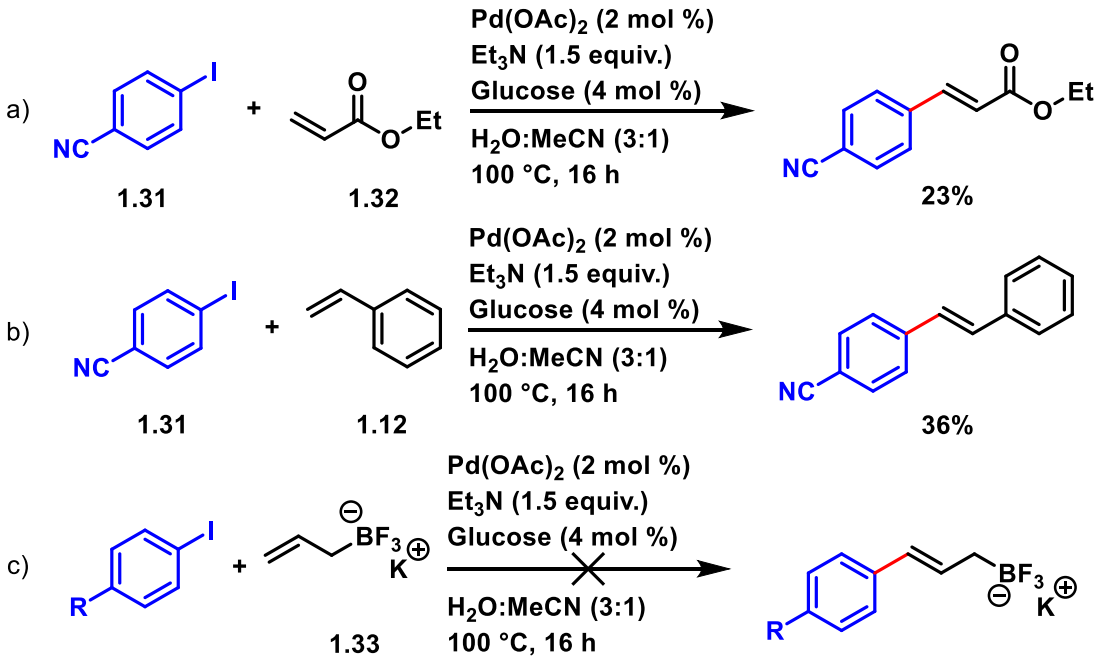
1.3.1 Sugar-derived palladium(0) cross-coupling

Following from the work on sugar-derived palladium nanoparticles and the revelation that the reaction proceeds, in spite of the reaction medium becoming acidic over time, reactions without base present were investigated (Scheme 1.24)[39].



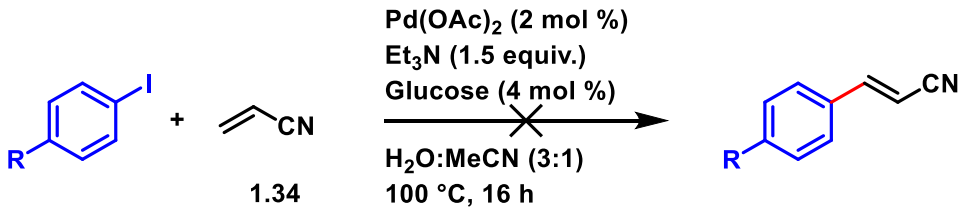
Scheme 1.24

The research began via a further examination of the substrate scope of the sugar-derived palladium-catalysed Mizoroki-Heck reaction described above. Thus, the methods developed previously within the Camp group in which sugar-derived palladium nanoparticles serve as the active catalyst in cross-coupling reactions were employed for the reaction of 4-iodobenzonitrile **1.31** with ethyl acrylate **1.32** and styrene **1.12** (Scheme 1.25a & b). While similar reactions provided products with excellent yields the reactions with 4-iodobenzonitrile **1.31** were poor yielding with just 23% isolated yield for the coupling with ethyl acrylate **1.32** and 36% yield when coupling with styrene **1.12**. While it was shown that acrylate and styrene based alkenes were able to couple under these conditions, other alkenes were also reviewed in an attempt to expand the substrate scope. The reaction of aryl iodides with potassium allyltrifluoroborate **1.33** was attempted using the standard conditions, however, only starting material was recovered from the reaction (Scheme 1.25c)[40]. This is possibly due to the formation of a boron-glucose adduct that does not participate in the cross-coupling process and prevents formation of the active palladium catalyst[41, 42].



Scheme 1.25

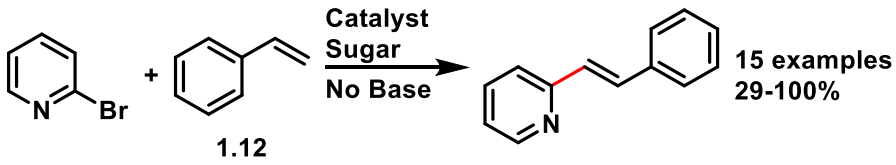
Additionally the use of acrylonitrile **1.34** as the alkene source of for the Mizoroki-Heck reaction was also found not to be successful (Scheme 1.26)[43].



Scheme 1.26

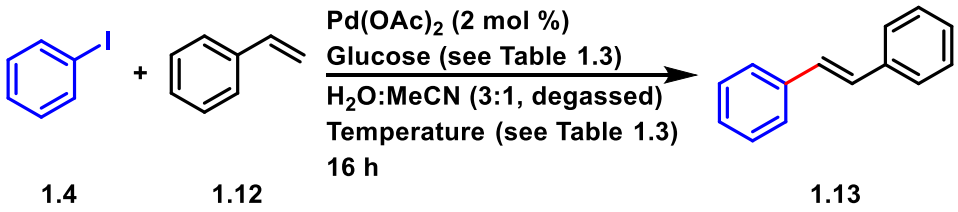
1.3.2 Acidic Heck

Having previously shown that the reaction medium for the cross-coupling under aqueous conditions using *in situ* glucose derived palladium nanoparticles becomes acidic as the reaction proceeds (Scheme 1.21), the feasibility of a base-free Heck reaction was explored. Ideally, this process would be done under acidic conditions using the reducing power of the sugar to generate the active catalyst, stabilise the metal and then regenerate the catalyst – sugar powered catalysis. This approach is in contrast to the recent work by Liotta and co-workers who reported an exogenous base free Suzuki-Miyaura reaction in which the substrate had to contain a basic nitrogen (Scheme 1.27)[44].



Scheme 1.27

The cross-coupling reaction between iodobenzene **1.4** and styrene **1.12** was initially investigated (Scheme 1.28), however without base in the reaction mixture no product was isolated (Scheme 1.28, Table 1.3, Entry 2)[39]. In an attempt to force the reaction to completion the temperature was increased from 100 °C to 150 °C. Some of the desired product stilbene **1.13** was isolated, albeit in a low yield of 5% (Scheme 1.28, Table 1.3, Entry 3). Degassing the solvents was found to be key to allowing the reaction to proceed as the competing reaction of molecular oxygen with the palladium(0) catalyst uses the reducing agents until depleted, thus ceasing the reaction (*cf*. Figure 1.5). The concentration of glucose in the reaction was then studied (Scheme 1.28, Table 1.1, Entries 3-7). It was found that a palladium/sugar ratio of 1:25 was optimal with an isolated yield of 97% Table 1.3, Entry 5). This isolated yield compares favourably to that of the reaction using 1.5 equivalents of triethylamine at 100 °C (Scheme 1.28, Table 1.3, Entry 1).



Scheme 1.28

Table 1.3: Development of the Mizoroki-Heck cross-coupling under acidic conditions

Entry	Pd/sugar ratio	Temperature (°C)	Yield (%)
1[a]	1 : 2	100	97
2	1 : 2	100	0
3	1 : 2	150	5
4	1 : 10	150	41
5	**1 : 25**	**150**	**97**
6	1 : 50	150	40
7	1 : 100	150	33

[a] Et_3N (1.5 equiv) was added[45].

1.3.2.1 Determination of isomer distribution

Interestingly, using the optimal conditions developed (Scheme 1.28, Table 1.3 Entry 5), two compounds were observed in the sample after workup. These were determined to be a mixture of the linear **1.13** and branched chain **1.35** isomers of stilbene. This formation of branched chain isomer hadn't been observed previously in the Camp group. High temperature Mizoroki-Heck reactions have been previously reported and the distribution of products obtained in this series are consistent with the literature. The major isomer from the reaction is the linear isomer **1.13** which can be seen in the ^{1}H NMR spectrum as a singlet at 7.19 ppm for the alkene protons, while the terminal alkene protons in the branched isomer **1.35** are observed as a singlet at 5.55 ppm in a ratio of 88:12 (**1.13**:**1.35**) (Figure 1.2). These assignments were further supported by the isolation of the tolyl-substrate linear **1.36** and branched **1.37** isomers. The large downfield shift of the alkene protons in **1.13** arises from conjugation with the aromatic rings. The formation of linear and branched isomers of stilbene are indicative of the reaction procedure and so isolated yields are stated as a mixture of both isomers where the ratio stated is determined by ^{1}H NMR by comparison of the alkene protons of each isomer. Where the alkene protons could not be compared equivalent proton environments were chosen for comparison. Despite repeated attempts to isolate the different isomer by flash column chromatography, this was only possible for a limited range of substrate and therefore combined yields and isomer ratios are reported throughout this thesis.

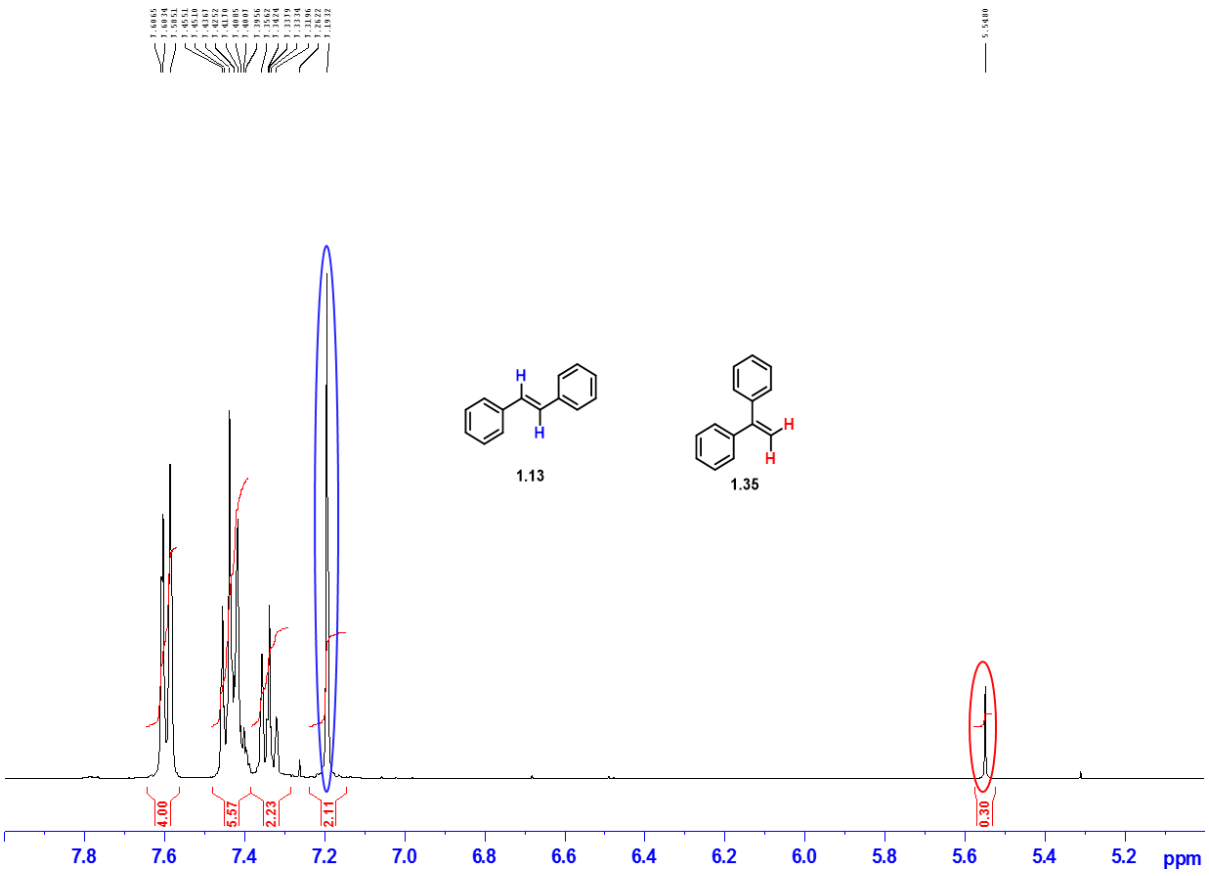


*Figure 1.2: ^{1}H ($CDCl_3$, 400 MHz) spectrum showing linear **1.13** and branched **1.35** chain isomers of stilbene*

Isolation of the tolyl-substrate isomers linear **1.36** and branched **1.37** was instrumental in the determination that the branched chain isomer was also produced in the reaction. Isolation of both isomers was achieved by repeated flash column chromatography on a Biotage® Isolera 4 automated purification system using SNAP Ultra Biotage® HP-Sphere™ 25 µm silica gel cartridges. By monitoring the UV absorption at 254 nm (red line) and 280 nm (black line), both isomers can be identified by the different intensities at these wavelengths. As the ^{1}H NMR ratio for the mixture of isomers shows that the linear chain isomer **1.36** is formed in much higher quantities compared to the branched chain isomer **1.37**, it can be safely assumed that the large purple area represents the linear isomer **1.36** and the small green area represents the branched chain isomer **1.37**. The branched chain isomer **1.36** shows a larger intensity absorption for 254 nm compared to 280 nm, whereas the linear chain isomer **1.37** has a larger intensity at 280 nm compared to 254 nm.

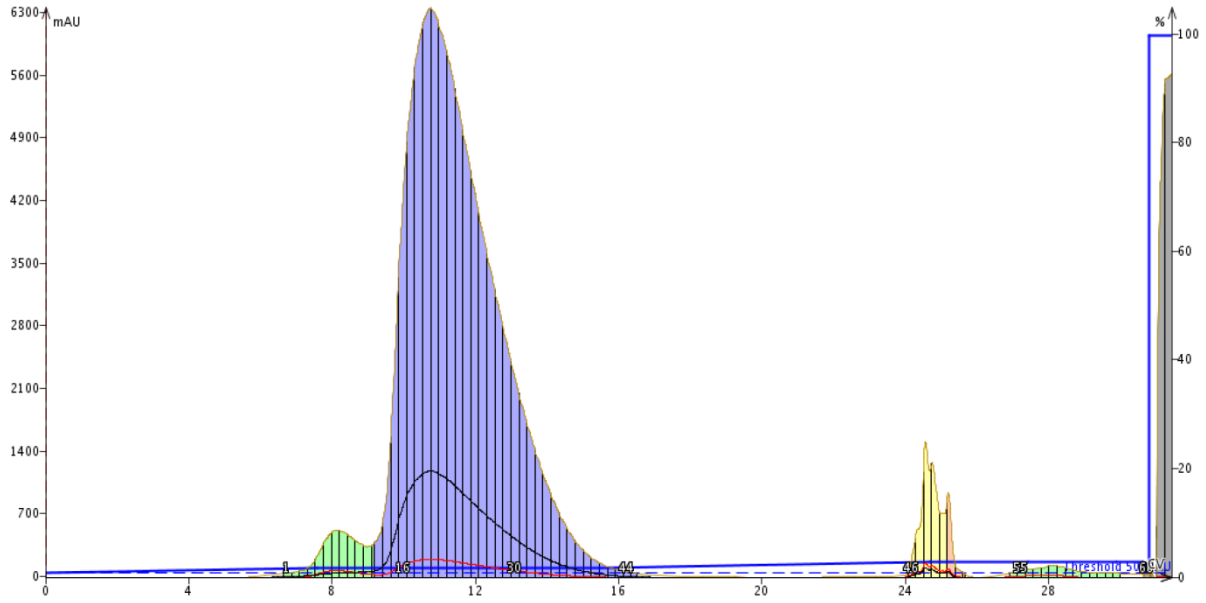


*Figure 1.3: Biotage Isolera report for the seperation of **1.36** and **1.37***

While both compounds contain 2 alkene protons, these environments are different in the linear **1.36** and branched **1.37** isomers. Conjugation of the alkene moiety with the two aromatic rings in the linear isomer **1.36** shifts the alkene peak in the ^{1}H spectrum downfield compared to the branched chain isomer **1.37** (Figure 1.4).

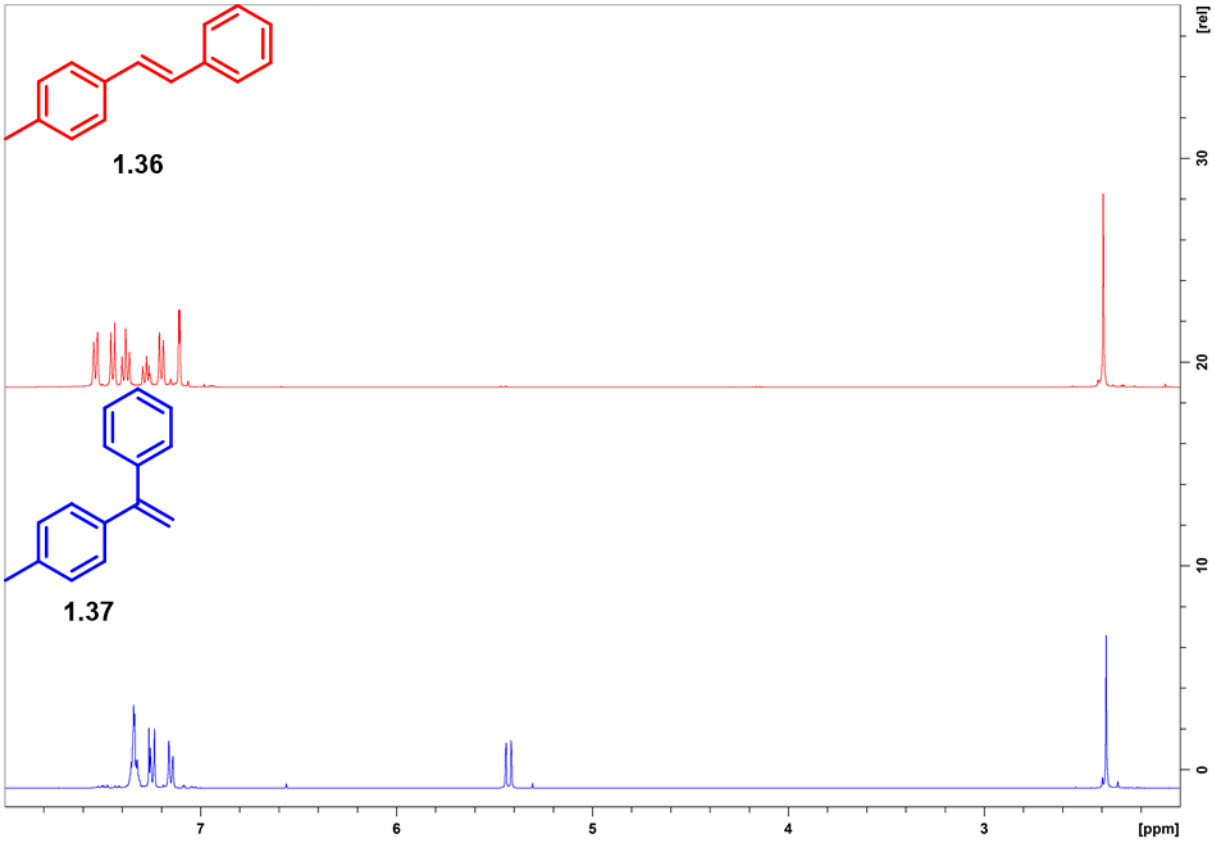


*Figure 1.4: A comparison of ^{1}H NMR of linear **1.36** and branched **1.37** chain isomers of the 4-tolyl substrate*

1.3.2.2 Additive investigation

In order to better understand the influence of acid on the system various additives were added to the reaction of 4-iodotoluene **1.38** and styrene **1.12** (Scheme 1.29, Table 1.4). First, formic acid (aqueous pH = 2.38 at 0.1 M) was added however, it was found that this had a detrimental effect on the isolated yield of the product (Scheme 1.29, Table 1.4, Entry 2). Despite the reduced yield it was noticed that the linear to branched isomer ratio was unaffected. Stronger acid HCl, (aqueous pH = 1 at 0.1 M) was added to the reaction mixture and also found to have a detrimental effect on the reaction with no products isolated (Scheme 1.29, Table 1.4, Entry 3).

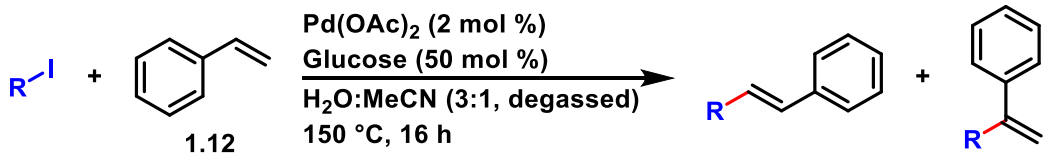
Scheme 1.29

Table 1.4: Table of additives investigated in the acidic Mizoroki-Heck reaction

Entry	Additive	Yield (%)	
1	-	83	85:15
2	Formic acid	63	84:16
3	HCl	-	

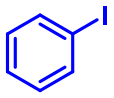
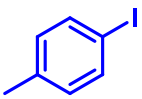
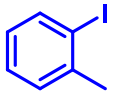
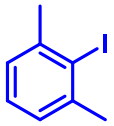
1.3.2.3 Steric study

Once the conditions were optimised, the substrate scope was expanded to explore the effects of steric interactions on both the yield and distribution of isomers. To do this 4-iodotoluene **1.38** and 2-iodotoluene **1.39** were reacted with styrene **1.12** using the improved method (Scheme 1.30, Table 1.5 Entry 2). While the reaction with iodobenzene **1.4** produced nearly quantitative yield (Scheme 1.30, Table 1.5 Entry 1), the reaction with 4-iodotoluene **1.38** yielded 83% product however, a significant loss of yield was seen when 2-iodotoluene **1.39** was used at 47%. This shows a significant reduction in yield caused by the sterics of the starting materials. Despite the reduced yield, the effect of sterics on the ratio of linear:branched isomers were relatively similar, 85:15 for the *para*-substituted toluene and 88:12 for the *ortho*-substituted toluene. The reaction involving 2-iodo-1,3-dimethylbenzene **1.40** was carried out however the material recovered from the reaction was found to be mainly starting material (84% by ^{1}H NMR) showing it is far too hindered to be used in the reaction effectively (Scheme 1.30, Table 1.5, Entry 4). Thus this substrate is far too hindered to be used in the reaction effectively. From ^{1}H NMR analysis it was found that the ratio of the isomer was 92:8 based on the alkene peaks at 6.68 ppm for the linear isomer and 6.05 and 5.18 ppm for the branched isomer. This is interesting to see as it also shows that the hindered starting material has a preference for the linear form.



Scheme 1.30

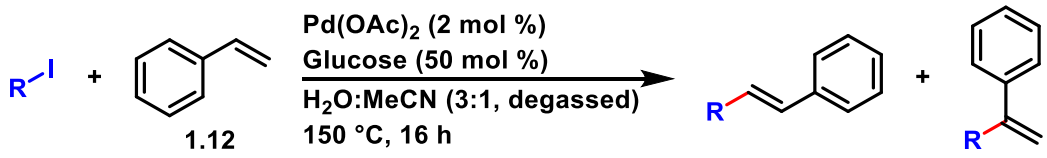
Table 1.5: Table of compounds investigating steric parameters of the acidic Mizoroki-Heck reaction

Entry	R =		Yield (%)[a]	Ratio
1		**1.4**	97	88:12
2		**1.38**	83	85:15
3		**1.39**	47	88:12
4		**1.40**	-	92:8[b]

[a] Isolated yields [b] Products seen in ^{1}H NMR but not isolated

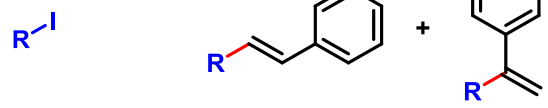
1.3.2.4 Electronic study

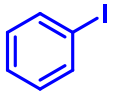
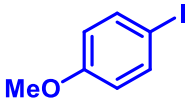
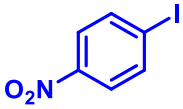
The effect on yield and distribution of isomers was examined when using electron rich and electron deficient substituted aryl iodides. Interestingly, the yields when using electron rich 4-iodoanisole **1.17** (Scheme 1.31, Table 1.6, Entry 2), and electron deficient 4-iodonitrobenzene **1.41** (Scheme 1.31, Table 1.6, Entry 3), were similar to the excellent yields of stilbene **1.13** (Scheme 1.31, Table 1.6, Entry 1). Electron donating methoxy functional group shifted the isomer distribution towards the branched isomer similar to that found when using 4-iodotoluene **1.38** (Scheme 1.31, Table 1.6, Entry 2) whereas the electron withdrawing nitro moiety **1.41** has a comparable distribution of isomers to stilbene **1.13** only shifting the ratio by 2% (Scheme 1.31, Table 1.6, Entry 3). Therefore, the electronics of the aryl-halide do not seem to have a significant effect on either isolated yield or isomer ratio.



Scheme 1.31

Table 1.6: Table of compounds investigating electronic parameters of the acidic Mizoroki-Heck reaction

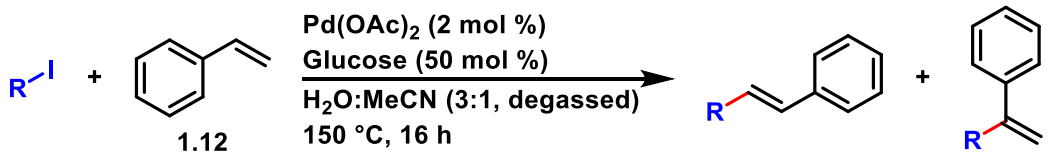


Entry	R =		Yield (%)[a]	Ratio
1		**1.4**	97	94:6
2		**1.17**	93	84:16
3		**1.41**	90	92:8

[a] Isolated yields

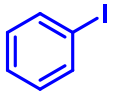
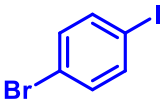
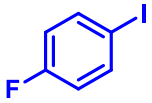
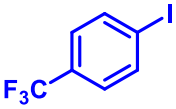
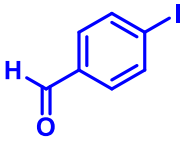
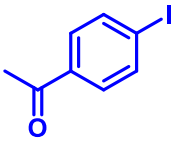
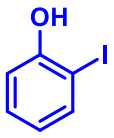
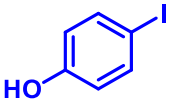
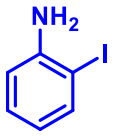
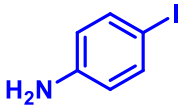
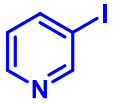
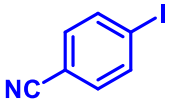
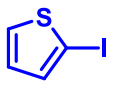
1.3.2.5 Functional group tolerance

To probe the functional group tolerance of the acidic Mizoroki-Heck reaction several substituted aryl-iodides were reacted. Halogenated compounds were found to afford the desired products **1.42**-**1.44** in high yield, 87-90% (Table 1.7, Entries 2-4). Aldehyde **1.45** and ketone **1.46** moieties (Table 1.7, Entries 5-6), were also tolerated under the conditions, however, this resulted in slightly lower yields compared to the iodobenzene substrate **1.4** (Table 1.7, Entry 1). Protic phenol substrates **1.47** & **1.48** were not tolerated under these reaction conditions (Table 1.7, Entries 7-8), while the same was also found for basic functionalities like aniline **1.49** & **1.50** or pyridine **1.51** (Table 1.7, Entries 9-11). The reactions of these substrates either returned starting material or lead to a complex mixture from which no products could be identified by ^{1}H NMR. Basic nitrogen containing compounds tend to struggle in metal mediated catalytic reactions due to the coordination of the nitrogen centres to the metal catalyst, reducing the catalytic activity. This is in contrast with the work by Liotta and co-workers where basic substrates are key for the progression of the base free Suzuki reaction. In this case the basic nitrogen centres aid the formation of hydroxide ions in the reaction which act as the base to regenerate the active catalyst[44].[16JOC8520] Branched and linear isomers could be identified in the NMRs for the reactions with 4-iodobenzonitrile **1.31** and 2-iodothiophene **1.52** however these proved difficult to isolate by column chromatography, (Table 1.7, Entries 12-13). It is possible that the nitrile moiety could have been hydrolysed under the reaction conditions, which would have made its isolation difficult. Additionally, no isomeric ratios could be determined from these reactions as the alkene proton peaks for the linear isomer overlap with the aromatic proton peaks of both isomers.



Scheme 1.32

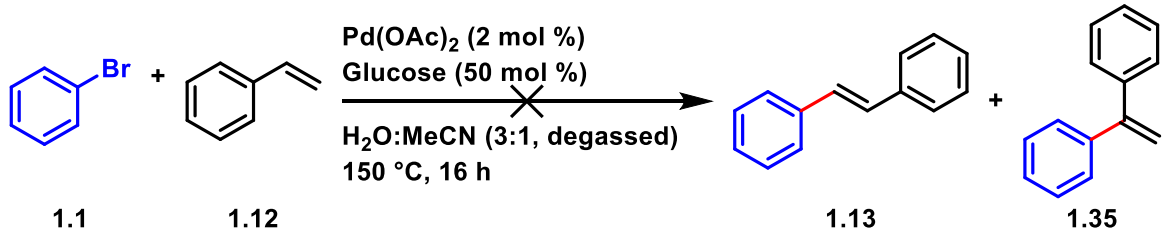
Table 1.7: Table of functional groups tolerated in the acidic Mizoroki-Heck reaction

Entry	R =		Yield (%)[a]	Ratio
1		**1.4**	97	94:6
2		**1.42**	87	86:14
3		**1.43**	90	92:8
4		**1.44**	89	87:13
5		**1.45**	39	90:10
6		**1.46**	45	93:7
7		**1.47**	-	-
8		**1.48**	-	-
9		**1.49**	-	-
10		**1.50**	-	-
11		**1.51**	-	-
12		**1.31**	-	-
13		**1.52**	-	-

[a] Isolated yields

1.3.2.6 Aryl-bromide investigation

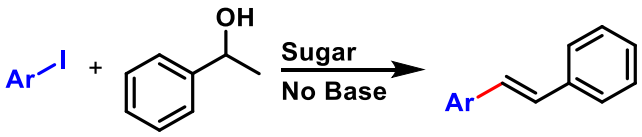
Due to the toxic and relative expensive nature of iodine reagents alternate substrates for cross-coupling reactions have been investigated[46]. Thus the use of aryl-bromides was investigated under the developed acidic cross-coupling conditions. Previous use of 4-iodobromobenzene **1.42** (Scheme 1.32, Table 1.7, Entry 2), did not result in sequential cross-coupling, however, an attempt was made to couple styrene **1.12** with bromobenzene **1.1** (Scheme 1.33), which was unsuccessful. In contrast to previous results in the Camp group (*cf.* Scheme 1.23), the use of degassed DMF also did not result in the formation of alkenes **1.13**:**1.35**.



Scheme 1.33

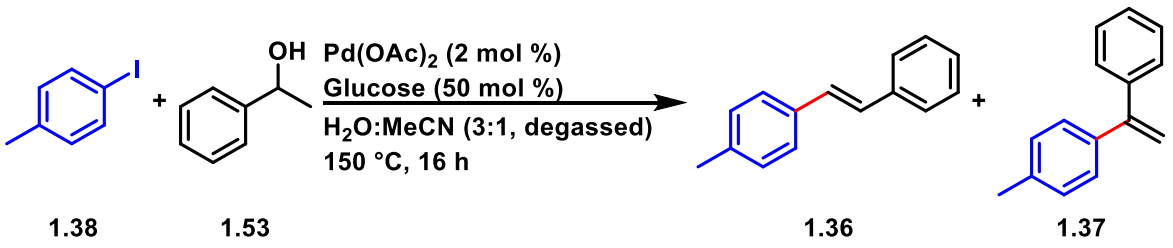
1.3.3 Dehydrative Heck

Having shown that the Mizoroki-Heck reaction can be performed under acidic conditions, an attempt at utilising the acidic nature of the reaction conditions to develop a tandem cross-coupling process was made (Scheme 1.34). It was envisioned that the acidic nature of the solution would promote the elimination of the benzylic alcohol of 1-phenylethanol **1.53** to styrene **1.12** *in situ*, which could then be intercepted by aryl iodide to afford the stilbene derivative.



Scheme 1.34

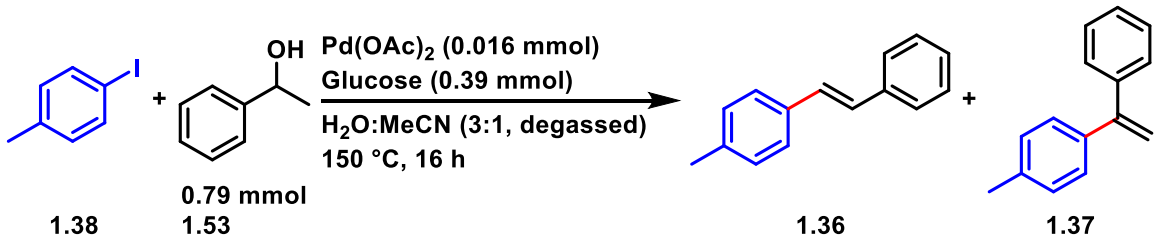
The storage of styrene over a long period of time can be problematic due to its tendency to self-polymerise[47]. Styrene can be made by the dehydration of 1-phenylethanol **1.53** under acidic conditions[48] and so it was theorised that the dehydration of 1-phenylethanol **1.53** would form styrene **1.12** *in situ* which would then cross-couple under the acidic Mizoroki-Heck reaction conditions that has been developed. To test this theory, 1-phenylethanol **1.53** was substituted for styrene **1.12** in a cross-coupling reaction with 4-iodotoluene **1.38** under the acidic Mizoroki-Heck conditions developed previously (Scheme 1.35). It was found that the reaction proceeded as theorised however the isolated yield was lower than that of the reaction with styrene **1.12** at 47%. Both branched **1.37** and linear **1.36** isomers of tolyl-stilbene were isolated from the reaction as was previously seen in the acidic Mizoroki-Heck reaction developed (Section 1.2.2).



Scheme 1.35

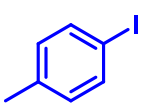
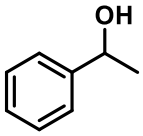
1.3.3.1 Reactant equivalents

Encouraged by the results above, it was decided to try and optimise the process to give an increased yield of cross-coupled product (Scheme 1.36). It was proposed that increasing the quantity of 4-iodotoluene **1.38** to 1.5 equivalents compared to 1-phenylethanol **1.53** would allow the cross-coupling to proceed more efficiently, however, there was little effect on the isolated yield (Scheme 1.36, Table 1.8, Entries 1 vs. 2). After work-up it was found that there was a significant amount of the 4-iodotoluene **1.38** starting material. Therefore the amount of 4-iodotoluene **1.38** was reduced to 0.5 equivalents compared to 1-phenylethanol **1.53**, which resulted in an increased isolated yield of alkenes **1.36**:**1.37** to 83% (Scheme 1.36, Table 1.8, Entry 3)..



Scheme 1.36

Table 1.8: Table of optimisation of reaction equivalents

Entry	Equiv.  1.38	 1.53	Combined Yield (%)	NMR Ratio (**1.36**:**1.37**)
1	1.0	1.0	47	-[a]
2	1.5	1.0	43	69:31
3	0.5	1.0	83	85:15

[a] No crude NMR data collected

1.3.3.2 Temperature

Running the reactions at 150 °C in sealed tubes caused several seals to fail on the reaction vials and so lower temperatures were trialled in an attempt to circumvent this problem (Scheme 1.37, Table 1.9). Unfortunately it was found that lower temperatures resulted in decreased yields, as low as 10% for the reaction at 120 °C, Entry 1, so the temperature was maintained at 150 °C, Entry 4.

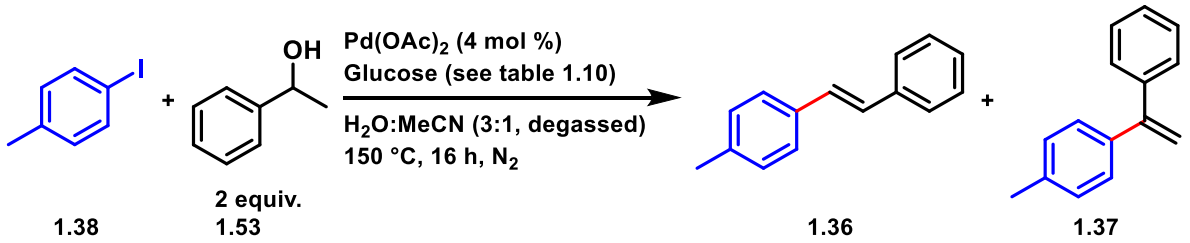
Scheme 1.37

Table 1.9: Table of temperatures investigated for the dehydrative cross-coupling reaction

Entry	Temp.	Combined Yield (%)	NMR Ratio (**1.36**:**1.37**)
1	120 °C	10	82:18
2	130 °C	27	85:15
3	140 °C	53	84:16
4	150 °C	83	85:15

1.3.3.3 Glucose quantities

While an increased quantity of glucose was required when developing the acidic Mizoroki-Heck reaction (*cf.* Section 1.2.2) compared to the work developed previously on sugar derived palladium cross-couplings (*cf.* Section 1.1.3) it was decided that the effect of glucose quantity on the dehydrative cross-coupling would be investigated (Scheme 1.38). In the absence of sugar it was found that the reaction proceeded moderately well achieving 55% yield, this is consistent with high temperature Heck reactions (06DT421) (Scheme 1.38, Table 1.10, Entry 1). Having too little or too much glucose in the reaction medium resulted in a poorer outcome of the reaction compared to that seen in the absence of glucose (Scheme 1.38, Table 1.10, Entries 2, 5 and 6). This is most likely a result of either too little sugar to prevent palladium black formation or too much sugar, which covers all of the palladium catalyst active sites. Keeping the glucose quantity the same as the optimised acidic Mizoroki-Heck reaction afforded the best yield at 83% (Scheme 1.38, Table 1.10, Entry 4).



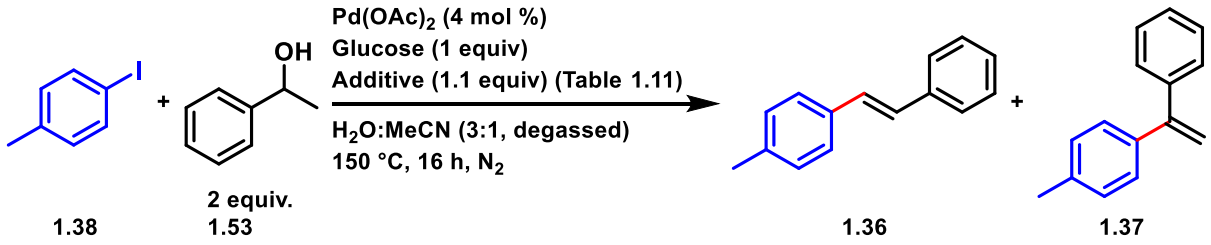
Scheme 1.38

Table 1.10: Table of palladium/glucose ratios for the dehydrative cross-coupling reaction

Entry	Pd /sugar ratio	Yield (%)
1	1:0	55
2	1:2	43
3	1:10	56
4	1:25	83
5	1:50	47
6	1:100	40

1.3.3.4 Additives

Understanding that the dehydration of 1-phenylethanol **1.53** to form styrene **1.12** *in situ* is acid catalysed a range of acids were added to the reaction mixture to determine whether the yield could be increased. (11BKC1327) Using strong acids like hydrochloric acid and sulfuric acid was found to hinder the cross-coupling reaction reducing yields to 52% and 15% respectively (Scheme 1.39, Table 1.11, Entries 2 and 3). It was thought that increasing the availability of the aryl-iodide, by increasing the amount in the reaction, the strong acids might not hinder the reaction as much. While the yield marginally increased for sulfuric acid the yield for hydrochloric acid reaction decreased significantly (Scheme 1.39, Table 1.11, Entries 4 and 5). The addition of formic acid to the reaction mixture increased the yield of the reaction by 10%, Entry 6, when compared to the reaction with no additives present (Scheme 1.39, Table 1.11, Entry 1). In an attempt to reduce the overall material input for the reaction a reduced amount of formic acid was investigated however the yield drastically reduced. Oxidative addition of the aryl-iodide to the active palladium catalyst is understood as the rate limiting step of the Mizoroki-Heck reaction and research has shown that the addition of tetra-butylammonium chloride to cross-coupling reactions increases the rate of this step, unfortunately the addition of this salt reduced the yield significantly (Scheme 1.39, Table 1.11, Entry 8)[49].



Scheme 1.39

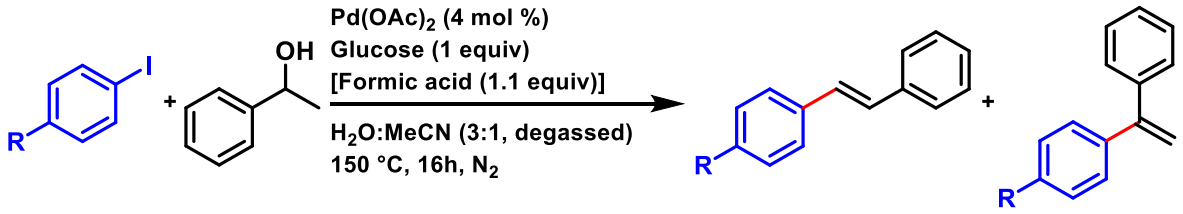
Table 1.11: Table of additives investigated in the acidic Mizoroki-Heck reaction

Entry	Additive	Combined Yield (%)	NMR Ratio (**1.36**:**1.37**)
1	none	83	85:15
2	HCl	52	87:13
3	H_2SO_4	15	83:17
4	HCl	34[a]	84:16
5	H_2SO_4	26[a]	83:17
6	Formic Acid	93	84:16
7	Formic Acid	22[b]	83:17
8	$Bu_4N^+Cl^-$	45	88:12

[a] 0.78 mmol 4-iodotoluene used, [b] 0.1 equiv. formic acid used

1.3.4 Electronic study

With a better understanding of the effect of additives on the system, the effects of electron donating and withdrawing functional groups on the dehydrative cross-coupling were investigated using the developed conditions (Scheme 1.40). As it was unclear as to whether the addition of formic acid was a beneficial or adverse addition to the reaction, all reactions were performed both in the presence and absence of formic acid. The electron donating methoxy moiety **1.17** caused the yield to drop to 67% (Scheme 1.40, Table 1.12, Entry 5) while keeping the ratio of linear to branched isomers relatively similar. The yield of the reaction with the nitro moiety **1.41** (Scheme 1.40, Table 1.12, Entry 3) did not differ from the reaction with 4-iodotoluene **1.38** (Scheme 1.40, Table 1.12, Entry 1), however decreased the ratio of isomers to form 10% of the branched chain isomer. This may be caused by the electron withdrawing nature of the nitro group reducing the viability of the cationic mechanistic pathway. Interestingly the addition of formic acid to the reactions of both methoxy and nitro groups decreased the yield for both reactions (Scheme 1.40, Table 1.12, Entries 4 and 6).



Scheme 1.40

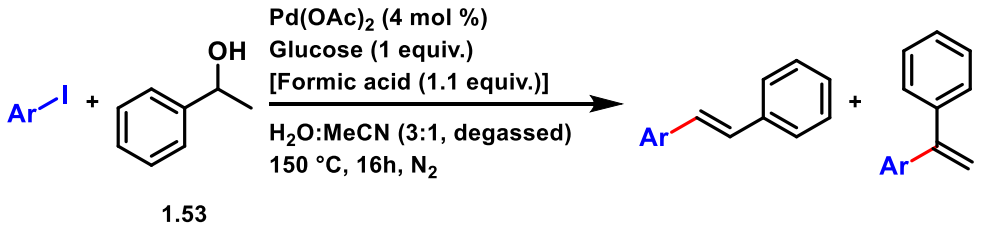
Table 1.12: Table results for the investigation of electronic functional group effects on the dehydrative cross-coupling reaction

Entry	R-group	Combined Yield (%)	NMR Ratio (linear:branched)
1	Me	83	85:15
2	Me [a]	93	84:16
3	NO_2	83	90:10
4	NO_2 [a]	22	90:10
5	OMe	67	88:12
6	OMe [a]	48	86:14

[a] *1.1 equiv. formic acid used*

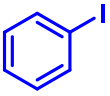
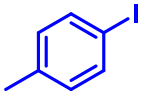
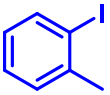
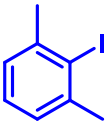
1.3.5 Steric Study

The steric tolerance of the developed dehydrative cross-coupling was then investigated where the yield and ratio of isomer products were examined. Unsubstituted iodobenzene **1.4** reacted moderately well under the reaction conditions yielding 62% but surprisingly produced a very small percentage of branched chain isomer at only 6% (Scheme 1.41, Table 1.13, Entry 1). It is possible the steric hindrance caused by the methyl moiety in 2-iodotoluene **1.39** is the cause of the low 37% yield in this reaction (Scheme 1.41, Table 1.13, Entry 5), however this did not seem to affect the isomer ratio very much when compared to 4-iodotoluene **1.38** (Scheme 1.41, Table 1.13, Entry 3). Similarly the steric hindrance of having 2 methyl moieties flanking the carbon-iodine bond would seem to be the cause for the very poor yield in the reaction with 2,6-dimethyliodobenzene **1.40**, while also restricting the formation of branched chain isomer to 7% (Scheme 1.41, Table 1.13, Entry 7). Unlike with the electronic study (*cf.* Section 1.2.4), the addition of formic acid to the reaction increased the yield of all substrates investigated in this study while also keeping the ratio of isomers produced similar.



Scheme 1.41

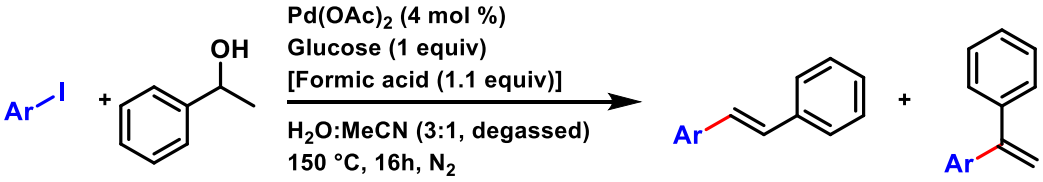
Table 1.13: Table of sterically hindered substrates investigated in the dehydrative cross-coupling reaction

Entry	Ar–I		Combined Yield (%)	NMR Ratio (linear:branched)
1		**1.4**	62	94:6
2			79[a]	93:7
3		**1.38**	83	85:15
4			93[a]	84:16
5		**1.39**	37	87:13
6			78[a]	88:12
7		**1.40**	21	93:7
8			28[a]	93:7

[a] *1.1equiv. formic acid used*

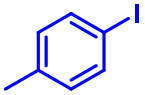
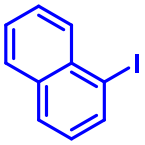
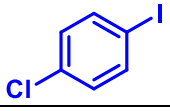
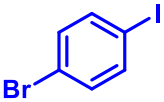
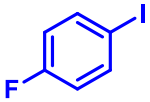
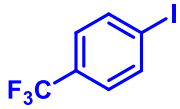
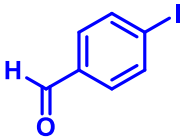
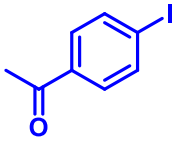
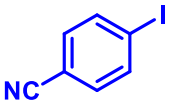
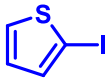
1.3.6 Functional group tolerance

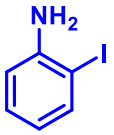
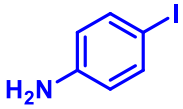
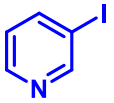
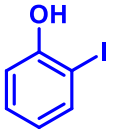
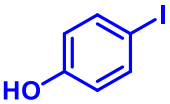
Finally the functional group tolerance of the dehydrative cross-coupling reaction was investigated (Scheme 1.42, Table 1.14). In the reaction involving 1-iodonapthalene the yield did not suffer as a result of the fused ring being in close proximity to the C-I bond (Table 1.14, Entry 3) unlike what was observed for the reaction with 2-iodotoluene (Table 1.14 Entry 5). The yield of the reaction increased in the presence of formic acid as was observed with similar aryl substrates, however the ratio of isomers produced by the reaction saw a significant change of 10% more branched chain isomer produced with the addition of formic acid (Table 1.14, Entry 4). Halogenated substrates were tolerated well with reasonable yields and as seen previously in the acidic Mizoroki-Heck reaction, bromo- substituted compounds did not undergo a bis-reaction (Table 1.14, Entries 5, 7 and 9). With the exception of the chloro- substituted aryl-iodide the yields of the reactions decreased while the ratio of isomers remained the same (Table 1.14, Entries 6, 8 and 10). Trifluoromethyl substituted aryl-iodide saw the largest increase in yield when comparing reactions with and without formic acid where a 20% increase was seen in the presence of formic acid (Table 1.14, Entries 11 and 12). Carbonyl moieties were tolerated well in the reaction, both aldehyde and ketone functional groups producing ≤10% branched chain isomer (Table 1.14, Entries 13-16). The addition of formic acid to these reactions were not similar where an increase in yield was seen for the aldehyde substrate but a dramatic loss of yield was observed in the ketone reaction when performed with formic acid present. Nitrile functional group remained unchanged under the reaction conditions and gave good yields in the absence of formic acid but a decrease in yield was observed in the presence of formic acid (Table 1.14, Entries 17 and 18). Phenolic substrates were not tolerated by the reaction conditions and resulted in starting material being returned from the reaction. The presence of formic acid had no effect on this outcome (Table 1.14, Entries 27-30). Basic nitrogen containing compounds such as aniline and pyridine were also not tolerated well under these reaction conditions, either retuning the starting material or creating a complex NMR spectrum from which no products could be isolated. This was the same outcome for the reaction involving 2-iodothiophene (Table 1.14, Entries 19 and 20).



Scheme 1.42

Table 1.14: Table of substrates investigated in the dehydrative cross-coupling reaction

Entry	Ar =		Combined Yield (%)[a]	Ratio (linear:branched)
1		**1.38**	83	85:15
2			93[b]	84:16
3		**1.54**	90	93:7
4			94[b]	83:17
5		**1.55**	55	85:15
6			62[b]	85:15
7		**1.42**	66	88:12
8			63[b]	88:12
9		**1.43**	60	89:11
10			55[b]	90:10
11		**1.44**	69	89:11
12			89[b]	87:13
13		**1.45**	43	91:9
14			61[b]	93:7
15		**1.46**	83	90:10
16			58[b]	90:10
17		**1.31**	70	90:10
18			51[b]	90:10
19		**1.52**	-	-
20			-	-

Entry	R =		Combined Yield (%)[a]	Ratio (linear:branched)
21		**1.49**	-	-
22			-	-
23		**1.50**	-	-
24			-	-
25		**1.51**	-	-
26			-	-
27		**1.47**	-	-
28			-	-
29		**1.48**	-	-
30			-	-

[a] Combined isolated yields.for both isomers [b] *1.1equiv. formic acid used*

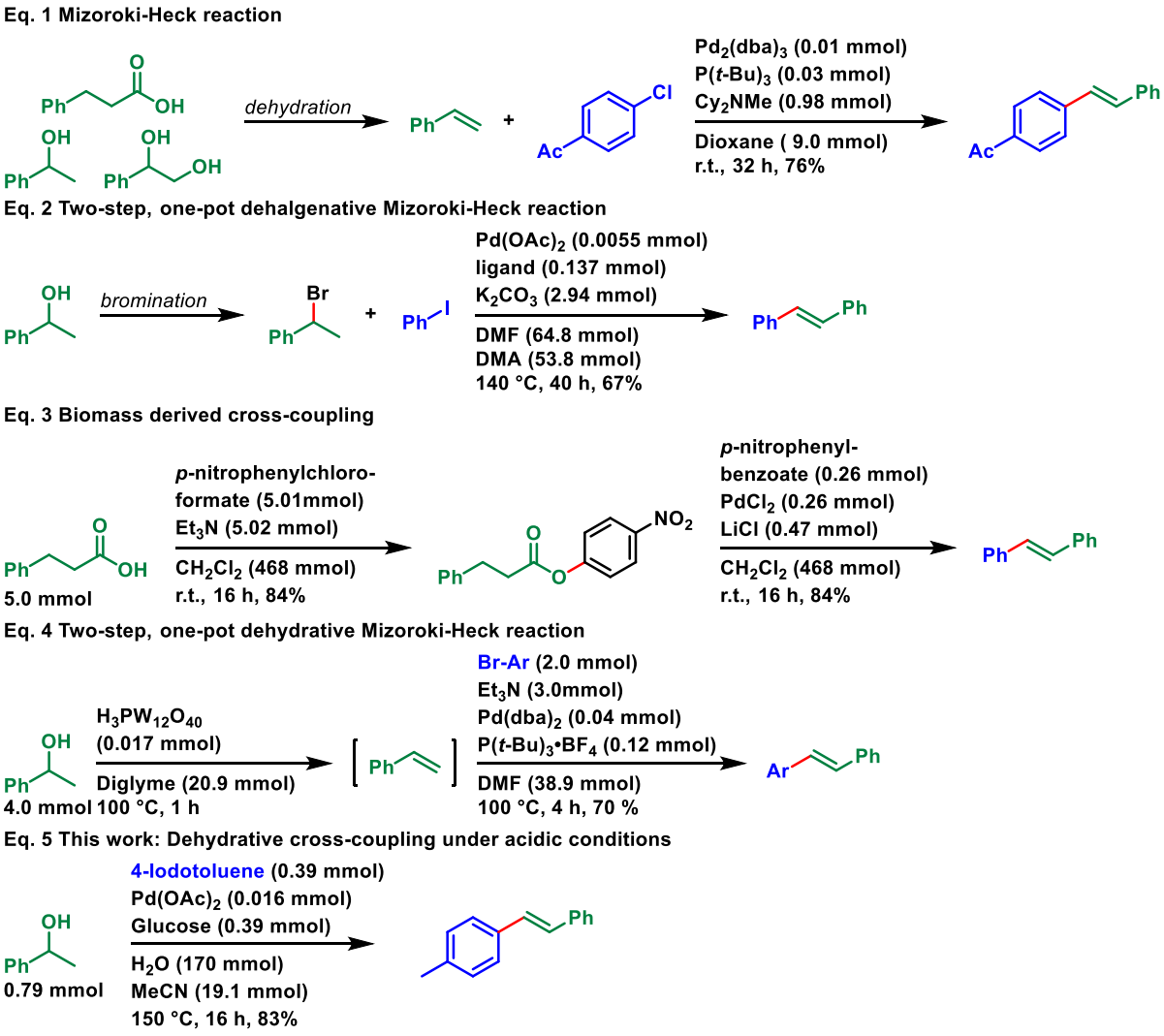
1.4 Molar efficiency

With the dehydrative cross-coupling reaction developed and optimised it was important to compare these conditions with similar cross-coupling reactions. This comparison was done using the method described by Watson *et al*. in which the molar efficiency of a given reaction is calculated based on the molarity of all the reactants and additives of the reaction as well as taking into account the overall yield of the reaction (**Error! Reference source not found.**)[50].

Equation 1.1

$$\text{molar efficiency (Mol. E\%)} = \frac{\text{moles product}}{\text{moles starting material + additives + catalysts + solvents}} \times 100$$

In order to compare the dehydrative cross-coupling reaction developed here several reactions were chosen and their Mol. E% was calculated. During the course of this project a collaboration with Dr Angelis-Dimakis was developed in which an Excel spreadsheet was devised with the aim of automating the calculations that are used to calculate the Mol. E% of the dehydrative cross-coupling reaction and the comparison reactions[39, 51]. In order to standardise work-up procedures several assumptions have been made in the calculator. These assumptions include the use of 100g of silica gel for every 1.0 mmol of material to be purified, as well as the use of 1.0 L of solvent for the first 1.0 mmol and 500 mL for each additional 1.0 mmol (Appendix B, Section 4.2). Four methods for the synthesis of stilbene derivatives from alcoholic or acidic starting materials were examined. Initially methods for the production of styrene from these starting materials were examined. The average Mol. E% of these reactions was then used to determine the Mol. E% of a cross-coupling reaction using mild conditions detailed by Littke and Fu (Scheme 1.43, Eq. 1)[52]. Secondly, several bromination reactions of 1-phenylethanol were examined as 1-bromo-1-phenylethane is the starting material for several dehalogenation cross-coupling reactions. As before the average Mol. E% of the bromination reactions was used to determine the Mol. E% of a cross coupling reaction developed by Saiyed and Bedekar for the synthesis of stilbene derivatives (Scheme 1.43, Eq. 2)[33]. Next the Mol. E% for the 2-step synthesis of stilbene derivatives from the biomass feedstock hydrocinnamic acid reported by Tolman *et al.* was calculated (Scheme 1.43, Eq. 3)[53]. The Mol. E% for the synthesis of stilbene derivatives in a 2-step process developed by Xiao and co-workers where a strong acid is used to dehydrate 1-phenylethanol before excess base is added to allow the cross-coupling reaction to proceed was also determined (Scheme 1.43, Eq. 4)[36]. Finally the work outlined here was also input into the Mol. E% calculator (Scheme 1.43, Eq. 5)[39].



Scheme 1.43

It was found that the Mol. E% for the varying reactions differed significantly where a 250-12000 fold increase in efficiency was found when comparing the method developed here and previously reported 2-step processes for the synthesis of stilbenes from alcohols or carboxylic acids (Table 1.15). In a direct comparison with the 2-step one-pot synthesis developed by Xiao *et al.* a 2 fold increase in Mol. E% was found when using the method developed here.

Table 1.15: Mol. E% comparison

Entry	Mol. $E\%_{total}$ (%)	Fold Difference from Dehydrative Method
Eq. 1	3.6×10^{-5}	510
Eq. 2	1.5×10^{-6}	12,304
Eq. 3	7.3×10^{-5}	254
Eq. 4	0.01	2
Eq. 5	0.02	-

1.5 Dehydrative cross-coupling mechanism

The hypothesis for the mechanism of the dehydrative cross-coupling is based on existing knowledge regarding the Mizoroki-Heck reaction. While standard cross-coupling reactions require base to regenerate the active catalyst it is thought that the glucose present in the reaction medium provides this function (Figure 1.5)[39]. It has been shown that glucose can reduce the palladium pre-catalyst to form the nanoparticles as the active catalyst. This process also produces an equivalent of gluconic acid, the presence of which has been confirmed by mass spectrometry performed on a curtailed reaction. Each glucose unit has multiple reducing equivalents allowing it to regenerate the active catalyst many times before eventually turning into carbon dioxide and water. Once acids begin to form in the reaction medium the dehydration of 1-phenylethanol **1.53** would begin which would then start the desired cross-coupling reaction. As the reaction proceeds a stoichiometric quantity of HI is produced which, in combination with the acid produced by the oxidation of glucose as well as further oxidised products, results in the acidic conditions found during previous investigations in the Camp group. It was found that degassing the solvents was vital for the reaction to proceed. This is thought to be caused by the competing process of Pd^0 oxidation by molecular oxygen in the solvents.

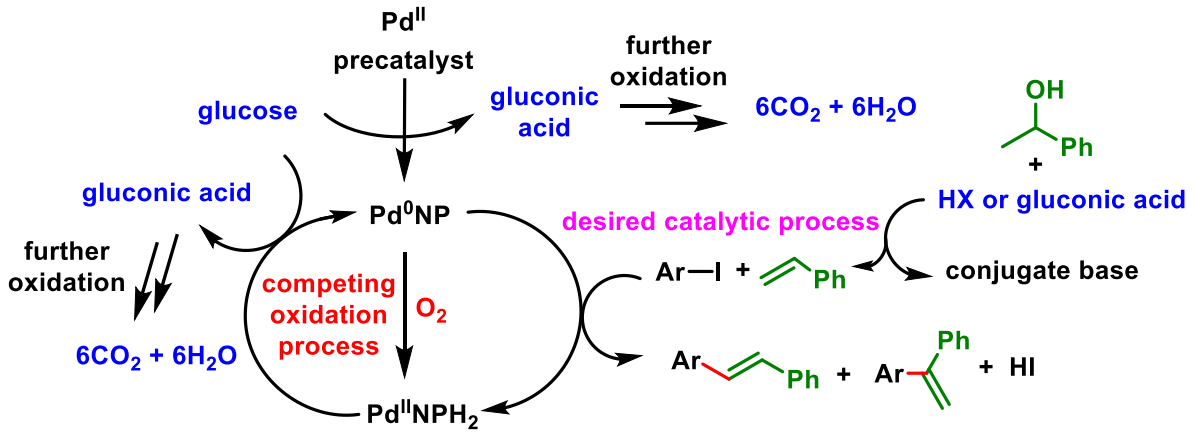


Figure 1.5: Proposed reaction mechanism for the dehydrative cross-coupling reaction

1.6 Conclusions

Preliminary studies within the Camp group found that sugar-derived palladium nanoparticles formed *in situ* were suitable catalysts for several palladium mediated cross-coupling reactions. Several examples of Mizoroki-Heck, Sonogashira and Suzuki-Miyaura reactions were successfully carried out using palladium nanoparticles. During this investigation it was discovered that the reaction media would become acidic over time despite the presence of base, therefore it was prudent to investigate the elimination of base from the reactions altogether. Focussing on the Mizoroki-Heck reaction of iodobenzene and styrene in water and acetonitrile in the presence of palladium(II) acetate and glucose, optimisation found that the ideal palladium:glucose ratio was 1:25 at 150 °C. In addition, degassed solvents were found to be crucial to the success of the reaction due to competing oxidation of the palladium catalyst. Acidic additives were investigated within the reaction, however, they were found to be detrimental to the reaction resulting in low yields or no reaction.

During the optimisation of the Mizoroki-Heck reaction under acidic conditions, it was apparent that the desired product, stilbene, was present as an inseparable mixture of linear (major) and branched chain isomers, each having a characteristic alkene peak in the ^{1}H NMR. The isomers could however be separated from 4-iodotoluene by automated column chromatography using a Biotage Isolera system. Using the developed acidic Mizoroki-Heck conditions a range of sterically different aryl-iodides was reacted with styrene, as the aryl iodides became more hindered the yield of product was reduced. The distribution of isomers continued to favour the linear product as the major isomer, however, there was no observed pattern to the distribution. The electronic tolerance of the reaction was evaluated, and electron rich and electron deficient reagents were found to react in excellent yields. A wide range of functional groups were then investigated in the reaction. It was found that the introduction of an additional halogen on the aryl-iodide worked well in the reaction, and the other halogen was maintained rather than reacting. Carbonyl groups were also tolerated, however, phenolic, nitrile-containing and anilinic reagents proved troublesome in the reaction and provided no indication of products in the crude ^{1}H NMR spectra and no product could be isolated. In a similar manner the reactions conducted using iodoheteroaromatics also provided no evidence of desired product. The use of an aryl-bromide as a replacement for iodine based starting materials was attempted, however, only starting material was recovered from the reaction.

In order to utilise the acidic nature of the developed Mizoroki-Heck conditions, a tandem dehydrative cross-coupling reaction was attempted using 1-phenylethanol as a replacement for

styrene. The reaction with 4-iodotoluene proceeded as expected but in a reduced yield. The reaction conditions were optimised further by reduction the equivalents of aryl-iodide (0.5 equiv.) with respect to 1-phenylethanol (1 equiv.). The temperature of the reaction was also investigated, however, reduction in temperature resulted in a large reduction in yield. The palladium:glucose ratio was also at its optimum at 1:25, where increasing and decreasing the amount of glucose had a detrimental effect on the yield. Acidic additives were further investigated to aid dehydration, addition of formic acid (1.1 equiv.) was found to increase the yield. TBAC was employed to try and aid oxidative addition however this had a negative impact on the reaction.

Using the optimised conditions, a range of aryl-iodides with varying electronic and steric functionality were reacted with 1-phenylethanol both with and without formic acid present. Electron donating and withdrawing substituents resulted in an overall reduction in yield when compared with 4-iodotoluene, further reduction to the yield was observed in the presence of formic acid. The addition of formic acid to alkyl aryl-iodides used to investigate sterically different compounds was found to have the opposite effect, with all compounds showing an increase in yield. Interestingly, the product from the reaction of 2,6-dimethyliodobenzene was successfully isolated. Additional investigation into the functional group tolerance found an array of functionality could be introduced through this method including halogenated aryl-iodides, naphthyl, carbonyl and nitrile substituents in modest to good yields. In a similar manner to the acidic Mizoroki-Heck reaction, phenolic, anilinic and heterocyclic substituents failed to afford any isolable products. Finally, the molar efficiency of the dehydrative Mizoroki-Heck reaction was calculated by an in house Excel-based calculator and compared against several standard conditions and found to have a 250-12000 fold increase in efficiency.

Thus, two novel acidic Mizoroki-Heck protocols have been developed that use either styrene or 1-phenylethanol as coupling partners. The dehydrative Mizoroki-Heck process has led to an increase in molar efficiency when compared against existing two-step protocols that used alternative feedstocks.

1.7 Experimental

1.7.1 Equipment and reagents

Unless otherwise stated, reagents were used as supplied. Reagents were purchased from Alfa Aesar, Fluorochem, and Sigma Aldrich.

NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H 400 MHz and ^{13}C 100 MHz). Coupling constants are given in Hz.

Accurate mass measurements were obtained from the IPOS Mass Spectrometry Service at the University of Huddersfield. Single crystal studies were recorded on a Bruker D8 Venture diffractometer with a Dual IμS Microfocus Sources using Mo and/or Cu radiation. The temperature of data collection was 100K.

Melting point ranges were determined in capillary tubes using a Stuart SMP10 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Nicolet 380 Spectrum Spotlight system equipped with a diamond probe ATR attachment (neat sample). TLC was performed on Merck TLC Aluminium sheets, silica gel 60 F_{254} using a range of eluent systems of differing polarity. Flash column chromatography separations were performed on Aldrich, 35-70μ, 60A silica gel or Fluorochem 40-63μ, 60A silica gel or purified using a Biotage® Isolera 4 Automated Purification System equipped with Biotage® Snap Ultra Biotage® HP-Sphere™ 25μm cartridges.

1.7.2 Chapter 1 experimental

Where isomers were formed in the acidic and dehydrative cross coupling reactions efforts were made to isolate each isomer. In most cases the major isomer, the linear chain, was isolated and experimental data is written as such. When enough sample of the minor isomer, the branched chain, was also isolated and the experimental data has also been provided. Where neither isomer could be isolated the experimental data is provided as a mixture of isomers.

1.7.3 General methods

Method 1[38]; To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (5.0 mg, 0.032 mmol) in acetonitrile / water (1:3, 4 mL) at r.t. were added triethylamine (0.14 mL, 1.0 mmol), aryl-iodide (0.78 mmol) and ethyl acrylate or styrene (0.97 mmol). The vial was then sealed and the mixture heated at 100 °C for 16 h. The mixture was cooled and diluted with water (10 mL) before extraction with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane).

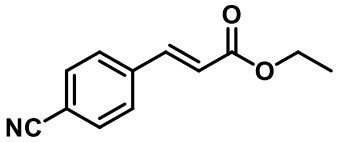
Method 2[39]; To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and aryl-iodide (0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled and diluted with water (10 mL) before extraction with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was passed through a silica plug (5% EtOAc in hexane) and further purified by flash column chromatography.

Method 3[39]; To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and aryl-iodide (0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 ml) at r.t. was added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled and diluted with water (10 mL) before extraction with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was passed through a silica plug (5% EtOAc in hexane) and further purified by flash column chromatography.

Method 4[39]; To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and aryl-iodide (0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 ml) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled and diluted with water (10 mL) before extraction with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was passed through a silica plug (5% EtOAc in hexane) and further purified by flash column chromatography.

1.7.4 Chapter 1 Compound Experimental

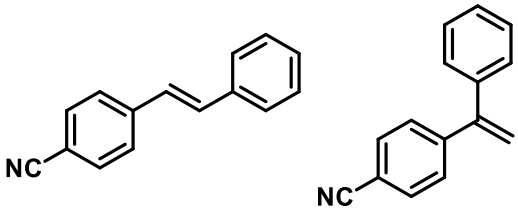
1.7.4.1 Ethyl (*E*)-3-(4-cyanophenyl)acrylate 1.56



Method 1: From 4-iodobenzonitrile (178 mg) and ethyl acrylate (106 µL) as a white solid (37 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.59 (m, 5H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400MHz, $CDCl_3$): δ166.1, 142.1, 138.8, 132.7, 128.4, 121.9, 118.4, 113.3, 61.0, 14.3; IR (neat): 2989, 2921, 2226, 1705, 1637 cm^{-1}. HRMS (TOF) *m/z* $[C_{12}H_{12}NO_2]^+$ calcd. for, 202.0863; found 202.0861.

1.7.4.2 (*E*)-4-Styrylbenzonitrile 1.57 and 4-(1-phenylvinyl)benzonitrile 1.58



Method 1: From 4-iodobenzonitrile (178 mg) and styrene (112 µL) as a white solid (58 mg, 36%, **1.57**).

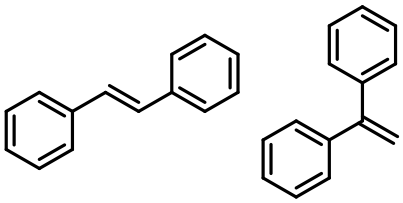
Method 3: From 4-iodobenzonitrile (89 mg) and 1-phenylethanol (95 µL) as a white solid (56 mg, 70%, 90:10 **1.57**:**1.58**).

Method 4: From 4-iodobenzonitrile (89 mg) and 1-phenylethanol (95 µL) as a white solid (41 mg, 51%, 90:10 **1.57**:**1.58**).

(*E*)-4-Styrylbenzonitrile **1.57**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-55 (m, 6H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37-7.33 (m, 1H), 7.24 (d, *J* = 16.4 Hz, 1H), 7.11 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 136.3, 132.5 (2 × C), 132.4, 128.9 (2 × C), 128.7, 126.93 (2 × C), 126.88 (2 × C), 126.7, 119.1, 110.6; IR (neat): 3023, 2920, 2854, 2223, 1600, 1503, 972, 823, 756, 689 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{15}H_{11}N]^+$, 205.0886; found 205.0890.

1.7.4.3 (*E*)-Stilbene 1.13 and 1,1-diphenylethene 1.35



Method 2: From iodobenzene (87 µL) and styrene (87 µL) as a white solid (136 mg, 97%, 88:12 **1.13**:**1.57**).

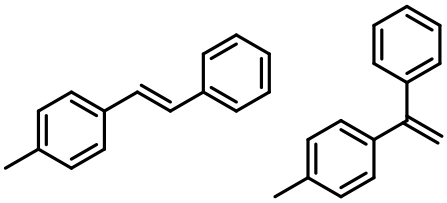
Method 3: From iodobenzene (44 µL) and 1-phenylethanol (95 µL) as a white solid (44 mg, 62%, 88:12 **1.13**:**1.57**).

Method 4: From iodobenzene (44 µL) and 1-phenylethanol (95 µL) as a white solid (55 mg, 79%, 87:13 **1.13**:**1.57**).

(*E*)-Stilbene **1.13** and 1,1-diphenylethene **1.57**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 4H), 7.45-7.39 (m, 5.57H), 7.35-7.31 (m, 2H), 7.18 (s, 2H), 5.54 (s, 0.26H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 128.8, 127.7, 126.6; IR ($CHCl_3$): 3021, 2915, 1494, 1451, 983, 808, 688 cm^{-1}; HRMS (APPI) *m/z* calcd. for $C_{14}H_{12}$, 180.0934; found 180.0932.

1.7.4.4 (*E*)-1-Methyl-4-styrylbenzene 1.36 and 1-(4-methylphenyl)-1-phenylethene 1.37



Method 2: From 4-iodotoluene (170 mg) and styrene (87 µL) as a white solid (80 mg, 42%, 88:12 **1.36**:**1.37**).

Method 3: From 4-iodotoluene (85 mg) and 1-phenylethanol (95 µL) as a white solid (63 mg, 83%, 85:15 **1.36**:**1.37**).

Method 4: From 4-iodotoluene (85 mg) and 1-phenylethanol (95 µL) as a white solid (67 mg, 89%, 84:16 **1.36**:**1.37**).

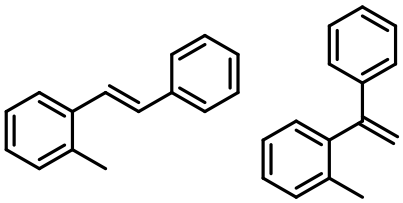
(*E*)-1-Methyl-*trans*-stilbene **1.36**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.26 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 16.4 Hz, 1H), 7.08 (d, *J* = 16.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (2 × C), 134.6, 129.4 (2 × C), 128.7 (2 × C), 128.6, 127.7, 127.4, 126.5 (2 × C), 126.4 (2 × C), 21.3; IR (neat): 3020, 2915, 1593, 1508, 1493, 1448, 969, 803, 706 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{15}H_{14}]^{+}$, 194.1090; found 194.1087.

1-Methyl-4-(1-phenylvinyl)benzene **1.37**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.32 (m 5H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.44 (d, *J* = 1.1 Hz, 2H), 5.41 (d, *J* = 1.2 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 141.7, 138.6, 137.5, 128.9 (2 × C), 128.3 (2 × C), 128.2 (2 × C), 128.1 (2 × C), 127.6, 113.7, 21.2.

1.7.4.5 (*E*)-2-Methyl-trans-stilbene 1.59 and 1-methyl-2-(1-phenylvinyl)benzene 1.60



Method 2: From 2-iodotoluene (99 µL) and styrene (87 µL) as a white solid (71 mg, 47%, 88:12 **1.59**:**1.60**).

Method 3: From 2-iodotoluene (50 mg) and 1-phenylethanol (95 µL) as a white solid (28 mg, 37%, 87:13 **1.59**:**1.60**).

Method 4: From 2-iodotoluene (50 mg) and 1-phenylethanol (95 µL) as a white solid (59 mg, 78%, 88:12 **1.59**:**1.60**).

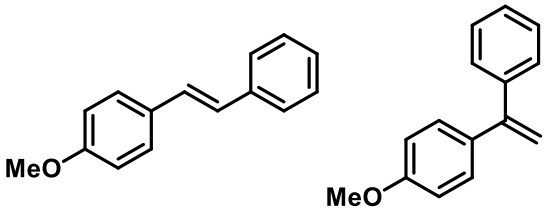
(*E*)-2-Methyl-*trans*-stilbene **1.59**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.1 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 3H), 7.37-7.23, (m, 5H), 7.06 (d, *J* = 16.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.5, 135.9, 130.5, 130.1, 128.8 (2 × C), 127.7, 127.6, 126.64 (2 × C), 126.61, 126.3, 125.4, 20.0; IR ($CHCl_3$): 3023, 2923, 1540, 1494, 959, 756, 711 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{15}H_{14}]^{+}$, 194.1090; found 194.1088.

1-Methyl-2-(1-phenylvinyl)benzene **1.60**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 9H), 5.77 (d, *J* = 1.3 Hz, 1H), 5.22 (d, *J* = 1.3 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.5, 130.5, 130.1, 128.8 (2 × C), 127.7, 127.6, 126.64 (2 × C), 126.61, 126.3, 125.4, 20.0.

1.7.4.6 (*E*)-1-Methoxy-trans-stilbene 1.61 and 1-methoxy-4-(1-phenylvinyl)benzene 1.62



Method 2: From 4-iodoanisole (183 mg) and styrene (87 µL) as a white solid (152 mg, 93%, 84:16 **1.61**:**1.62**).

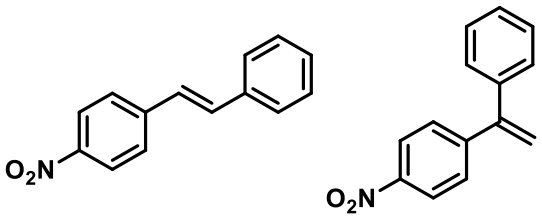
Method 3: From 4-iodoanisole (91 mg) and 1-phenylethanol (95 µL) as a white solid (64 mg, 67%, 88:12 **1.61**:**1.62**).

Method 4: From 4-iodoanisole (91 mg) and 1-phenylethanol (95 µL) as a white solid (43 mg, 48%, 86:14 **1.61**:**1.62**).

(*E*)-1-Methoxy-*trans*-stilbene **1.61**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.48 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28-7.22 (m, 2H), 7.10 (d, *J* = 16.3 Hz, 1H), 7.00 (d, *J* = 16.3 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 137.7, 130.2, 128.7 (2 × C), 128.2, 127.7 (2 × C), 127.2, 126.6, 126.3 (2 × C), 114.1 (2 × C), 55.3; IR ($CHCl_3$): 3022, 3002, 2933, 2836, 1600, 1508, 1266, 1028, 811, 686 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{15}H_{14}O]^+$, 210.1039; found 210.1039.

1.7.4.7 (*E*)-4-Nitro-trans-stilbene 1.63 and 1-nitro-4-(1-phenylvinyl)benzene 1.64



Method 2: From 4-iodonitrobenzene (194 mg) and styrene (87 µL) as a yellow solid (194 mg, 90%, 92:8 **1.63**:**1.64**).

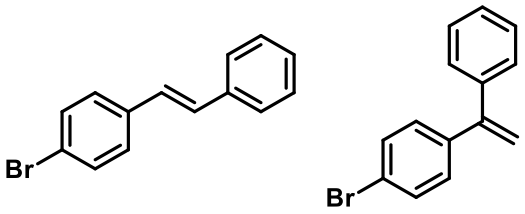
Method 3: From 4-iodonitrobenzene (97 mg) and 1-phenylethanol (95 µL) as a yellow solid (62 mg, 83%, 90:10 **1.63**:**1.64**).

Method 4: From 4-iodonitrobenzene (97 mg) and 1-phenylethanol (95 µL) as a yellow solid (19 mg, 22%, 90:10 **1.63**:**1.64**).

(*E*)-1-Nitro-*trans*-stilbene **1.63**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.36-7.32 (m, 1H), 7.28 (d, *J* = 16.3 Hz, 2H), 7.15 (d, *J* = 16.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 143.9, 136.2, 133.3, 128.91 (2 × C), 128.86, 127.0 (2 × C), 126.9 (2 × C), 126.3, 124.2 (2 × C); IR ($CHCl_3$): 3089, 2920, 1593, 1569, 1505, 1336, 1105, 849, 692 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{14}H_{11}NO_2]^+$, 225.0784; found 225.0778.

1.7.4.8 (*E*)-4-Bromo-trans-stilbene 1.65 and 1-(4-bromophenyl)-1-phenylethene 1.66



Method 2: From 4-iodobromobenzene (221 mg) and styrene (87 µL) as a white solid (176 mg, 87%, 86:14 **1.65**:**1.66**).

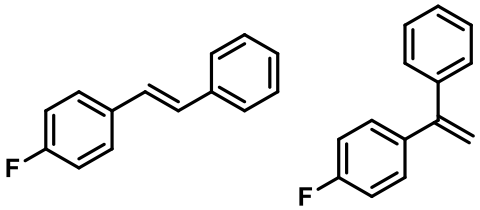
Method 3: From 4-iodobromobenzene (110 mg) and 1-phenylethanol (95 µL) as a white solid (67 mg, 66%, 88:12 **1.65**:**1.66**).

Method 4: From 4-iodobromobenzene (110 mg) and 1-phenylethanol (95 µL) as a white solid (64 mg, 63%, 88:12 **1.65**:**1.66**).

(*E*)-4-Bromo-*trans*-stilbene **1.65**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.46 (m, 4H), 7.40-7.34 (m, 4H), 7.30-7.25 (m, 1H), 7.07 (dd, *J* = 16.4 Hz, *J* = 28.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 136.3, 131.8, 129.4, 128.8, 128.0, 127.9, 127.4, 126.6121.3; IR ($CHCl_3$): 3025, 2921, 2852, 1485, 1072, 964, 840, 688 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{14}H_{11}{}^{79}Br]^+$, 258.0039; found 258.0029.

1.7.4.9 (*E*)-4-Fluoro-trans-stilbene 1.67 and 1-fluoro-4-(phenylvinyl)benzene 1.68



Method 2: From 4-fluoroiodobenzene (90 µL) and styrene (87 µL) as a white solid (83 mg, 60%, 94:6 **1.67**:**1.68**).

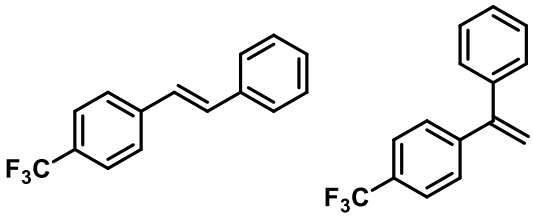
Method 3: From 4-fluoroiodobenzene (45 µL) and 1-phenylethanol (95 µL) as a white solid (60 mg, 60%, 89:11 **1.67**:**1.68**).

Method 4: From 4-fluoroiodobenzene (45 µL) and 1-phenylethanol (95 µL) as a white solid (42 mg, 55%, 90:10 **1.67**:**1.68**).

(*E*)-4-Fluoro-*trans*-stilbene **1.67**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.48 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.30 Hz, 1H), 7.12-7.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.3 Hz), 137.2, 133.5 (d, *J* = 3.4 Hz), 128.7, 128.5 (d, *J* = 2.4 Hz), 128.0 (d, *J* = 8.0 Hz), 127.7, 127.5, 126.5, 115.6 (d, *J* = 21.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.2 (s, 1F); IR ($CHCl_3$): 3022, 2923, 2851, 1592, 1504, 1226, 999, 822, 751 cm^{-1}; HRMS (APPI) *m/z* calcd. for $C_{14}H_{12}$, 198.0839; found 198.0835

1.7.4.10 (*E*)-4-Trifluoromethyl-trans-stilbene 1.69 and 1-(1-phenylvinyl)-4-trifluoromethyl)benzene 1.70



Method 2: From 1-iodo-4-(trifluoromethyl)benzene (114 µL) and styrene (87 µL) as a white solid (172 mg, 89%, 87:13 **1.69**:**1.70**).

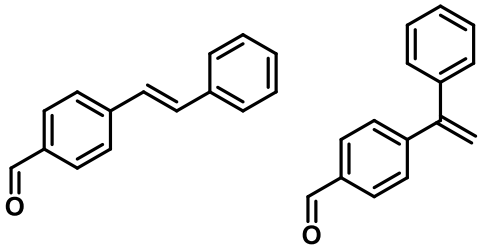
Method 3: From 1-iodo-4-(trifluoromethyl)benzene (57 µL) and 1-phenylethanol (95 µL) as a white solid (67 mg, 89%, 87:13 **1.69**:**1.70**).

Method 4: From 1-iodo-4-(trifluoromethyl)benzene (57 µL) and 1-phenylethanol (95 µL) as a white solid (86 mg, 89%, 87:13 **1.69**:**1.70**).

(*E*)-4-Trifluoromethyl-*trans*-stilbene **1.69**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.59 (m, 4H), 7.55 (d, *J* = 7.04 Hz, 2H), 7.41 (t, *J* = 7.48 Hz, 2H), 7.33 (t, *J* = 7.28 Hz, 1H), 7.21 (d, *J* = 16.4 Hz, 1H), 7.13 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 136.6, 131.2, 129.7, 129.4, 129.1, 128.8, 127.1, 126.8, 126.6, 125.7 (q, 2 × C), 122.9, 123.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 (s, 3F); IR ($CHCl_3$): 3028, 2928, 2854, 1612, 1450, 1321, 1164, 1105, 1066, 843, 756, 692 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{15}H_{11}F_3]^+$, 248.0807; found 248.0809.

1.7.4.11 (*E*)-4-Styrylbenzaldehyde 1.71 and 4-(1-phenylvinyl)benzaldehyde 1.72



Method 2: From 4-iodobenzaldehyde (170 mg) and styrene (87 µL) as a white solid (63 mg, 39%, 90:10 **1.71**:**1.72**).

Method 3: From 4-iodobenzaldehyde (85 mg) and 1-phenylethanol (95 µL) as a white solid (35 mg, 43%, 91:9 **1.71**:**1.72**).

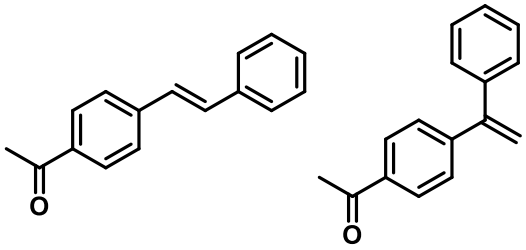
Method 4: From 2-iodotoluene (50 mg) and 1-phenylethanol (95 µL) as a white solid (50 mg, 61%, 93:7 **1.71**:**1.72**).

(*E*)-4-Styrylbenzaldehyde **1.71**

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34-7.25 (m, 2H), 7.15 (t, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 143.4, 136.6, 135.3, 132.2, 130.3, 128.9, 128.5, 127.3, 126.9 (2 × C); IR ($CHCl_3$): 3028,

2820, 2729, 1692, 1590, 1209, 1166, 968, 816, 759, 688 cm^{-1}; HRMS (Dual ESI) *m/z* calcd. for $[C_{15}H_{13}O]^+$, 209.0961; found 209.0961.

1.7.4.12 (*E*)-1-(4-Styrylphenyl)ethan-1-one 1.73 and 1-(4-(1-phenylvinyl)phenyl)ethan-1-one 1.74



Method 2: From 1-(4-iodophenyl)ethan-1-one (78 mg) and styrene (87 µL) as a white solid (78 mg, 45%, 93:7 **1.73**:**1.74**).

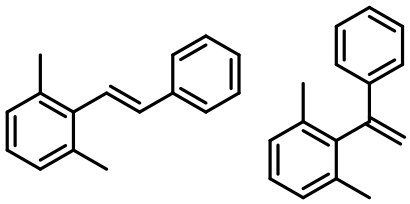
Method 3: From 1-(4-iodophenyl)ethan-1-one (50 mg) and 1-phenylethanol (95 µL) as a white solid (50 mg, 83%, 90:10 **1.73**:**1.74**).

Method 4: From 1-(4-iodophenyl)ethan-1-one (50 mg) and 1-phenylethanol (95 µL) as a white solid (50 mg, 58%, 90:10 **1.73**:**1.74**).

(*E*)-1-(4-Styrylphenyl)ethan-1-one **1.73**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33-7.29 (m, 1H), 7.26-7.22 (m, 1H), 7.14 (d, *J* = 16.4 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 136.7, 136.0, 131.5, 128.9 (2 × C), 128.8 (2 × C), 128.3, 127.5, 126.8 (2 × C), 126.5 (2 × C), 26.6; IR ($CHCl_3$): 3010, 2922, 2853, 1673, 1633, 1410, 1356, 1260, 999, 843, 753, 688, 610 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{16}H_{14}O]^+$, 222.1039; found 222.1039.

1.7.4.13 (*E*)-2,6-Dimethyl-trans-stilbene 1.75 and 1-(2,6-dimethylphenyl)-1-phenylethene 1.76



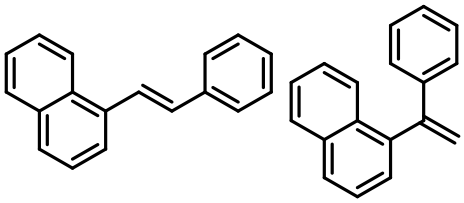
Method 3: From 2-iodo-1,3-dimethylbenzene (57 µL) and 1-phenylethanol (95 µL) as a white solid (17 mg, 21%, 93:7 **1.75**:**1.76**).

Method 4: From 2-iodo-1,3-dimethylbenzene (57 µL) and 1-phenylethanol (95 µL) as a white solid (23 mg, 28%, 93:7 **1.75**:**1.76**).

(*E*)-2,6-Dimethyl-*trans*-stilbene **1.75**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.17-7.11 (m, 4H), 6.64 (d, *J* = 16.8 Hz, 1H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.0, 136.3 (2 × C), 134.0, 128.7 (2 × C), 127.7 (2 × C), 127.6, 127.0, 126.8, 126.3 (2 × C), 21.1 (2 × C); IR ($CHCl_3$): 3023, 2922, 2853, 1595, 1464, 968, 766, 690 cm^{-1}; HRMS (APPI) *m/z* calcd. for $[C_{16}H_{16}]^+$, 208.1247; found 208.1248.

1.7.4.14 (*E*)-1-Styrylnaphthalene 1.77 and 1-(1-phenylethenyl)naphthalene 1.78



Method 3: From 1-iodonaphthalene (57 µL) and 1-phenylethanol (95 µL) as a white solid (45 mg, 90%, 93:17 **1.77**:**1.78**).

Method 4: From 1-iodonaphthalene (57 µL) and 1-phenylethanol (95 µL) as a white solid (85 mg, 94%, 83:17 **1.77**:**1.78**).

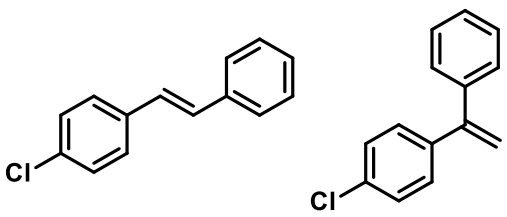
(*E*)-1-Styrylnaphthalene **1.77**

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.3 Hz, 1H), 7.93-7.88 (m, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.58-7.50 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 3H), 7.34-7.31 (m, 1H), 7.18 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.1, 133.8, 131.8, 131.4, 128.8 (2 × C), 128.7, 128.1, 127.8, 126.7 (2 × C), 126.1, 125.9, 125.8, 125.7, 123.8, 123.; IR ($CHCl_3$): 3056, 2928, 2852, 1493, 1263, 959, 774, 734, 692 cm^{-1}; HRMS (*m/z*) [M] calcd. for $[C_{18}H_{14}]^+$, 230.1090; found 230.1089.

1-(1-Phenylethenyl)naphthalene **1.78**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86, 7.84 (m 2H), 7.77-7.75 (m, 1H), 7.51-7.48 (m, 1H), 7.44-7.41 (m, 2H), 7.34-7.30 (m, 3H), 7.27-7.24 (m, 3H), 5.98 (d, *J* = 1.4 Hz, 2H), 5.39 (d, *J* = 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7148.3, 141.1, 139.8, 133.7, 131.9, 128.4 (2 × C), 128.2, 128.0, 127.7, 127.2, 126.6 (2 × C), 126.4, 125.9, 125.7, 125.4, 116.3.

1.7.4.15 (*E*)-1-Chloro-4-styrylbenzene 1.79 and 1-chloro-4-(1-phenylvinyl)benzene 1.80



Method 3: From 4-chloroiodobenzene (93 mg) and 1-phenylethanol (95 µL) as a white solid (46 mg, 55%, 85:15 **1.79**:**1.80**).

Method 4: From 4-chloroiodobenzene (93 mg) and 1-phenylethanol (95 µL) as a white solid (52 mg, 62%, 85:15 **1.79**:**1.80**).

(*E*)-1-Chloro-4-styrylbenzene **1.79**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.4 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.40-7.27 (m, 5H), 7.12-7.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.9, 133.2, 129.3, 128.9 (2 × C), 128.8 (2 × C), 127.9, 127.7, 127.4, 126.6; IR ($CHCl_3$): 3055, 2987, 2928, 1558, 1540, 1264, 730, 701, 669 cm^{-1}; GCMS (EI) *m/z* calcd. for $[C_{14}H_{11}{}^{35}Cl]^+$, 214.1; found 214.0.

Chapter 2

Synthesis of ureas, amides and carbamates in the bio-available solvent Cyrene™

Chapter 2: Cyrene™: synthesis of ureas, amides and carbamates in the bio-available solvent Cyrene™

2.1 Introduction

2.1.1 Solvents

Solvents are of vital importance in chemistry, whether used in chemical reactions or in the purification process[54, 55]. Solvents are chosen based on their properties for example solubility, boiling points and polarity. Despite having many positive aspects, many solvents also have undesirable toxic and environmental properties. To reduce the environmental effects of toxic solvents several solvent selection guides have been created by various companies to highlight alternate solvents which can be used. For example, GlaxoSmithKline's solvent selection guide highlights solvents with major problems associated with them (red) and displays alternatives that can be used as replacements (Figure 2.1). Although this resource works well for some types of solvents, such as alcohols that have several green options, one classification that does not have many green alternatives are the dipolar aprotic solvents. These solvents, like *N*-methylpyrrolidine (NMP) and dimethyl formamide (DMF), have high boiling points and do not possess an acidic proton. Solvents with these properties are typically good for S_N2 type reactions as the reaction substrates are able to dissolve in the solvent without the solvent interfering with the hydrogen bonding of the reaction. Despite these valuable properties, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation from the European Union has begun to limit the production and use of these solvents due to their toxicity[56].

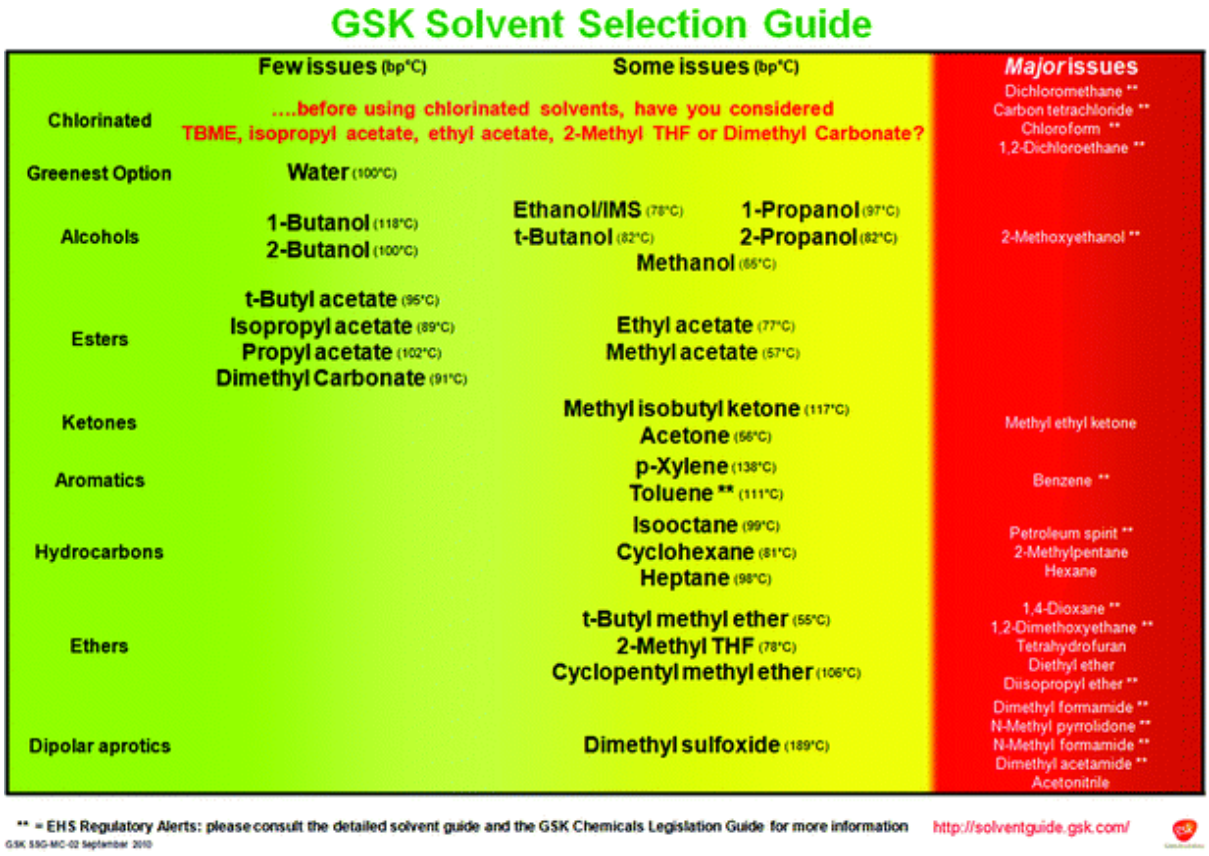


Figure 2.1: GSK solvent selection guide

2.1.2 Green solvents

The principles of green solvents are that they are liquids that are not harmful to the environment or human health and hold very low toxicity[57]. Hallett and co-workers[58] split green solvents into 4 directions; 1) substitution of hazardous solvents with solvents that show better environmental, health and safety, for example swapping methanol with ethanol[59], 2) using solvents produced from renewable biomass, for example replacing tetrahydrofuran with 2-methyltetrahydrofuran[60], 3) using supercritical fluids, for example the use of supercritical CO_2 in the synthesis of heterocyclic compounds[61] and 4) using ionic liquids, for example the use as a solvent for polymerisation processes[62].

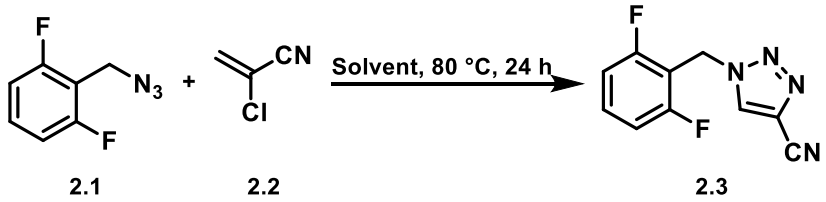
2.1.2.1 Water

Water is seen as the most environmentally friendly and safest solvent that can be used in chemical processing[63]. The properties of water are what make it a valuable solvent such as its dipole, ability to hydrogen bond, high boiling point and non-toxic nature (Table 2.1). The dipole present in water produces a large dissociation constant, which allows water to dissolve ionic compounds very well. This however also makes water a good nucleophile, therefore it unsuitable as a solvent for reactions involving compounds with functional groups that are susceptible to nucleophilic attack. In addition to this, there are many compounds which react violently when they come into contact with water producing toxic or highly flammable gasses[64]. Water has a high specific heat capacity allowing it to hold a stable temperature due to the need to apply a lot of energy to increase the temperature. Water also has a high boiling point allowing high temperature reactions to occur but also a high freezing/melting point so reactions which need to occur at dry ice temperatures cannot happen in water.

Table 2.1: Selected properties of water at 25 °C and 100 °C

Property	25 °C	100 °C
Density ρ (g/dm^3)	1001	962.9
Dynamic viscosity η (mPa s)	0.89	0.28
Dissociation constant pK_w	13.99	12.25
Specific heat capacity C_p (kJ/kg K)	4.15	4.19

The use of water in place of an organic solvent was utilised by Novartis in the synthesis of 1-substituted-4-cyano-1,2,3-triazoles from azides, such as 2-(axidomethyl)-1,3-difluorobenzene **2.1** and 2-chloroacrylonitrile **2.2**[65a]. During a solvent selection study for the synthesis of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carbonitrile **2.3** it was found that ethanol, n-heptane and toluene afford the desired product in moderate yields (Scheme 2.1, Table 2.2)[65]. Either performing the reaction neat or using DMF provided the desired product in much higher yields however the best isolated yield was found in the aqueous bi-phasic reaction (Table 2.2). It was found in this case that HCl produced as a by-product interfered with the reaction and so using water separated the HCl from the organic phase where the reaction was taking place. Isolation of products can sometimes be problematic, in this example the product precipitated from the reaction mixture so could be easily filtered, however it was necessary to wash the product with copious amounts of cyclohexane, followed by drying under vacuum at 60 °C. The yield was also increased by seeding the reaction mixture with previously recovered material to promote precipitation. The use of water to form bi-phasic solvent mixtures can exploit the use of homogeneous catalysts to aid recycling[66].



2.1 2.2 2.3

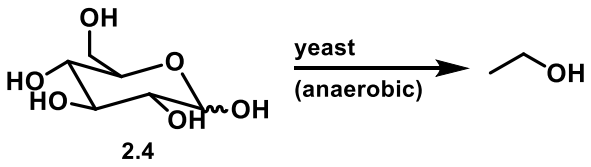
Scheme 2.1

*Table 2.2: Solvent study for the synthesis of 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carbonitrile*

Solvent	Yield (%)
n-Heptane	46
Toluene	51
Dimethylformamide (DMF)	78
Ethanol	40
Neat	72
Water	98

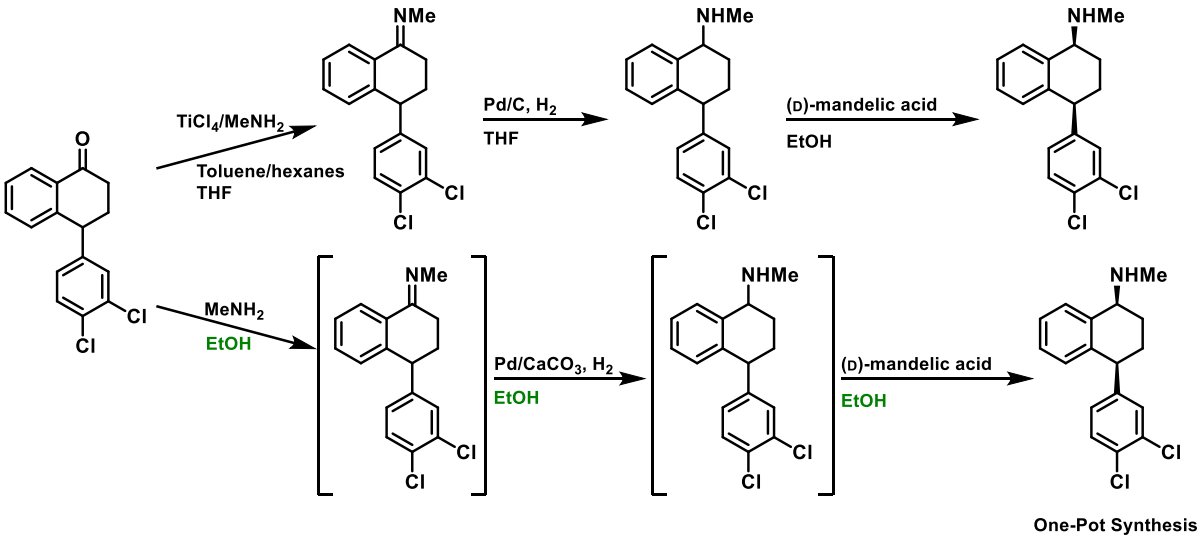
2.1.2.2 Ethanol

Ethanol is a polar protic solvent, considered a universal solvent due to its ability to dissolve polar and non-polar compounds as well as hydrophilic and hydrophobic compounds. Production of ethanol can be performed in several different ways; conversion of CO_2 by ruthenium based catalysts in the presence of H_2[67, 68], catalytic hydration of ethylene[69a] or by the fermentation of simple sugars like glucose **2.4** (Scheme 2.2)[69]. A disadvantage of using ethanol is that it is a nucleophile as well as a proton source and so can interfere with the desired reaction, for example, the reaction of alcohols with strong electrophiles as in the Williamson ether synthesis[70], or reactions with esters resulting in transesterification[71].



Scheme 2.2

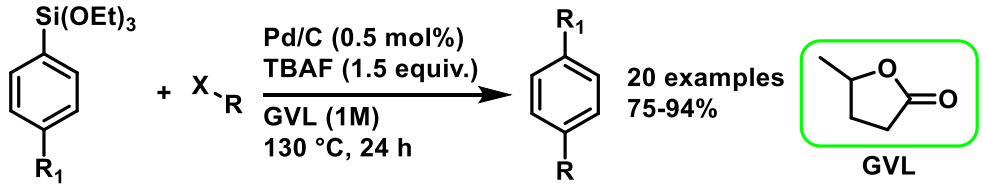
In 2002 Pfizer sought to redesign the synthesis of anti-depressant Sertraline to improve the yield, reduce reaction waste and reduce solvent usage[54]. The original synthesis involved several solvents and disposal of undesired *trans*-isomer which was recycled. The new route combined 3-steps of synthesis without the need for isolation and therefore could be carried out in only ethanol; with the absence of titanium tetrachloride for imine formation, the disposal and removal of titanium oxide amongst other waste materials was no longer necessary, and the optimisation of the catalyst (Pd/C to $PdCaCO_3$) in the imine reduction step had much higher regioselectivity thus increasing the yield of product. For the improvements to the synthesis of Sertraline, Pfizer won a Green Chemistry Challenge Award for Greener Synthetic Pathways in 2002[72, 73].


NMe
NHMe
NHMe
O
TiCl4/MeNH2
Toluene/hexanes
THF
Pd/C, H2
THF
(D)-mandelic acid
EtOH
Cl
Cl
MeNH2
EtOH
Pd/CaCO3, H2
EtOH
(D)-mandelic acid
EtOH
One-Pot Synthesis

Scheme 2.3

2.1.2.3 γ-Valerolactone (GVL)

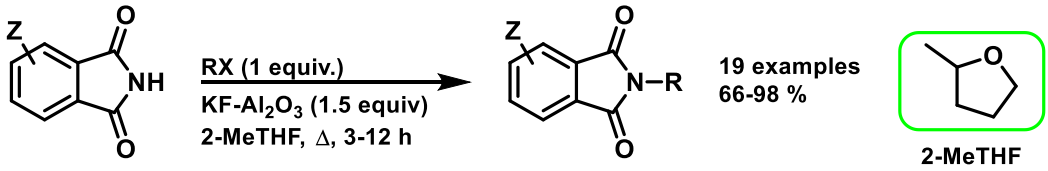
γ-Valerolactone (GVL) has caught much attention from the chemical industry as a potential source of fuel and high value compounds over recent years. C_{8+} alkanes can be synthesised from sequential polymerisation and hydrogenation of butylene monomers, formed from catalysed decarboxylation[74]. This allows for the production of alkanes of suitable size for the transportation industry from GVL. By performing the reaction this way, it allows for the capture of CO_2 produced as a by-product which can then be used further. Importantly GVL can be produced from biomass by several different methods which have been developed recently[75]. Many methods for this are based around the conversion of levulinic acid, which can be produced from simple sugars. The physical properties of GLV; melting point -31 °C, boiling point 207-208 °C and dielectric constant 36.5 make it an ideal candidate for use as a dipolar aprotic solvent[76]. While the Hiyama cross-coupling reaction has not gained as much attention in synthetic chemistry like the Heck, Suzuki and Sonogashira reactions, it is a useful carbon-carbon bond forming reaction. Vaccaro *et al*. showed that GVL was a viable solvent for this reaction, where aryl halides were reacted with arylsilanes in the presence of Pd/C and TBAF (Scheme 2.4). In this work 20 examples were synthesised in good to excellent yields.



Scheme 2.4

2.1.2.4 2-Methyltetrahydrofuran (2-MeTHF)

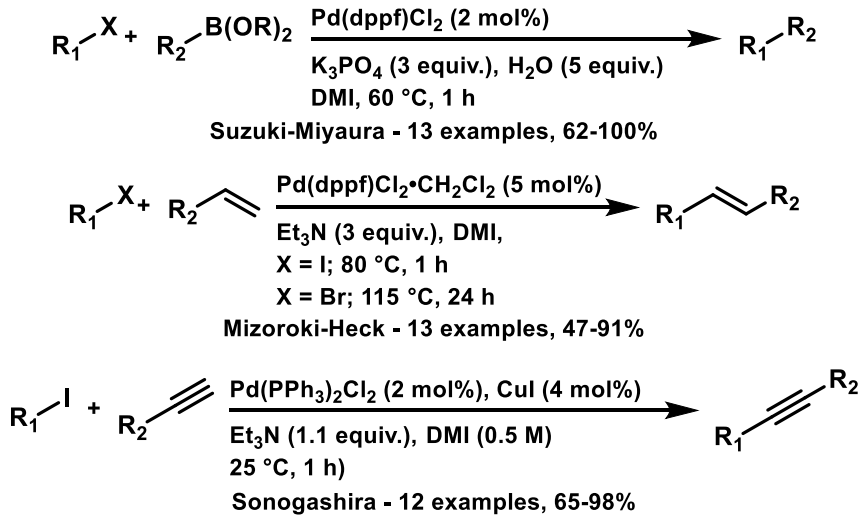
2-MeTHF is another promising compound which can be formed from renewable sources, such as furfural or levulinic acid[77]. With a low melting temperature of -136 °C and a boiling point of 80 °C, 2-MeTHF is similar to tetrahydrofuran (THF) and so a suitable solvent for low and high temperature reactions. Synthesis of 2-MeTHF from furfural is a result of successive hydrogenations which can be done over a range of catalysts. Many reactions types have been studied where 2-MeTHF was used as a solvent such as organometallic reactions like Grignard and lithium exchange reactions[60]. *N*-Alkylation reactions have also been studied using 2-MeTHF as the solvent such as the alkylation of phthalimide derivatives[78]. This is performed using Al_2O_3 supported KF and using a variety of alkyl, allyl and aryl halides, with 19 examples synthesised in good to excellent yields. Interestingly, it was found that under these conditions the reaction was selective for the cyclic imide functionality when using 3-aminophthalimide, with no addition seen for the arylamino functional group.



Scheme 2.5

2.1.2.5 Dimethyl isosorbide (DMI)

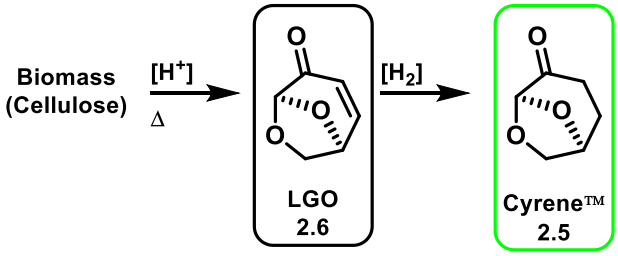
Isosorbide is an attractive compound in the chemical industry as it contains functionalities that can be easily converted[79]. Additionally, this compound can be synthesised from biomass like glucose, making it a valuable bio-based platform compound. Isosorbide can be derivatised into many useful compounds including surfactants, polymers and pharmaceuticals including nitriate derivatives which can act as vasodilators. Another important chemical which can be produced from isosorbide is DMI, a potential solvent for use in synthetic chemistry and has been shown to be synthesised in a one-pot, 2-step method utilising dimethyl carbonate as the cyclisation agent[80]. DMI has a very high boiling point of 235 °C and is considered a moderately polar aprotic solvent, making it a viable substitute for solvents such as DMF[81]. Recently the use of DMI as a solvent for some of the most used palladium catalysed reactions was demonstrated by Watson *et al*. Suzuki-Miyaura, Mizoroki-Heck and Sonogashira reactions were all shown to proceed efficiently in the DMI solvent (Scheme 2.6)[82]. In the case of the Suzuki-Miyaura reaction, DMI was used as a replacement for THF in previously reported conditions and was found to proceed as expected with no problems with the presence of the water or base. Bromo and iodo compounds were found to be tolerated in the Mizoroki-Heck reaction using DMI as the solvent with an increased temperature being required for the bromo compounds. Finally the Sonogashira reaction was also found to proceed efficiently in DMI showing that the solvent was able to tolerate the reaction conditions.



Scheme 2.6

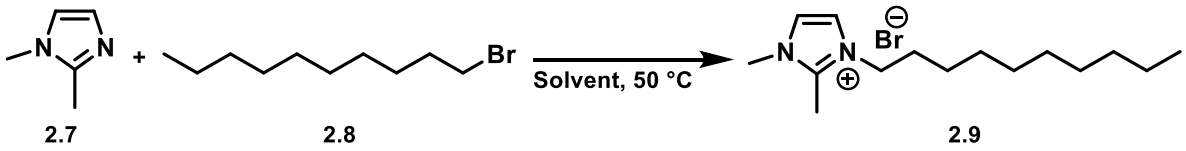
2.1.2.6 Cyrene™

It is important for the chemical industry to find replacements for the toxic solvents DMF and NMP due to the regulations being enforced on their use and production[83]. Efforts to determine replacements for these dipolar aprotic solvents are being made and one such candidate is Cyrene™ **2.5**. Cyrene™ **2.5** is formed in a two-step process from cellulose via an intermediate compound called levoglucosenone (LGO) **2.6** (Scheme 2.7). LGO **2.6** was synthesised by decomposing cellulose using a pyrolysis method and characterised by Broido *et al*. in 1973 and since then the conversion of cellulose to LGO **2.6** by pyrolysis has been extensively studies[84-90]. Circa Group has recently patented a thermal method for the synthesis of LGO **2.6** under acidic conditions using waste wood pulp as the biomass source[91]. The high temperature (430 °C) treatment of wood pulp in H_3PO_4 (0.1-10%) affords LGO **2.6** in moderate yields and has been scaled up to produce 50 tonnes per year. The conversion of LGO **2.6** into Cyrene™ **2.5** has been less well studied however all reported methods use hydrogenation protocols to reduce the alkene bond. Hydrogenation of LGO **2.6** can be performed at room temperature when the reaction was performed at high pressure (3-80 bar) in the absence of a solvent. The synthesis of Cyrene™ **2.5** has also been performed in a one-pot synthesis from cellulose by using Pd/Al_2O_3 catalyst in an ionic liquid under an atmosphere of hydrogen.



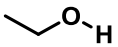
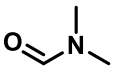
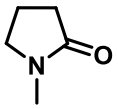
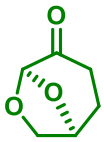
Scheme 2.7

Cyrene™ **2.5** has a dielectric constant similar to that of DMF and NMP, is considered non-toxic and has a high theoretical boiling point of 227 °C making it a viable replacement for these regulated solvents[92]. Clark and co-workers have demonstrated the use of Cyrene™ **2.5** as a solvent in reactions of significant importance to the pharmaceutical and agrochemical industries. The Menschutkin reaction is an S_N2 alkylation reaction which is used in the synthesis of imidazolium ionic liquids among other compounds. It is known that the rate of this reaction is proportional to the dipolarity of the solvent being used and so the reaction between 1,2-dimethylimidazole **2.7** and 1-bromodecane **2.8** was performed in a number of solvents to synthesise 1-decyl-2,3-dimethylimidazolium bromide **2.10** (Scheme 2.8). This study showed that Cyrene™ **2.5** was a very good solvent for this reaction outperforming many other solvents (DMF, NMP, dioxane and DMA) while only being bested by sulfur containing solvents (DMSO and sulpholane).



Scheme 2.8

Table 2.3: Comparison of physical and environmental properties of several key solvents in synthetic organic chemistry

Solvent	Structure	Physical Properties	Health & Safety	Cost[a]
Water		b.p. = 100 °C ρ = 1.00 g mL^{-1}	• Low mutagenicity • LD_{50} > 90000 mg/kg • Low ecotoxicity	-
Ethanol		b.p. = 78 °C ρ = 0.79 g mL^{-1}	• Low mutagenicity • LD_{50} > 10000 mg/kg • Low ecotoxicity • Mutagenic	£20.10 for 100 mL
DMF		b.p. = 153 °C ρ = 0.94 g mL^{-1}	• Rapidly absorbed through skin • LD_{50} > 2800 mg/kg • High ecotoxicity • Reproductive toxin	£33.90 for 250 mL
NMP		b.p. = 202 °C ρ = 1.03 g mL^{-1}	• Low mutagenicity • LD_{50} > 4000 mg/kg • High ecotoxicity • Reproductive toxin	£34.50 for 1000 mL
Dimethyl Sulfoxide		b.p. = 189 °C ρ = 1.10 g mL^{-1}	• Low mutagenicity • LD_{50} > 22000 mg/kg • Low ecotoxicity	£59.70 for 100 mL
Cyrene™		b.p. = 227 °C ρ = 1.25 g mL^{-1}	• Low mutagenicity • LD_{50} > 2000 mg/kg • Low ecotoxicity	£84.40 for 100 mL

Since Clark and co-workers proposed Cyrene™ **2.5** as a bio-available solvent in 2014, several applications have been performed[92]. In addition to the Menschutkin reaction, Clark and co-workers also demonstrated the fluorination of 2-chloro-5-nitropyridine with potassium fluoride, using Cyrene™ **2.5** as the reaction solvent, to afford 2-fluoro-5-nitropyridine in reasonable yield. The ability of Cyrene™ **2.5** to swell solid-phase peptide synthesis resins was tested by Routledge *et al*. and compared against other green solvents[81]. Cyrene™ **2.5** was found to swell the resins in an equal or to a greater extent than the traditional solvents used for this process like CH_2Cl_2, NMP and DMF. The processing of graphene using Cyrene™ **2.5** as an exfoliant and dispersion agent has been reported by 2 research groups, Clark, Shuttleworth and co-workers and Moulton and co-workers[93, 94]. Watson and co-workers conducted the first research into the use of Cyrene™ **2.5** as a solvent in a metal-catalysed process. The Sonogashira reaction was found to proceed efficiently in Cyrene™ **2.5** between sp^2-hybridised halogens and terminal alkynes with 34 examples synthesised in 60-100%

yields[95]. In addition to this work the stability of Cyrene™ **2.5** in the presence of several bases was investigated. During this investigation it was found that Cyrene™ **2.5** would readily react with itself to form either the Aldol adduct or aldol condensation product in the presence of many common bases. Cyrene™ **2.5** was found to be most stable in the presence of two bases, Et_3N and *N*,*N*-diisopropylethylamine, even at elevated temperatures up to 50 °C. Recently it has been shown that Cyrene™ **2.5** can be a suitable solvent for the Suzuki-Miyaura cross-coupling reaction. Watson and co-workers demonstrated the reaction between various aryl, heteroaryl and vinyl halides with organoboranes and found that the desired cross-coupled products were formed in good to excellent yields. The reaction was also shown to work well on larger scale reactions.

2.2 Aims & objectives

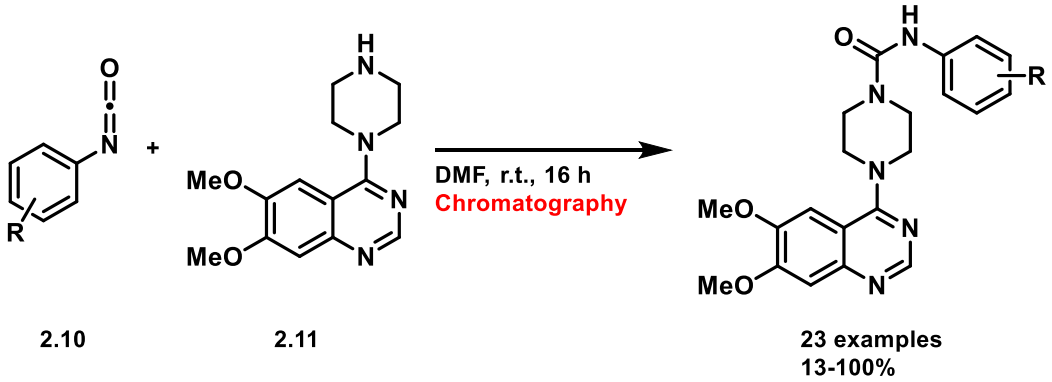
The aim of this project is to evaluate the potential for the use of the bio-available compound Cyrene™ as a dipolar-aprotic solvent in the synthetic reaction protocols as well as examine its use as a chiral scaffold. This aim will be met by achieving the following goals:

1. Explore the use of Cyrene™ as an alternative dipolar-aprotic solvent in the synthesis of ureas, amides and carbamates
2. Determine the rates of these reactions to compare the speed at which these reactions occur in several solvents usually used in these reactions such as DMF and NMP
3. Calculate the molar efficiency of reactions investigated to compare work-up procedures as well as to other dipolar-aprotic solvents
4. Test the recyclability of Cyrene™ in the reactions utilising efficient work-up procedures to return reusable solvent
5. Perform Aldol reactions on Cyrene™ with varying benzylic aldehydes and determine the structures of products formed

2.3 Results and discussion

2.3.1 Synthesis of ureas

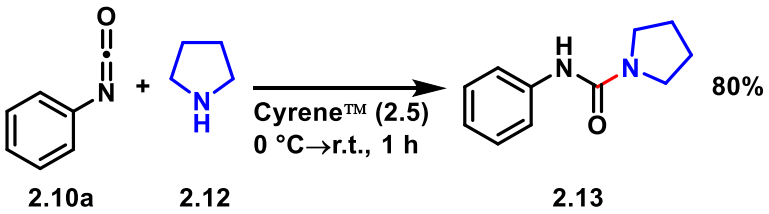
Urea functionalities are found in many types of chemicals the world relies upon, especially in agrochemicals, pharmaceuticals and polymers to name a few[96, 97]. The urea functionality is present in many drug compounds across a wide variety of therapeutic targets including antimicrobial, anti-inflammatory and antidepressants[98]. The most common way to synthesise ureas is by reacting amines with isocyanates[99], which can be formed by the oxidative carbonylation of amines, done using high temperatures and pressures in a CO/CO_2 atmosphere or under milder metal catalysed conditions[100]. Another method for the synthesis of ureas which has become more popular in recent years is the reaction of amines with preformed isocyanates. While this reaction can be performed in many different solvents, nearly 80% of the reaction in literature occur using DMF or halogenated solvents[101]. Matsuno and co-workers demonstrated the synthesis of ureas from aryl isocyanates **2.10** and 6,7-dimethoxy-4-(piperazin-1-yl)quinazoline **2.11** in DMF (Scheme 2.9)[102]. 23 examples were made with a wide range of yields from 13-100%. As the reaction was performed in DMF, aqueous work-up procedures and column chromatography are required to purify the reaction products. Purification like this produces considerable amounts of waste.



Scheme 2.9

Initial work in the Camp group showed that the synthesis of ureas from the reaction of aryl isocyanates **2.10** with secondary amines would proceed efficiently using Cyrene™ **2.5** as the solvent instead of DMF or NMP, for example the reaction of phenyl isocyanate **2.10a** with pyrrolidine **2.12** to form *N*-phenylpyrrolidine-1-carboxamide **2.13** (Scheme 2.10)[103, 104]. Aqueous work up followed by purification by flash column chromatography provided the desired products in high yields. However it was noticed that when water was added to the reaction mixture a precipitate formed. The precipitate was isolated and was found to be the urea product. Further investigation into the precipitation of products from Cyrene™ **2.5** allowed the simple and quick isolation of products from

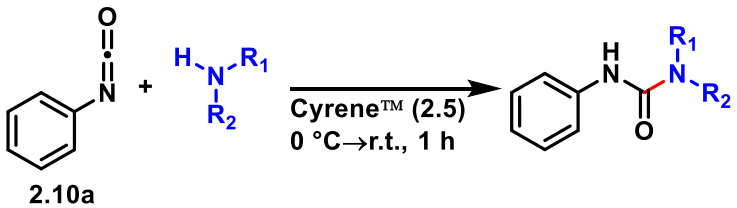
the reaction mixture by diluting the reaction with water and stirring for an hour. The filtered precipitate contained no starting materials or Cyrene™ **2.5**. This meant that no further purification, other than drying to remove the excess water, was required.



Scheme 2.10

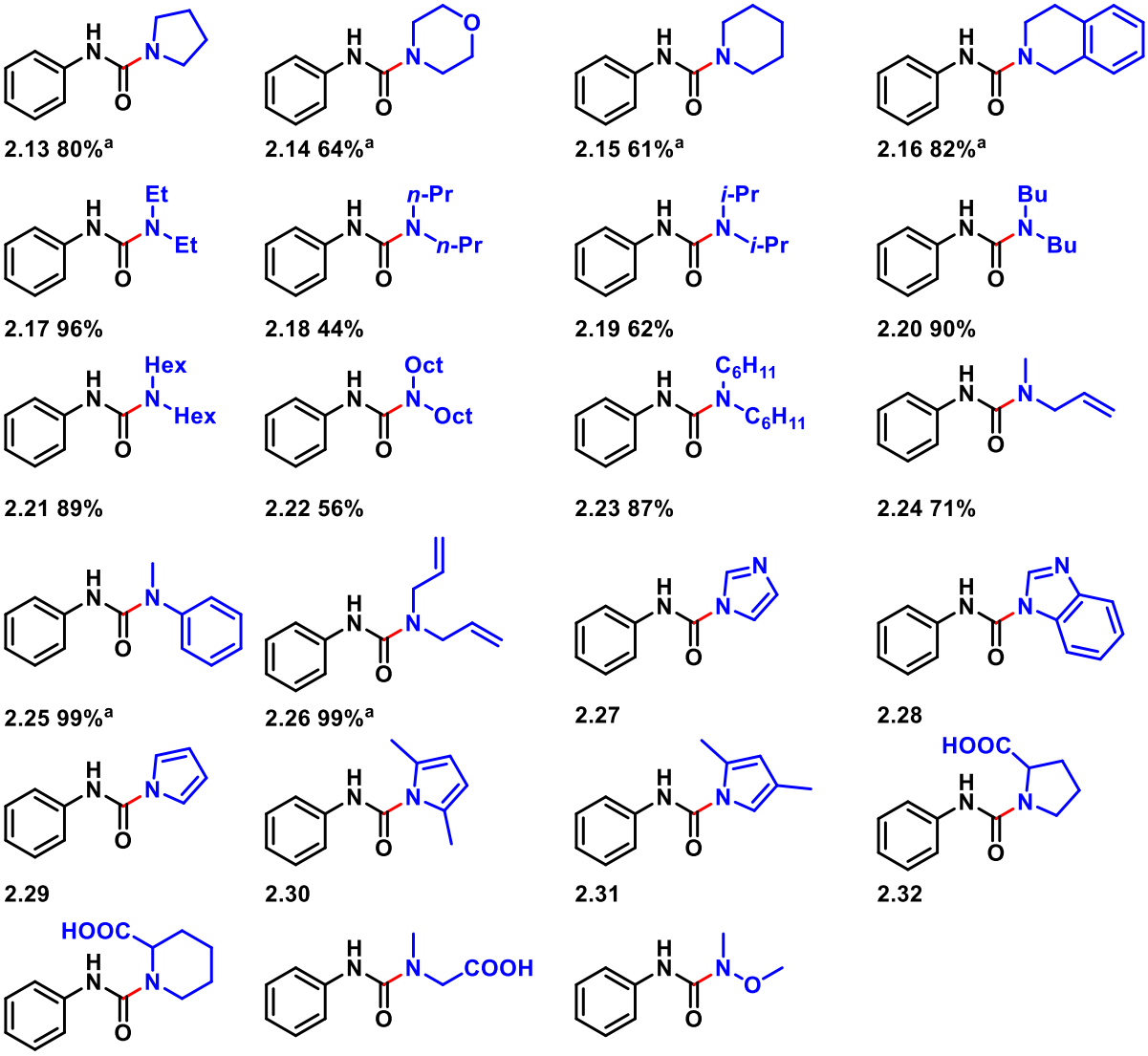
2.3.1.1 Substrate scope

The substrate scope for the synthesis of ureas was investigated by reacting various secondary amines with phenyl isocyante **2.10a** using Cyrene™ **2.5** as the solvent (Scheme 2.11, Table 2.4)[105]. Cyclic aliphatic amines pyrrolidine **2.12**, morpholine and piperidine were tolerated well with yields ranging between 61-80% (Scheme 2.11, Table 2.4, Products **2.13, 2.14 & 2.15**). Fused ring 1,2,3,4-tetrahydroisoquinoline was also tolerated in the reaction, with the product isolated in 82% yield (Scheme 2.11, Table 2.4, Product **2.16**). Acyclic aliphatic amines also worked well under the reaction conditions with yields ranging between 44-96% (Scheme 2.11, Table 2.4, Products **2.17-2.22**). Dicyclohexyl amine was found to react well under the conditions and isolation by precipitation afforded the desired product in excellent yield (Scheme 2.11, Table 2.4, Product **2.23**). Unsymmetrical amines *N*-methylprop-2-en-1-amine and *N*-methylaniline were also isolated in good to excellent yields, 71-99%, following the reaction in Cyrene™ (Scheme 2.11, Table 2.4, Products **2.4 & 2.5**). Diallylamine was also found to react and precipitate efficiently with an isolated yield of 99% (Scheme 2.11, Table 2.4, Product **2.26**). It was found with aromatic pyrroles and benzoimidazole that no precipitates were formed upon the addition of water to the reaction mixture, even if left to stir for 24 h (Scheme 2.11, Table 2.4, Products **2.27-2.31**). It is unknown whether these reactions proceeded as intended as no additional attempt to isolate products was attempted. However, it is possible some of the reactions may have proceeded with the urea products being soluble in the water/Cyrene™ mixture and not precipitating. The same could be assumed for the amino acids as well as *N*,*O*-dimethylhydroxylamine where the urea products were formed, but were not isolated (Scheme 2.11, Table 2.4, Entries **2.32-2.35**). As the aim of the project was to reduce the time and waste materials the products that did not precipitate were not examined further. From this table it can be seen that both cyclic and non-cyclic aliphatic amines were found to react very well under the reaction conditions whereas aromatic and amino acids were not isolated.



Scheme 2.11

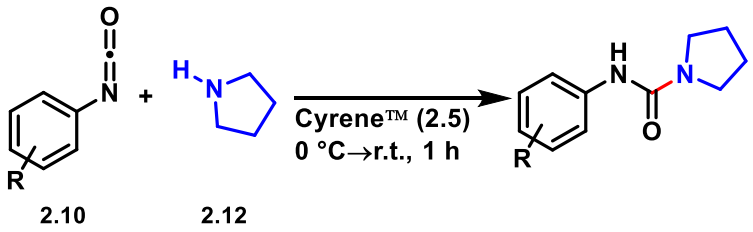
*Table 2.4: Table of ureas attempted to be synthesised using bioavailable solvent Cyrene™ **2.5***



[a] **Synthesis performed by Liam Mistry and Kopano Mapesa**

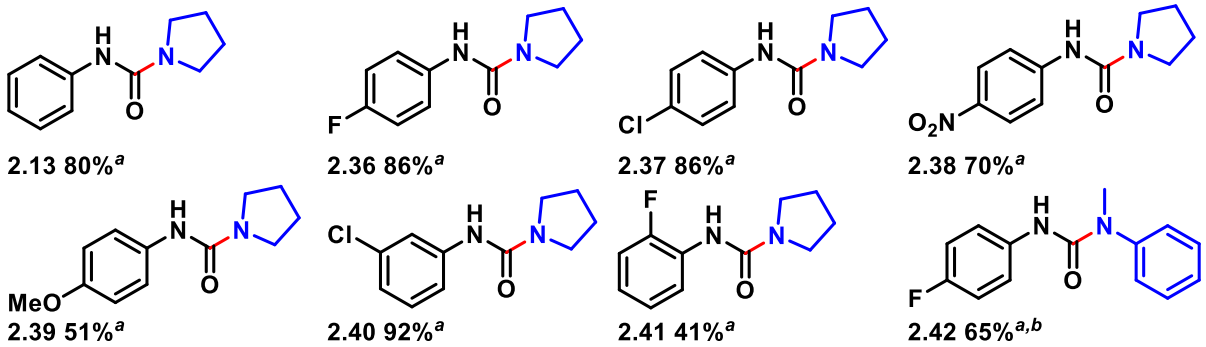
Having shown that ureas can be synthesised from phenyl isocyanate and various secondary amines using Cyrene™ **2.5** as the solvent, the synthesis of ureas using various isocyanates and a secondary amine was investigated in order to examine the electronic tolerances of the reaction and the viability of the work-up conditions (Scheme 2.12, Table 2.5). Pyrrolidine **2.12** was chosen as the secondary amine for this investigation as it was previously shown that the urea product with phenyl isocyanate **2.10a** precipitated upon the addition of water to the reaction mixture. *para*-Substituted halogenated isocyanates worked well under the reaction conditions and precipitated as hoped with high isolated yields of 86% (Scheme 2.12, Table 2.5, Products **2.36 & 2.37**). When the isocyanate containing an electron withdrawing nitro moiety was subjected to the reaction conditions, the product was isolated in significantly decreased yield, 10% lower compared to the unsubstituted isocyanate (Scheme 2.12, Table 2.5, Products **2.38** and **2.13** respectively). Electron rich 4-

methoxyphenyl isocyante was lower yielding than the unsubstituted phenyl isocyante reaction at 51% (Scheme 2.12, Table 2.5, Products **2.39** and **2.13** respectively). *meta*-Substituted chlorophenyl isocyante was isolated in a higher yield when compared to the *para*-substituted chlorinated isocyanate at 92% vs 86% (Scheme 2.12, Table 2.5, Products **2.40** and **2.37** respectively). *ortho*-Substituted fluorophenyl isocyanate had a large drop in isolated yield when compared to the para-substituted isomer down at 41% compared to 86% (Scheme 2.12, Table 2.5, Products **2.41** and **2.36** respectively). The product of the reaction between phenyl isocyanate **2.10a** and *N*-methylaniline was isolated in quantitative yield (Scheme 2.11, Table 2.4, Product **2.25**), so the reaction between 4-fluorophenyl isocyanate and *N*-methylaniline was attempted. As hoped the reaction proceeded well with the urea precipitating however at a significantly lower isolated yield of 65% (Scheme 2.12, Table 2.5, Product **2.42**). Electron deficient isocyanates were found to give high yields of isolated product in the reactions with pyrrolidine, whereas electron rich isocyanates were found to result in decreased yields relative to phenyl isocyanate. Steric interactions also lead to a drop in yield when comparing reactions with 4-fluorophenyl isocyanate and 2-fluorophenyl isocyanate.



Scheme 2.12

*Table 2.5: Table of ureas synthesised by reacting various aryl isocyanates **2.10** with pyrrolidine **2.12** using bioavailable solvent Cyrene™ **2.5***

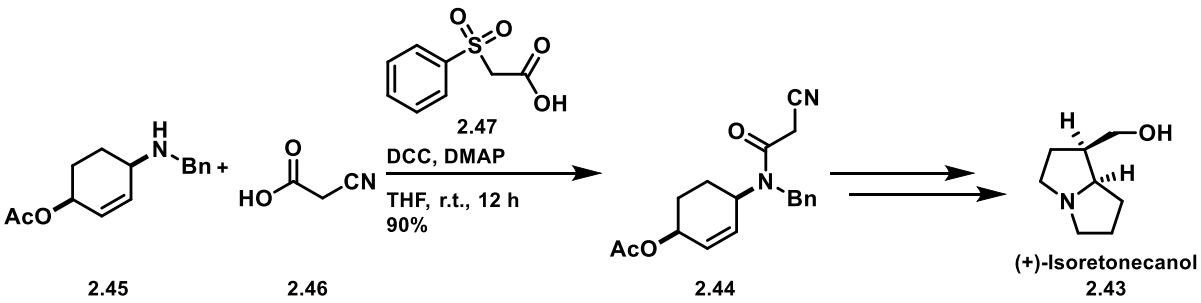


[a] Synthesis performed by Liam Mistry and Kopano Mapesa, [b] *N*-methylaniline used

This method offers an alternative procedure for the synthesis of ureas which doesn't use toxic solvents like DMF. This allows for a method which only uses water and bio-derived solvents, providing a green synthetic route. Additionally the addition of water to the reaction provided a solution to one of the key problems with Cyrene™ **2.5**, the removal of product from the solvent.

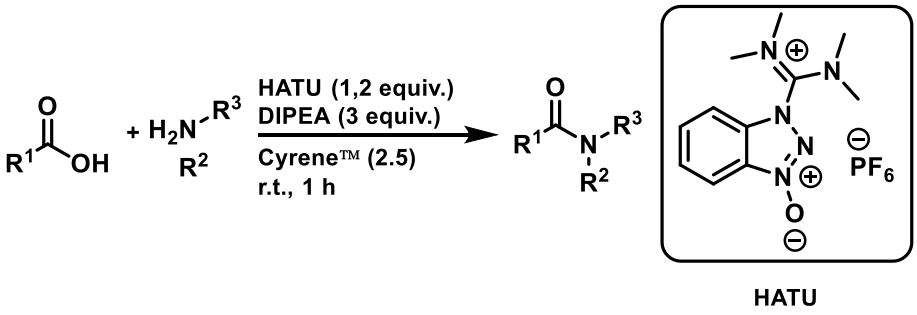
2.3.2 Synthesis of amides

The synthesis of amides is one of the most used disconnections used in the pharmaceutical industry and is also one of the largest producers of waste[106]. The waste generated from amide bond formation can be comprised of coupling agents, used to combine the carboxylic acid with the amine to form the amide, as well as solvents used for both the reaction and the purification of products. A review of amidation reaction performed in 2016 by GSK found that 45% of these reactions required a coupling reagent and 39% of these reactions occurred in DMF or THF[107]. The synthetic route towards alkaloid (+)-isoretencanol **2.43** utilised the amide coupling to form intermediate **2.44** by the coupling of **2.45** and **2.46** in the presence of DCC, DMAP and (phenylsulfonyl)acetic acid **2.47** (Scheme 2.13)[108]. DCC is a useful chemical coupling agent as the by-product formed once used is insoluble and in most cases can be easily filtered from the reaction medium. Column chromatography of the reaction residue afforded the desired amide in 90% yield. Despite the excellent yield, the use of DCC and flash column chromatography in the reaction produces a lot of waste.



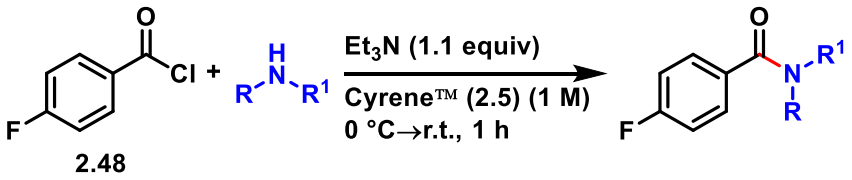
Scheme 2.13

In an effort to reduce the environmental impact of the solvents used in amide formations, Watson and co-workers recently published work on HATU coupled amide synthesis in the bioavailable solvent Cyrene™ **2.5** (Scheme 2.14)[109]. It was found that Cyrene™ **2.5** was a suitable solvent for the reaction between various carboxylic acids and amines with yields ranging from 63-100%. Additionally, it was found that the synthesis of peptides also proceeded efficiently, with substrates containing unprotected and protected heteroatoms as well as aryl and alkyl side chains being well tolerated. Comparing different solvents for the reaction between *p*-toluic acid and aniline, it was found that the conversion of stating material to product was very high for both DMF and Cyrene™ **2.5**.



Scheme 2.14

The objective for this project was to develop a method of amide synthesis which reduces the need for both coupling agents and solvents needed to purify the products. The initial study was focussed on the synthesis of amides from acid chlorides and amines using the solvent Cyrene™ **2.5** and was performed by reacting 4-fluorobenzoyl chloride **2.48** with a variety of amines in the presence of triethylamine (Scheme 2.15). The presence of triethylamine is needed to remove free HCl from the reaction mixture which is produced as the reaction proceeds. The reactions with pyrrolidine **2.12**, aniline and benzylamine proceeded efficiently and the optimisation of the reaction was simple, however, the isolation and purification of products required greater thought. No precipitate was formed upon the addition of water to the reaction mixture with the reaction involving pyrrolidine **2.12**, contrary to previous work using secondary amines in the synthesis of ureas, instead requiring both an aqueous work-up and purification by flash column chromatography, leading to large quantities of waste being produced. Despite this a high yield of 91% was attained upon isolation (Scheme 2.15, Table 2.6, Entry 1). Attempting to reduce the amount of waste produced by the work-up procedure, the reaction mixture was wet loaded directly onto a flash column to afford the desired product in a good yield of 75% (Scheme 2.15, Table 2.6, Entry 2). When primary amines were reacted under the same conditions it was found that both aniline and benzylamine reaction products did precipitate upon the addition of water at the end of the reaction, requiring no further purification with good isolated yields of 72% and 81% (Scheme 2.15, Table 2.6, Entries 3 & 4 respectively). Utilising the molar efficiency calculations detailed in **Section 1.3**, the relative Mol. E% values were determined. A direct comparison of the two pyrrolidine work-ups reveal that by not performing the aqueous wash, the relative efficiency of the process increases to 1.4 times. This method of work-up still produces a lot of waste solvents from the flash column. It was found that isolation of the products by precipitation can increase the relative molar efficiency by >20 times.



Scheme 2.15

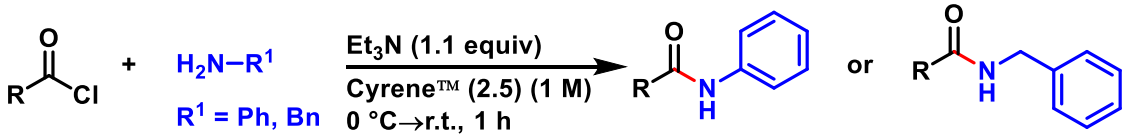
*Table 2.6: Optimisation table for the synthesis of amides from 4-fluorobenzoyl chloride **2.48** and amines*

Entry	Amine	Work-up	Yield (%)	Relative Mol. E%
1	Pyrrolidine	Aqueous; then column	91	1
2	Pyrrolidine	Column	75	1.4
3	Aniline	Precipitate	72	24
4	Benzylamine	Precipitate	81	28

From these results, the ideal substrates for this reaction method are primary amines due to the ability to isolate pure products by precipitation. Isolation by this method removes the need for purification by column chromatography, reducing the waste produced by the process which increases the Mol. E% of this method.

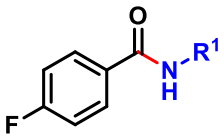
2.3.2.1 Substrate scope

After the preliminary viability of the reaction was established, along with an optimised isolation procedures, the substrate scope for the synthesis of amides from acid chlorides and primary amines, using Cyrene™ **2.5** as the solvent, was investigated by reacting various aryl acid chlorides with aniline or benzylamine in the presence of triethylamine (Scheme 2.16, Table 2.7). 4-Fluorobenzoyl chloride **2.48** reacted well in Cyrene™ **2.5** with both aniline and benzylamine with high yields of 72% and 81% (Scheme 2.16, Table 2.7, Products **2.49** and **2.50** respectively). Additionally, coupled products of both 2- and 3-fluorobenzoyl chloride were also isolated in high yields when reacted with both aniline and benzylamine (Scheme 2.16, Table 2.7, Products **2.51**-**2.54**). 4-Bromobenzoyl chloride reacted very well with aniline to afford a high isolated yield of 85%, however, the isolated yield with benzylamine was lower at 69% (Scheme 2.16, Table 2.7, Products **2.55** & **2.56**). Electron rich system 3,4-dimethoxybenzoyl chloride provided excellent yields with both aniline and benzylamine with yields in the low/mid 80% range (Scheme 2.16, Table 2.7, Products **2.57** & **2.58**). Heterocylic acid chlorides produced the desired products in good yields with the exception of the reaction between nicotinoyl chloride and benzylamine in which no product was isolated (Scheme 2.16, Table 2.7 Products **2.59**-**2.66**). It should also be noted that 4-fluoro-*N*-phenylbenzamide required 24 h stirring upon the addition of water to allow a precipitate to form (Scheme 2.16, Table 2.7, Product **2.59**). Cyclic aliphatic acid chlorides cyclopropanecarbonyl chloride and cyclobutanecarbonyl chloride reacted with aniline and benzylamine to afford the desired amides in moderate yields (Scheme 2.16, Table 2.7, Products **2.67**-**2.70**). It was found that allowing the reaction mixtures to stir for 24 h in water typically had a positive effect on isolated yields (Scheme 2.16, Table 2.7, Products **2.49**, **2.67**), however this was not always the case (Scheme 2.16, Table 2.7, Products **2.51** & **2.53**). Unsubstituted benzoyl chloride and long alkyl chain acid chloride valeroyl chloride did not provide a precipitate upon addition of water to the reaction mixture along with dimethylaminobenzoyl chloride, resulting in no isolated products for these reactions (Scheme 2.16, Table 2.7, Products and **2.71-2.76**). 2,5-Dichloropyrimidinecarbonyl chloride was also found not to provide the desired amide by precipitation (Scheme 2.16, Table 2.7, Product **2.77**). Finally, using 2 equivalents of benzylamine to react with 1,3-benzenedicarbonyl dichloride was found not to give the desired product by precipitation (Scheme 2.16, Table 2.7 Entry **2.78**).

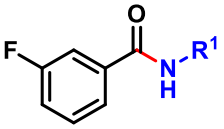


Scheme 2.16

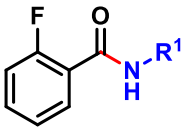
Table 2.7: Table of 1° amides attempted to be synthesised using bioavailable solvent Cyrene™ ***2.5***



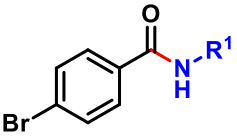
R^1 = Ph, 2.49 72% (91%)[b]
R^1 = Bn, 2.50 81%



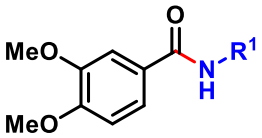
R^1 = Ph, 2.51 76% (75%)[b]
R^1 = Bn, 2.52 73%



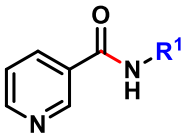
R^1 = Ph, 2.53 76% (75%)[b]
R^1 = Bn, 2.54 73%



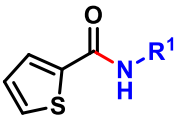
R^1 = Ph, 2.55 85%
R^1 = Bn, 2.56 69%



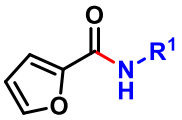
R^1 = Ph, 2.57 83%[a]
R^1 = Bn, 2.58 86%



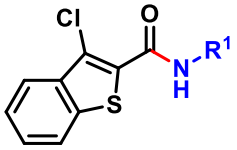
R^1 = Ph, 2.59 32%[b]
R^1 = Ph, 2.60



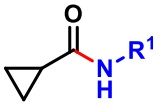
R^1 = Ph, 2.61 55%[a]
R^1 = Bn, 2.62 74%[a]



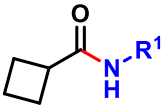
R^1 = Ph, 2.63 68%[a]
R^1 = Bn, 2.64 73%[a]



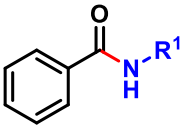
R^1 = Ph, 2.65 45%[a]
R^1 = Bn, 2.66 47%[a] (74%)[c]



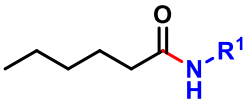
R^1 = Ph, 2.67 46% (49%)[b]
R^1 = Bn, 2.68 64%



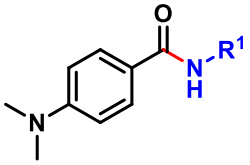
R^1 = Ph, 2.69 76%
R^1 = Bn, 2.70 42%



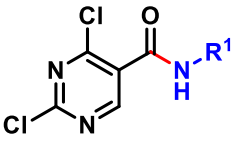
R^1 = Ph, 2.71
R^1 = Bn, 2.72



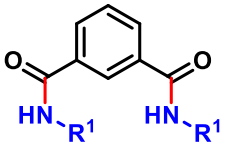
R^1 = Ph, 2.73
R^1 = Bn, 2.74



R^1 = Ph, 2.75
R^1 = Bn, 2.76



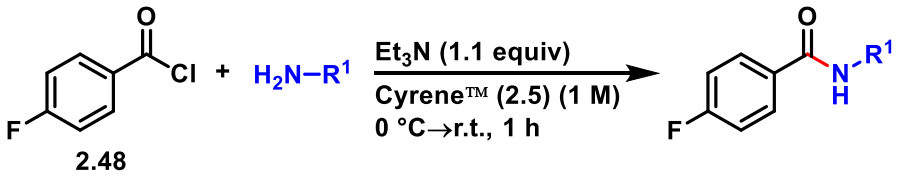
R^1 = Bn, 2.77



R^1 = Bn, 2.78

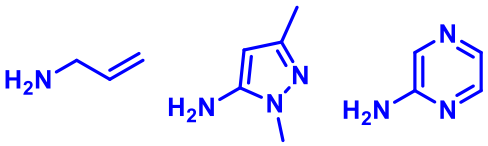
[a] Synthesis performed by Katharine Pearce, [b] 24 h stir in water, [c] 5.0 mmol scale

Allylic and heterocyclic primary amines were also reacted under the standard conditions with 4-fluorobenzoyl chloride, however these reactions did not provide the desired products by precipitation and so further investigations were not performed due to time restraints (Scheme 2.17, Table 2.8, Entries **2.79-2.81**).



Scheme 2.17

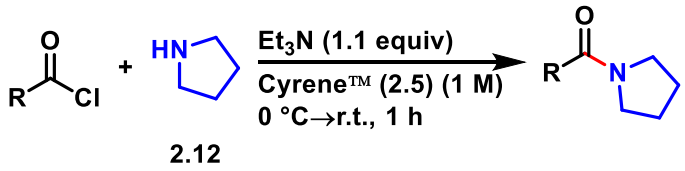
Table 2.8: Additional 1° amines tested in the synthesis of amides using the bioavailable solvent Cyrene™ ***2.5***



2.79 **2.80** **2.81**

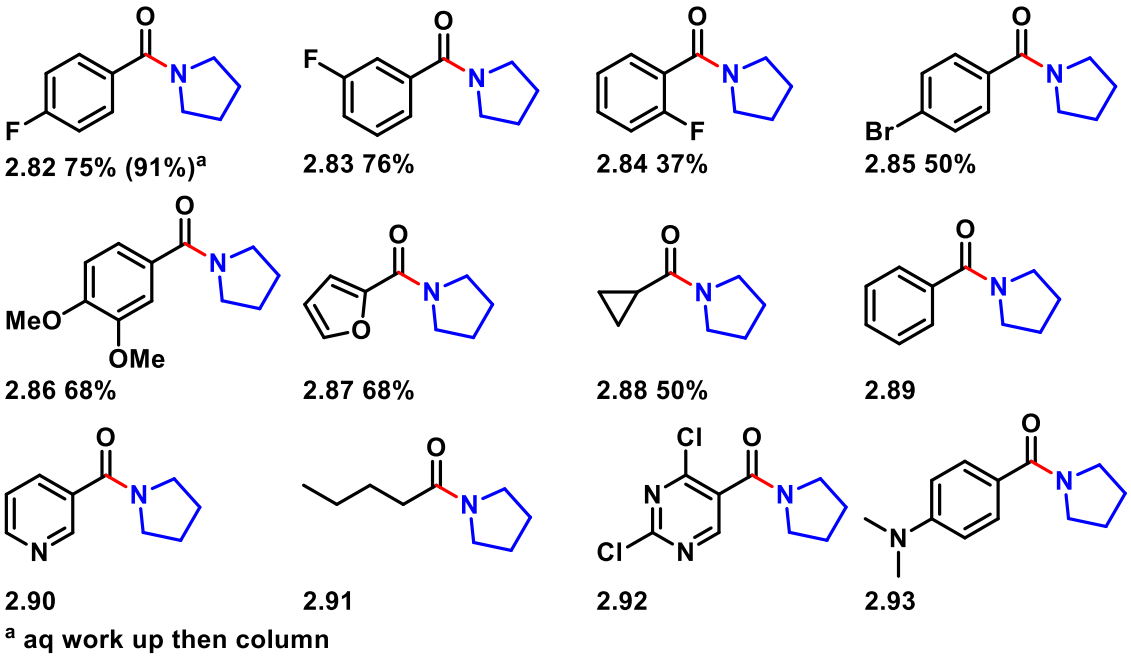
Although it was found that secondary amines reacted well with acid chlorides under the standard conditions, the products from this reaction did not precipitate upon addition of water. This meant that isolation of the desired products from this reaction required extended work-up procedures. It was found that aqueous work-up followed by column chromatography allowed the isolation of products in excellent yields (Scheme 2.18, Table 2.9, Product **2.82**^{a}). In an attempt to reduce waste from the work-up procedure the reaction mixture was wet-loaded directly onto a column. This process allowed the isolation of the desired products in good yields (Scheme 2.18, Table 2.9, Product **2.82**), while also increasing the molar efficiency of the reaction. By reacting pyrrolidine with various acid chlorides it was shown that 3-fluorobenzoyl chloride reacted well with pyrrolidine and was isolated in similar yields to that of the 4-fluoro isomer (Scheme 2.18, Table 2.9, Product **2.83**). However the 2-fluoro isomer was isolated in a much lower yield of 37%, most likely due to the steric hindrance caused by the fluorine atom (Scheme 2.18, Table 2.9, Product **2.84**), while the 4-bromobenzoyl chloride was also isolated in moderate yield (Scheme 2.18, Table 2.9, Product **2.85**). Electron-rich 3,4-dimethoxybenzoyl chloride was found to react well and desired product was isolated in good yields, as was heterocyclic furoyl chloride at 68% for both compounds (Scheme 2.18, Table 2.9, Products **2.86** and **2.87** respectively). Cyclic aliphatic cyclopropyl carbonyl chloride was also found to react well and isolation of the product by direct column chromatography afforded the product in 50% yield (Scheme 2.18, Table 2.9 Product **2.88**)**.** Products were not isolated when using benzoyl chloride or nicotinoyl chloride (Scheme 2.18, Table 2.9, Products **2.89** and **2.90** respectively). Purification of products from the reaction with valeroyl chloride afforded a complex mixture from

which no products could be isolated (Scheme 2.18, Table 2.9, Products **2.91**). Chlorinated pyrimidinecarbonyl chloride and dimethylaminobenzoyl chloride also did not provide any isolated products in the reaction with pyrrolidine (Scheme 2.18, Table 2.9 Products **2.92** & **2.93**). One reason for the lack of products from these reactions might be due to the water content of Cyrene™ **2.5**, where the water attacks the acid chloride faster than the amine can, forming the carboxylic acid instead of the amide, however this was not confirmed.



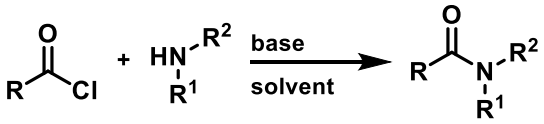
Scheme 2.18

*Table 2.9: Table of 2° amides attempted to be synthesised using bioavailable solvent Cyrene™ **2.5***



[a] aq work up then column

Utilising the Excel spreadsheet developed previously for the evaluation of Mol. E%, *vide infra* (Section 1.4), the method developed here was compared with several common approaches for the synthesis of amides (Scheme 2.19, Table 2.10). As mentioned earlier, isolation of products by precipitation was found to have a 28-fold increase in Mol. E% compared to performing an aqueous work up and column chromatography, (Table 2.6). The use of Cyrene™ **2.5** as solvent and the subsequent use of the precipitation method for isolation in similar amidation reactions were found to have up to a 55-fold increase in Mol. E% compared to reactions using DMF (Table 2.10, Entries 3 & 4 *vs.* 5 & 6). Reactions performed in CH_2Cl_2 were also found no be less efficient than the method in Cyrene™ **2.5** developed here, approximately 14-fold difference in efficiency (Table 2.10, Entries 3 & 4 *vs.* 7 & 8). Finally, the use of THF as a solvent for a similar amidation reaction was found to be one of the least efficient protocols of the methods assessed (Table 2.10, Entry 9).



Scheme 2.19

Table 2.10: Comparison of Mol. E% of several methods for the synthesis of amides

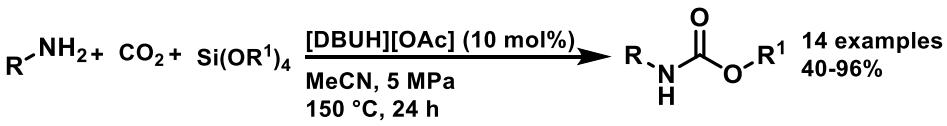
Entry	Acid chloride	Amine	Solvent	Work-up method[a]	Mol. E%	Relative Mol. E%
1	4-Fluorobenzyl chloride	Pyrrolidine	Cyrene™	A	0.0053	2
2	4-Fluorobenzyl chloride	Pyrrolidine	Cyrene™	B	0.0070	2.7
3	4-Fluorobenzyl chloride	Aniline	Cyrene™	C	0.123	47
4	4-Fluorobenzyl chloride	Benzylamine	Cyrene™	C	0.143	55
5[110]	Chloroformate	2-Phenylethylamine	DMF	A	0.0111	4.3
6[111]	4-Fluoro-3-(trifluoromethyl) benzoyl chloride	1-Benzyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolin-4-ylamine	DMF	A	0.0026	1
7[112]	4-Fluorobenzyl chloride	*N*-(2-Aminophenyl)-acetamide	CH_2Cl_2	A	0.0073	2.8
8[113]	4-Fluorobenzyl chloride	2-Bromoaniline	CH_2Cl_2	A	0.0115	4.4
9[114]	3-Fluorobenzyl chloride	5,7-Dichloroquinolin-8-amine	THF	A & D	0.0026	1

[a] work-up procedure: A) aqueous work-up followed by column chromatography, B) Column chromatography, C) precipitation, D) recrystallisation

The method developed here provides an alternative process for the synthesis of amides which allows for the use of bioavailable solvents instead of the halogenated and toxic solvents which are the norm for this type of chemical reaction. The quick and simple work-up procedure also enhances the method by removing the need for solvents to extract and purify, reducing the overall waste the reaction generates.

2.3.3 Synthesis of carbamates

Carbamates are found in many insecticides as well as pharmaceuticals and so play an important role in the world[115]. As it is such an important class of chemical many methods to form this functional group have been developed. One method for the synthesis of carbamates is the carbonylation of amines, typically done with phosgene. Phosgene however is very toxic and so replacements for this are being investigated. Recently, Choi et al. demonstrated a method for the synthesis of carbamates from amine, CO_2 and silicate esters using a task-specific ionic liquid, designed for the capture and use of CO_2 in reactions as a catalyst (Scheme 2.20). High temperatures and pressures were found to be crucial with optimum conditions 5 MPa and 150 °C. The reaction conditions developed tolerated many functional groups including nitro, methoxy and nitrile with 14 examples synthesised in 40-96% yields[116].



Scheme 2.20

Hofmann[117-119], Lossen[120-122] and Curtius[116] rearrangements are other examples of carbamate synthesis, all of which proceed via isocyanate formation followed by the subsequent nucleophilic attack by an alcohol. The use of hypervalent iodine as an oxidant for a Hofmann rearrangement was demonstrated by Zhdankin and co-workers where PhI and Oxone are used to convert the aryl amine into an isocyanate (Figure 2.2)[123]. The isocyanate is then converted into a carbamate by nucleophilic attack from a MeOH molecule from the solvent. Later it was shown that this process could be performed using a catalytic amount of PhI when using a solvent mixture of 1,1,1,3,3,3-hexafluoroisopropanol, methanol and water (10:10:1)[124].

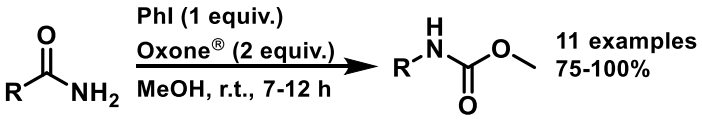
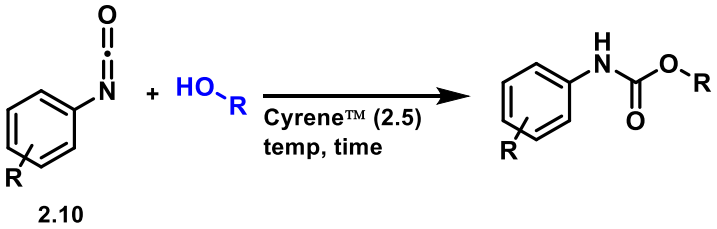


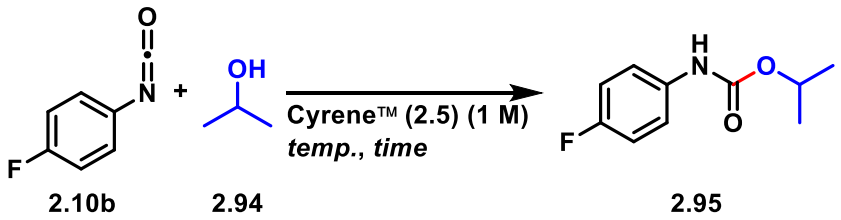
Figure 2.2: Hofmann rearrangement in the presence of PhI and Oxone®

Taking into consideration the work previously mentioned on the use of Cyrene™ as a solvent for the synthesis of ureas and amides, *vide infra* Section 2.3.1, its use as a solvent for the synthesis of carbamates was investigated, with the aim of using similar work-up procedures to reduce the amount of solvents needed to purify the products. With this in mind, the formation of carbamates would be performed in a similar manner to the synthesis of ureas where phenyl isocyanates react with alcohols in Cyrene™ (Scheme 2.21).



Scheme 2.21

Initial reactions were carried out at room temperature and required 1 week to achieve a yield of 67% when using *n*-propanol (Scheme 2.22, Table 2.11, Entry 1)[125]. Aqueous work-up followed by column chromatography was also required for the isolation of this product. It was found that isolation of product when using isopropanol **2.94** could be achieved by precipitation upon water addition to the reaction mixture. This allowed the isolation of isopropyl (4-fluorophenyl)carbamate **2.95** in an excellent yield of 97% (Scheme 2.22, Table 2.11, Entry 2). Leaving the reaction for 16 h only allowed isolation of product in 50% (Scheme 2.22, Table 2.11, Entry 3), and so in order to cut the reaction time down while keeping high yields the reaction was heated at 40 °C for 16 h. Isolation by precipitation afforded the desired product in a yield of 82% (Scheme 2.22, Table 2.11, Entry 4).



Scheme 2.22

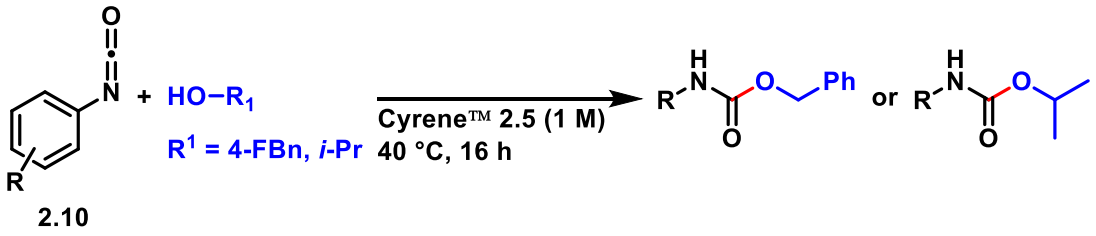
*Table 2.11: Optimization reactions for the synthesis of carbamates from aryl isocyantes **2.10** and alcohols*

Entry	Temp. (°C)	Time (h)	Yield
1[a]	20	168	67[b]
2[c]	20	168	96
3[c]	20	16	50
4[c]	40	16	82

[a] work-up: aqueous work-up followed by column chromatography [b] n-propanol was used [c] work-up: precipitation method

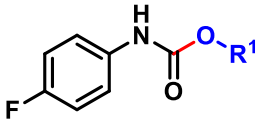
2.3.3.1 Substrate scope

With the optimisation of the reaction conditions was complete the substrate scope of the reaction was investigated. Initial investigations began with the reactions between various aryl isocyanates **2.10** with isopropanol **2.94** and 4-fluorobenzyl alcohol **2.96** (Scheme 2.23 Table 2.12). 4-Fluorophenyl isocyanate **2.10b** reacted well with both isopropanol **2.94** and 4-fluorobenzyl alcohol **2.96** with isolated yields of 82% and 78% (Scheme 2.23, Table 2.12, Products **2.95** and **2.97** respectively). It was also found that isolation of product from the reaction between 4-fluorophenyl isocyanate **2.10b** and isopropanol **2.94** on a 5 mmol scale afforded excellent yield of 94% (Scheme 2.23, Table 2.12, Entry **2.95**[a]). Unsubstituted phenyl isocyanate reacted well with both alcohols with good isolated yields of 61% and 64% (Scheme 2.23, Table 2.12, Products **2.98** and **2.99** respectively). Good yields were also isolated when both alcohols were reacted with 3,4-dichlorophenyl isocyanate **2.141** and 4-methoxyphenyl isocyanate (Scheme 2.23, Table 2.12, Products **2.100-2.103**). Electron deficient 4-nitro and halogenated 3-fluoro, 2-fluoro, 3-chloro and 4-bromo phenyl isocyanates were found not to precipitate upon addition of water and so these products were not isolated (Scheme 2.23, Table 2.12 **2.104**-**2.113**). As found in previous investigations where the desired reaction products were not isolated by the precipitation method, it is thought that the reactions did proceed as intended however the products are soluble in the water/Cyrene™ **2.5** mixture and so were not isolated by precipitation.

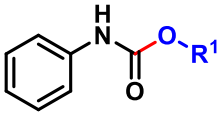


Scheme 2.23

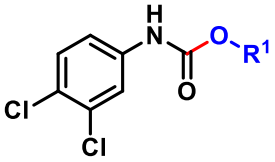
*Table 2.12: Table of carbamates attempted to be synthesised from a variety of aryl isocyanates **2.10** using bioavailable solvent Cyrene™ **2.5***



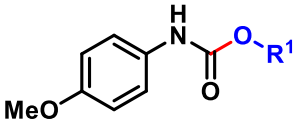
R^1 = *i*-Pr, 2.95 82% (94%)[a]
R^1 = 4-FBn, 2.97 78%



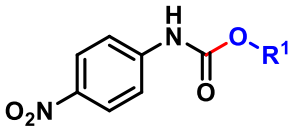
R^1 = *i*-Pr, 2.98 61%
R^1 = 4-FBn, 2.99 64%



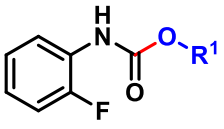
R^1 = *i*-Pr, 2.100 80%
R^1 = 4-FBn, 2.101 79%



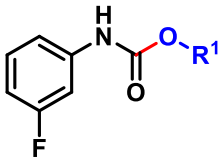
R^1 = *i*-Pr, 2.102 82%
R^1 = 4-FBn, 2.103 73%



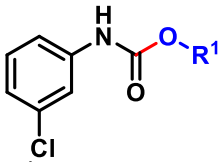
R^1 = *i*-Pr, 2.104
R^1 = 4-FBn, 2.105



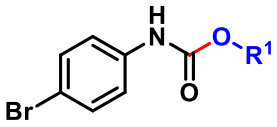
R^1 = *i*-Pr, 2.106
R^1 = 4-FBn, 2.107



R^1 = *i*-Pr, 2.108
R^1 = 4-FBn, 2.109



R^1 = *i*-Pr, 2.110
R^1 = 4-FBn, 2.111

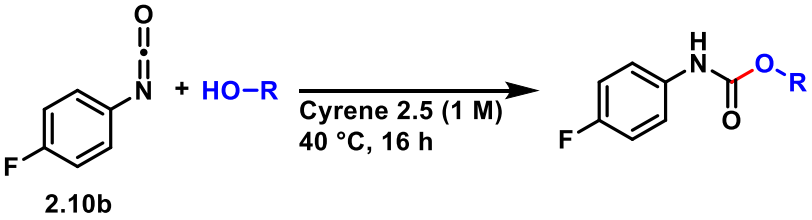


R^1 = *i*-Pr, 2.112
R^1 = 4-FBn, 2.113

[a] 5 mmol scale

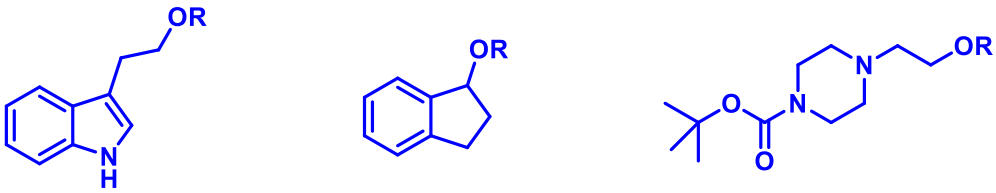
Next the substrate scope for the reaction between 4-fluorophenyl isocyanate **2.10b** with various alcohols was investigated (Scheme 2.24, Table 2.13). Interestingly, the indoline derivative reacted well under the reaction conditions to form the desired carbamate with an excellent isolated yield of 97% and did not form the urea with the cyclic amine (Scheme 2.24, Table 2.13, Product **2.114**). Both 1-indanol and Boc-protected piperazine derivative also reacted well and allowed for isolation of products by precipitation with high yields of 83% and 97% (Scheme 2.24, Table 2.13, Products **2.115** and **2.116** respectively). Boc-Protected pyrrolidine derivative reacted and was isolated by precipitation but in poor yield (Scheme 2.24, Table 2.13, Product **2.117**). 3,3,3-Trifluoropropan-1-ol was also found to afford the desired carbamates however the yield was lower at 48% however the desired product was not isolated when using the geometric isomer 1,1,1-trifluoropropan-2-ol (Scheme 2.24, Table 2.13, Products **2.118** and **2.134** respectively). Aromatic biphenyl-4-ol afforded

the desired carbamate in good yield as did cyclohexanol, (Scheme 2.24, Table 2.13, Products **2.119** and **2.120**), while unsaturated alcohols allyl alcohol and (*E*)-hex-2-en-1-ol were isolated in moderate yields (Scheme 2.24, Table 2.13, Products **2.121** and **2.122**). (1*S*,2*R*)-2-Phenylcyclohexan-1-ol was found to react well and the product was isolated in very good yields as a single diastereomer (Scheme 2.24, Table 2.13, Product **2.123**). Many compounds were tested which contained both free amines as well as alcohols which could react with the isocyanate however in these cases no products were isolated (Table 2.13, Entries **2.124-127**, **2.128-132** & **2.135**). It was not determined whether the isocyanate reacted with the alcohol, amine moieties or both in these cases and it is unclear if the reaction proceeds but the products were not isolatable by precipitation. Additionally, various other alcohols including adamant-1-ol and 1-phenylethane-1,2-diol were not isolated by precipitation (Table 2.13, Entries **2.128**, **2.129**, **2.133**, **2.136-2.140**).



Scheme 2.24

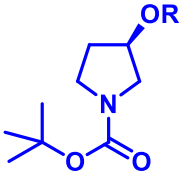
Table 2.13: Table of alcohols investigated in the synthesis of carbamates using bioavailable solvent Cyrene™ ***2.5***



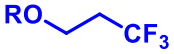
2.114 97%[a]

2.115 83%

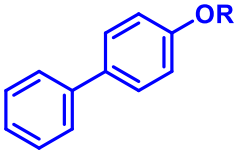
2.116 97%



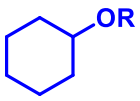
2.117 40%



2.118 48%

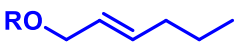


2.119 85%



2.120 74%

2.121 52%[a]



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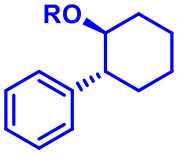

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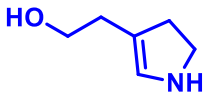

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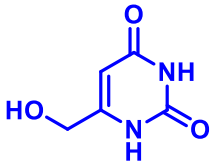

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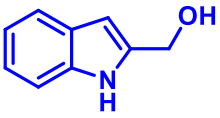

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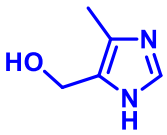

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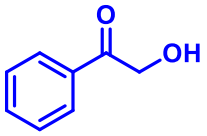

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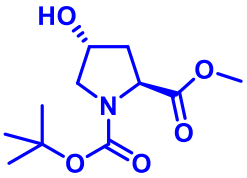

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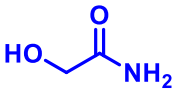

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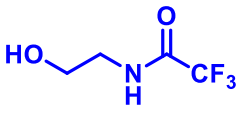

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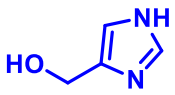

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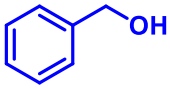

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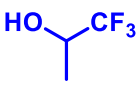

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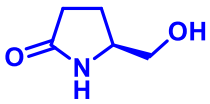

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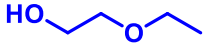

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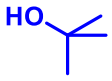

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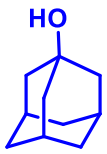

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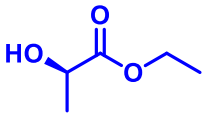

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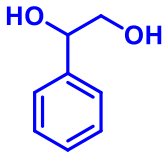

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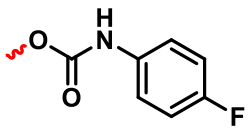
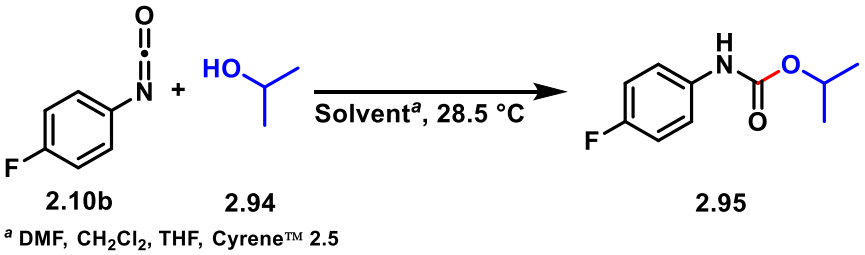
R = 

[a] **Synthesis performed by Kevan Padgett and Craig McDougal**

2.3.3.2 ^{19}F Kinetic Study

The formation of carbamates from aryl isocyanates **2.10** and alcohols is significantly slower than what was seen for the formation of ureas and amides. The use of ^{19}F NMR spectroscopy for reaction monitoring has been shown previously as a useful tool due to the high sensitivity for ^{19}F nucleus as well as the resolution of the spectrum[126]. Using this knowledge, ^{19}F NMR was used to track the disappearance of 4-fluorophenyl isocyanate **2.10b** and the appearance of product as the reaction proceeded in order to determine the rate of reaction for the formation of carbamate in different solvents (Scheme 2.25). In collaboration with Dr Christopher Wedge and Daniel Cheney, 4 reactions of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** were set up in NMR tubes, each with different solvents; DMF, DCM, THF and Cyrene™ **2.5** and the reactions monitored by ^{19}F NMR using a Magritek Spinsolve desktop NMR with hexafluorobenzene as an internal standard.



Scheme 2.25

The reaction using DMF as solvent was found to proceed very quickly, where very little starting material was observed in the initial spectrum recorded by the NMR, which can be seen as the small hump around -115 ppm, Figure 2.3. The product peak, -122 ppm, is seen to increase in intensity over a short period of time.

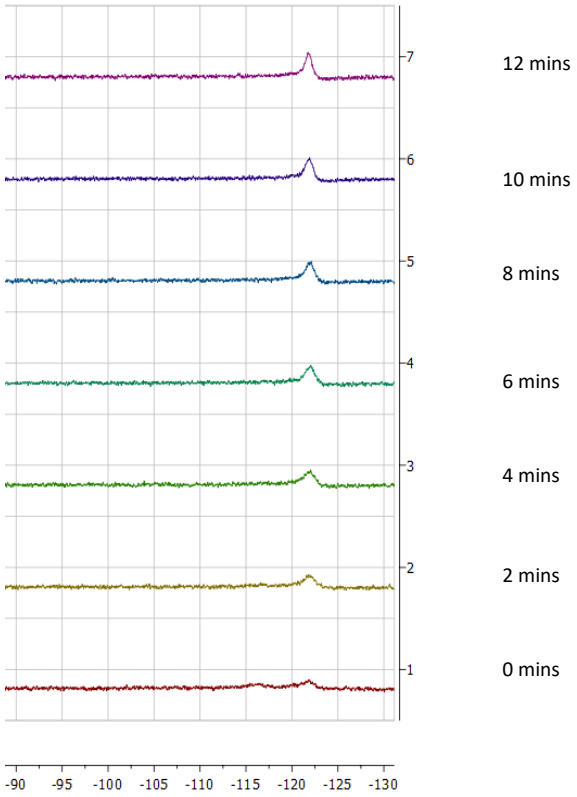


*Figure 2.3: ^{19}F Spectra for the reaction of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** in DMF*

The formation of the desired carbamate was found to proceed much slower with DCM as the chosen solvent, Figure 2.4. Only the starting material can be observed in the initial spectra however the product peak can be seen gradually increasing over time while the starting material decreases.

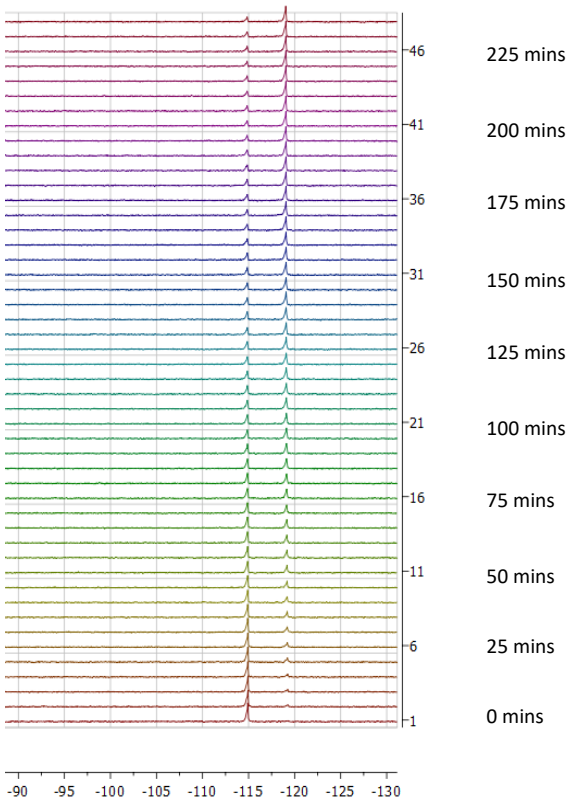


*Figure 2.4: ^{19}F Spectra for the reaction of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** in DCM*

The use of THF as solvent for this reaction reduced the rate of the reaction significantly, where several minutes pass before any peak can be seen in for the product, Figure 2.5. It can be seen that even after 40 minutes the height of the product peak is still lower than that of the peak for the starting material.

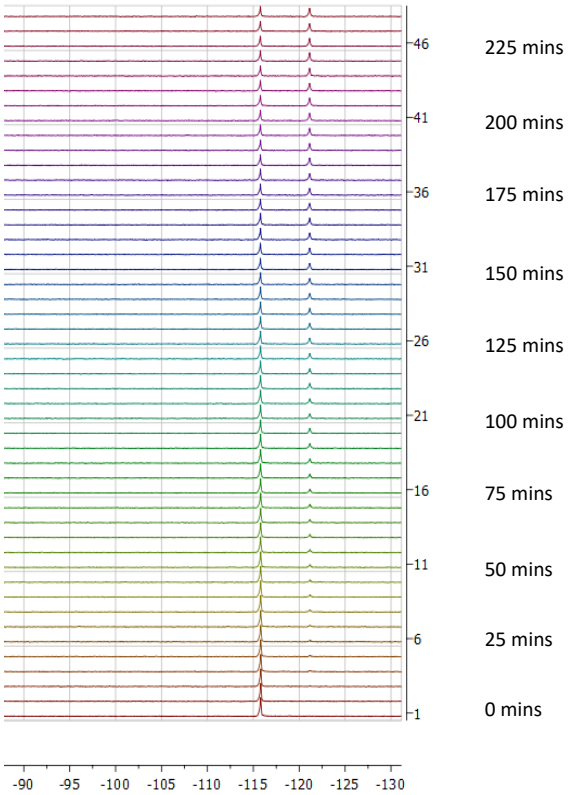


*Figure 2.5: ^{19}F Spectra for the reaction of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** in THF*

Finally using Cyrene™ **2.5** the product can be seen developing quickly in the NMR spectra, taking roughly 20 minutes to reach a 1:1 ratio of starting material and product (Figure 2.6). The reaction in Cyrene™ **2.5** appears to occur over the same timescale as the reaction in DCM, which is much quicker than the reaction in THF but significantly slower than DMF.

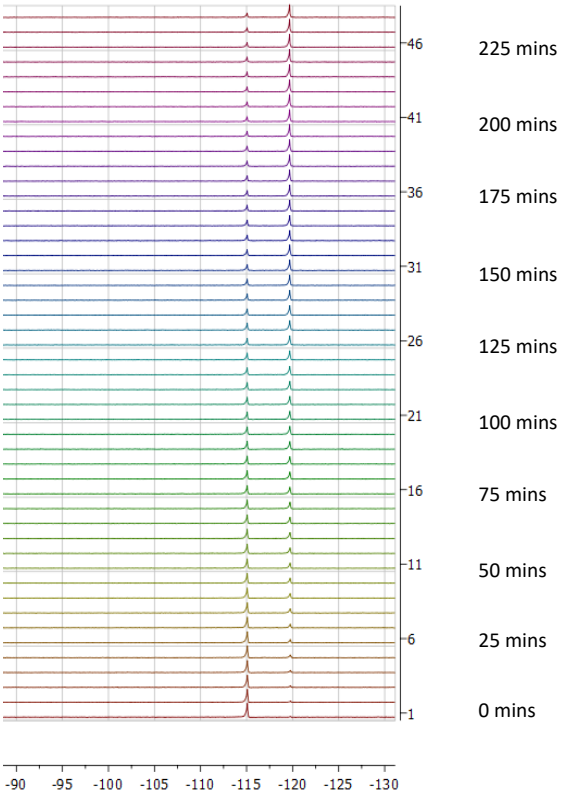


*Figure 2.6: ^{19}F Spectra for the reaction of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** in Cyrene™ **2.5***

The concentration of starting material and product in the reaction mixture was determined by integration of the fluorine peaks associated with the respective compound. These concentrations then used to determine the rate of the reaction for each of the solvents. Second order kinetics was assumed and so the rate equation can be written as the change in [I} divided by the change in time is equal to –k*[I][A], where [I] is the concentration of isocyanate and [A] is the concentration of alcohol present in the reaction (Figure 2.7, Eq. 1). As it is a 1:1 ratio reaction between the reactants the concentrations of both 4-fluorophenyl isocyanate **2.10b** and isopropanol **2.94** should be the same as the reaction proceeds, thus [I]=[A], and so the equation can be abbreviated (Figure 2.7, Eq. 2). Integrating this equation allows us to view the change in concentration over time, from t = 0 (Figure 2.7, Eq. 3). This can be rearranged to afford an equation for a straight line, which when plotted, can be used to provide the rate of the reaction by calculating the gradient of the line (Figure 2.7, Eq. 4 & 5)

$$\frac{d[I]}{dt} = -k[I][A] \qquad \textbf{Eq. 1}$$

$$\frac{d[I]}{dt} = -k[I]^2 \qquad \textbf{Eq. 2}$$

$$\frac{1}{[I]_t} - \frac{1}{[I]_0} = kt \qquad \textbf{Eq. 3}$$

$$\frac{1}{[I]_t} = kt + \frac{1}{[I]_0} \qquad \textbf{Eq. 4}$$

$$[I]_t^{-1} = kt + [I]_0^{-1} \qquad \textbf{Eq. 5}$$

Figure 2.7: Derivitisation of 2nd order rate equation

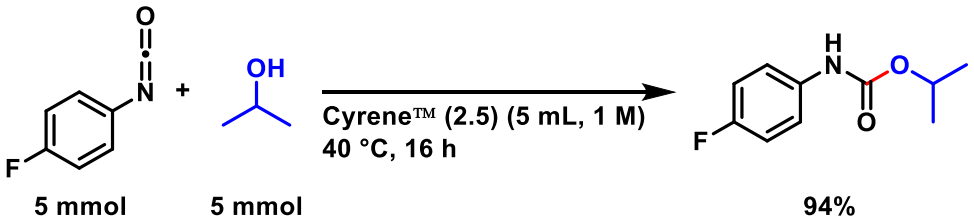
Using the data collected and the equations previously mentioned, the rates of reaction for the synthesis of isopropyl (4-fluorophenyl)carbamate **2.95** from 4-fluorophenyl isocyanate **2.10b** and isopropanol **2.94** can be determined for each of the solvents examined (Table 2.14). As seen in the NMR spectra, the rate for the reaction in THF is slower than the three other solvents used. DMF has the highest rate of reaction almost twice the rate seen for the reaction using Cyrene™ **2.5** which is close to what is seen for DCM.

Table 2.14: Table of rate constants for the reaction of 4-fluorophenyl isocyanate with isopropanol in different solvents.

Solvent	Rate constant (M^{-1} s^{-1})
DMF	$1.36\times_{10}{}^{-2}$
DCM	$3.75\times_{10}{}^{-4}$
Cyrene™	$1.45\times_{10}{}^{-4}$
THF	$6.17\times_{10}{}^{-5}$

2.3.3.3 Large scale reaction and solvent recycling

To reduce waste from the reaction, the possibility of recycling the solvent, Cyrene™ **2.5** was investigated. This is of particular importance as several reports have emerged where Cyrene™ **2.5** has degraded under some reaction protocols as well as Cyrene™ **2.5** currently being more expensive than traditional solvents[95, 127]. To explore this, the reaction was conducted on a larger scale increasing the quantity of reagents from 0.5 mmol to 5 mmol. Thus, the reaction of 4-fluorophenyl isocyanate **2.10b** with isopropanol **2.94** was conducted in Cyrene™ **2.5** at 40 °C for 16 h on a 5 mmol scale (Scheme 2.26). The reaction proceeded smoothly as expected with the product precipitating from the reaction mixture upon the addition of water yielding 94%.



Scheme 2.26

The water/Cyrene™ **2.5** mixture was then extracted with ethyl acetate, dried over magnesium sulfate and owing to the large difference in boiling point the ethyl acetate removed selectively under reduced pressure before the crude residue was passed through a silica plug to afford Cyrene™ **2.5** in 65% yield. ^{1}H NMR of the recovered solvent from this reaction showed no starting material and no products present in the Cyrene™ **2.5** sample (Figure 2.8).

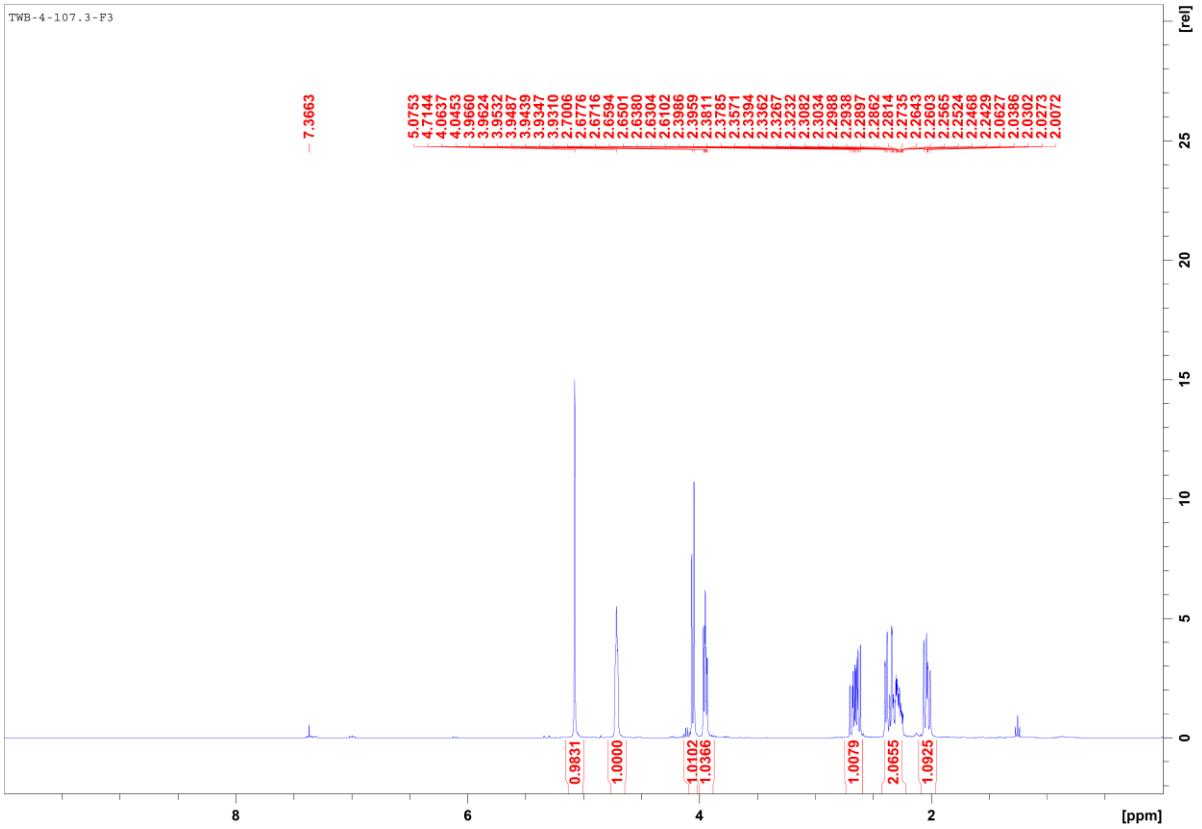
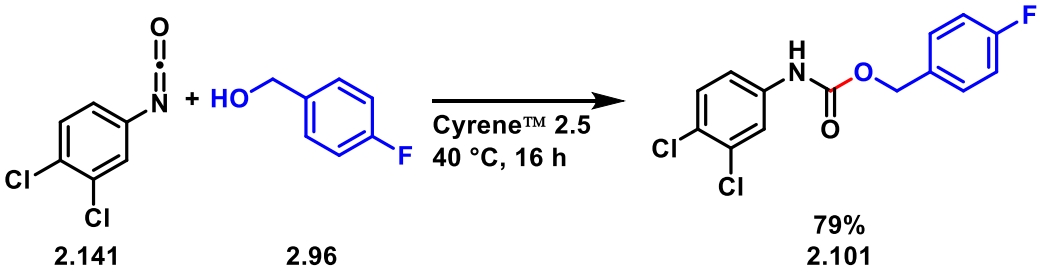


*Figure 2.8: ^{1}H NMR spectrum of recycled Cyrene™ **2.5** solvent*

Next the reaction between 3,4-dichlorophenyl isocyanate **2.141** and 4-fluorobenzyl alcohol **2.96** was performed under the standard conditions in which the recovered Cyrene™ **2.5** was used (Scheme 2.27). This reaction also proceeded smoothly and the desired product was isolated by precipitation with a yield of 79%, matching the previous investigation of this reaction. This shows that the recycled solvent works uncompromised by being used in a previous reaction or by the recycling process.



Scheme 2.27

The formation of carbamates by this method represents a green alternative to the standard protocols which use toxic solvents. The use of bioavailable solvent Cyrene™ **2.5** in this process allows for the isolation of pure compounds by precipitation, removing the waste solvents produced when purifying the desired compounds. Following the reaction by ^{19}F NMR showed that the reaction

proceeded significantly quicker in Cyrene™ **2.5** than in THF, however slightly slower than in DCM but much slower than in DMF. The reaction protocols were shown to perform well when using larger scale reactions without any decrease in performance. Additionally, it was shown that the solvent can be recycled from previous experiments without detriment to following reactions.

2.3.4 Use of Cyrene™ as a chiral scaffold

Converting biomass into chemical feedstocks is something being studied a lot in the research community[128]. Carbohydrates have long been used to make both chiral and achiral compounds for use as feedstocks or solvents like 2-methyltetrahydrofuran and furfural among others (Figure 2.9)[129].

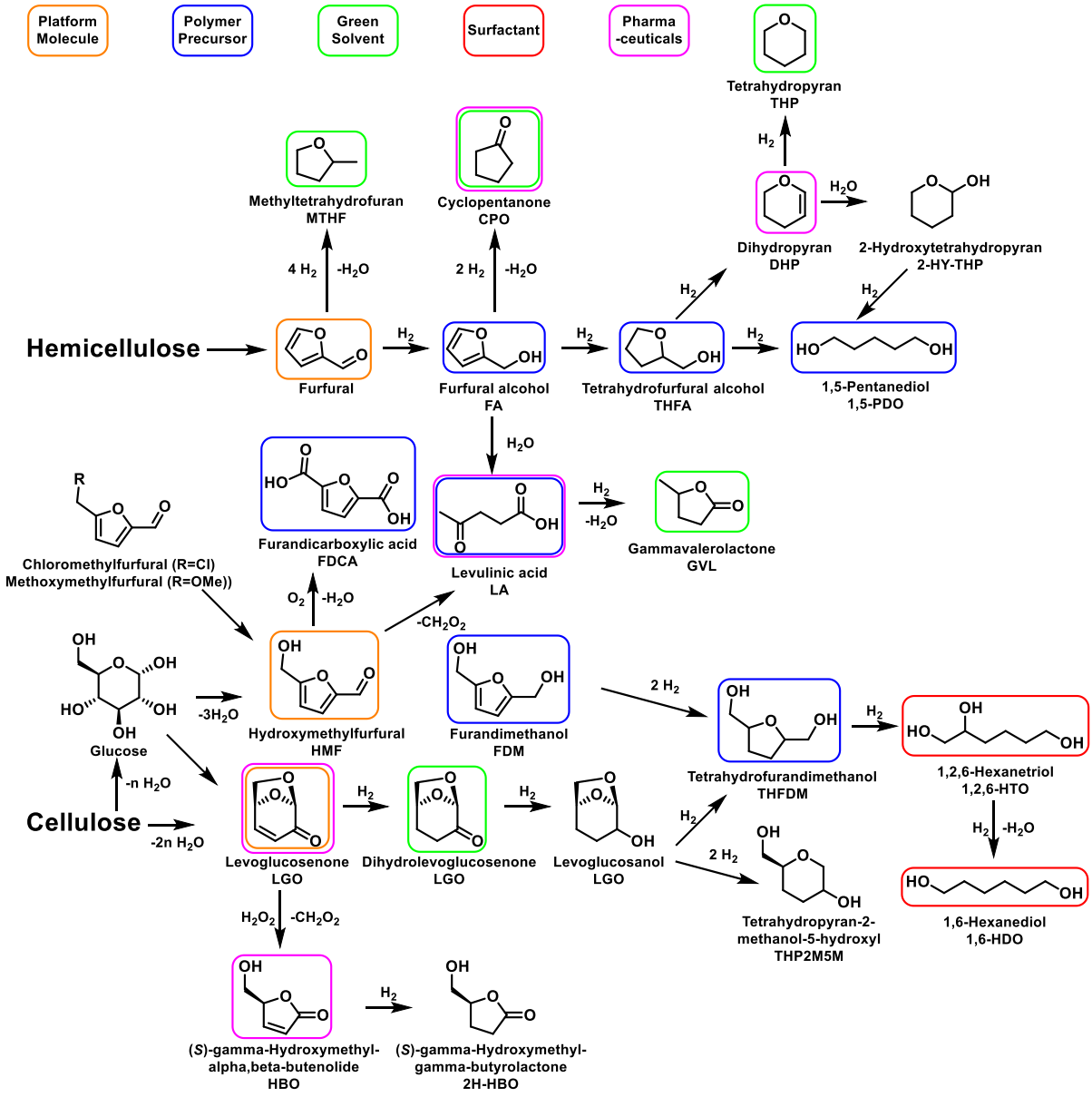
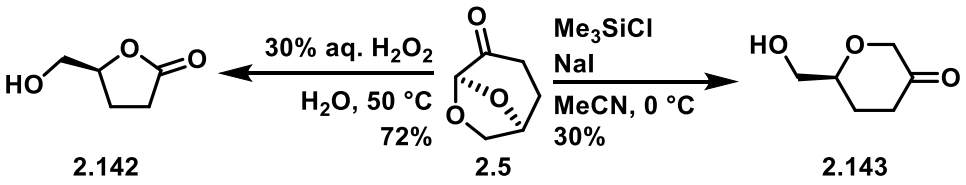


Figure 2.9: Reaction network for the synthesis of high value oxygenated compounds via conversion of biomass, highlighting proposed uses for selected compounds

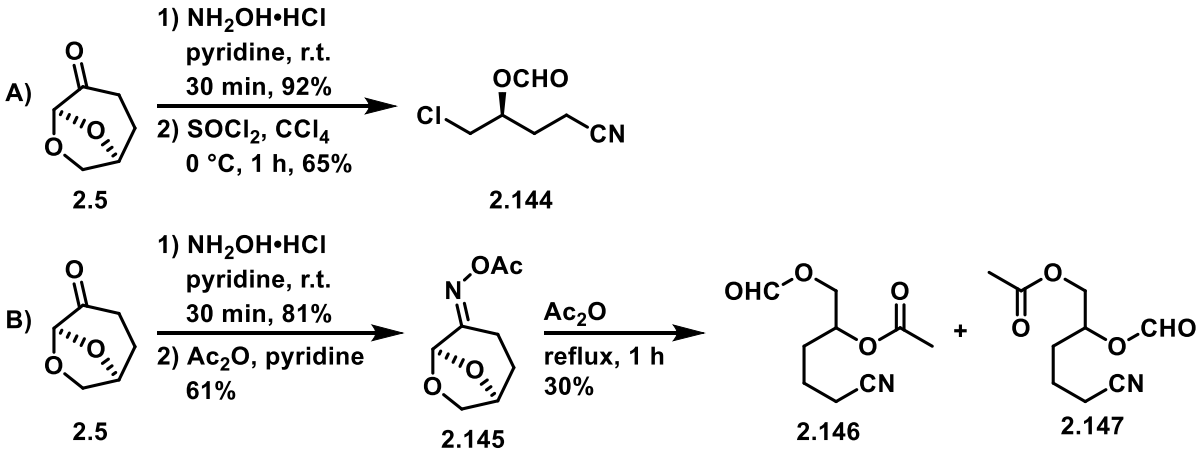
Cyrene™ **2.5** has been shown to be a viable solvent for several reactions however several reactivity limitations prevent it from being used in many more reactions. Despite these limitations as a solvent, it opens up an avenue for the use of Cyrene™ **2.5** as a bioavailable, chiral scaffold. Cleavage of the acetal moiety in Cyrene™ **2.5** is one such problem which prevents its use as a solvent in many reactions (Scheme 2.28). This can be achieved by treatment of Cyrene™ **2.5** with an aqueous

solution of hydrogen peroxide to afford the chiral lactone **2.142** in good yield[130]. Alternatively, the acetal group can be cleaved by reacting Cyrene™ **2.5** with chlorotrimethylsilane with sodium iodide to afford the chiral tetrahydropyranone derivative **2.143**[131].



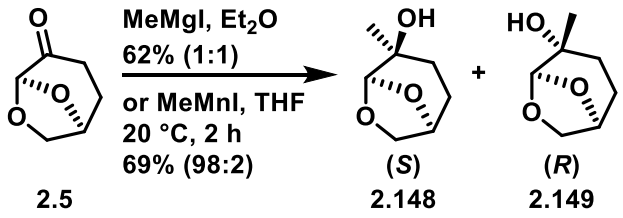
Scheme 2.28

Additionally, the Beckmann rearrangement of Cyrene™ **2.5** derivatives can be performed to give a variety of products depending on the conditions used. Valeev and co-workers performed the rearrangement on an oxime derivative to afford the chloro-nitrile compound **2.144** (Scheme 2.29A)[132], while Williams showed that an abnormal rearrangement was possible on an oxime acetate derivative **2.145** of Cyrene™ **2.5** to afford compounds **2.146** & **2.147** (Scheme 2.29B)[133].



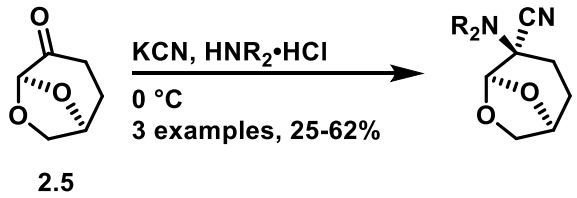
Scheme 2.29

The addition of nucleophiles to the ketone moiety represents some of the earliest work on the derivatisation of Cyrene™ **2.5**. In 1977, Shafizadeh and Chin showed the potential of reacting Cyrene™ **2.5** with methylmagnesium iodide in Et_2O to afford a 1:1 mixture of alcohols **2.148** and **2.149** (Scheme 2.30)[88]. More recently it has been shown that the addition of methylmanganese iodide to Cyrene™ **2.5** in THF was highly stereoselective to the (*S*) isomer **2.148**[134].



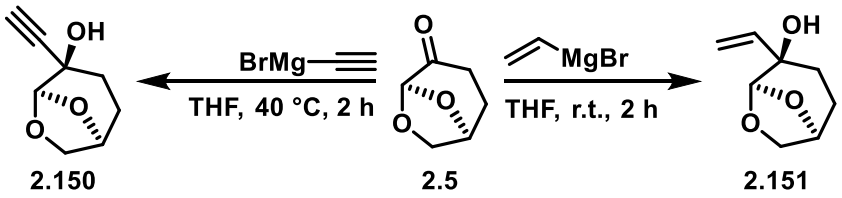
Scheme 2.30

The Strecker reaction was able to proceed with imine derivatives of Cyrene™ **2.5** to afford amino nitriles through addition of potassium cyanide (Scheme 2.31)[135]. This process is highly stereoselective and the scaffold can be transformed into biologically active compounds.



Scheme 2.31

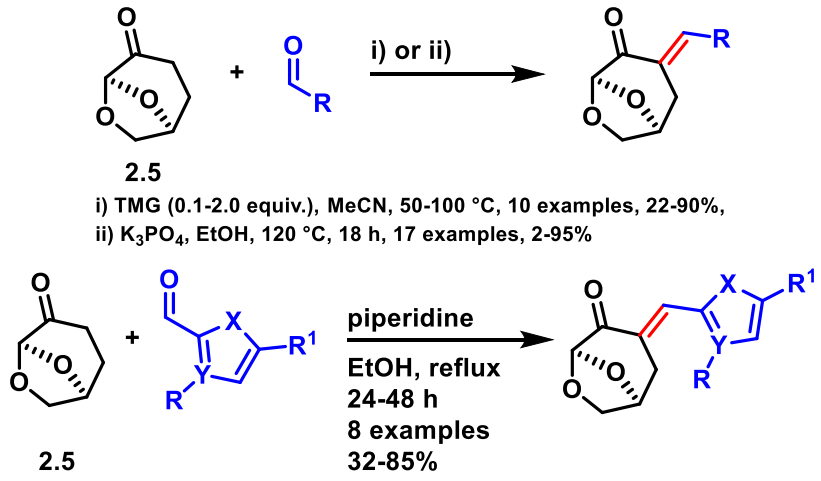
Finally, Brel and co-workers showed how Grignard reagents could be used for additions to the ketone moiety of Cyrene™ **2.5** where the use of ethynylmagnesium bromide and vinylmagnesium bromide afforded alcohols **2.150** and **2.151** respectively (Scheme 2.32)[136]. This highly selective process afforded the (*R*) isomers in >90% selectivity.



Scheme 2.32

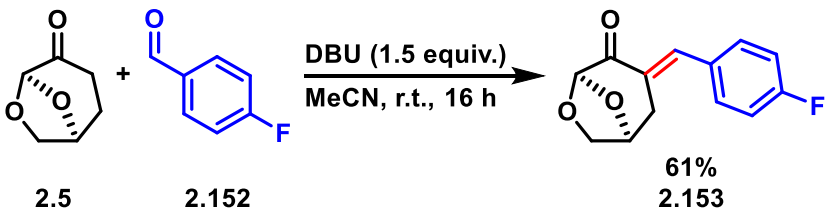
2.3.4.1 Aldol condensation

Aldol condensation reactions are a good way of forming new C-C bonds alpha to a carbonyl group and this process has found applications in the synthesis of many important chemicals including pharmaceuticals and dyes among others[137]. Containing a ketone moiety, Cyrene™ **2.5** is a good molecule to perform Aldol condensations with and as such several reports of this have emerged. Greatrex *et al.* showed that tetramethylguanidine (TMG) could catalyse the reaction and allow condensation of Cyrene™ **2.5** with several aromatic aldehydes (Scheme 2.33 eq. 1)[138]. 10 examples were synthesised in poor to excellent yields either in acetonitrile at 50 °C or solventless at 100 °C. Similarly Hunt and co-workers showed the same reaction could be performed with different conditions, utilising tripotassium phosphate as the base (Scheme 2.33 eq. 1)[132]. Witczak and co-workers found that using TMG as a base catalyst for Aldol condensation between Cyrene™ **2.5** and heterocyclic aldehydes produced a complex mixture of products[139]. A base screen found that piperidine was able to smoothly catalyse the reaction, forming the desired compounds as expected (Scheme 2.33 eq. 2).



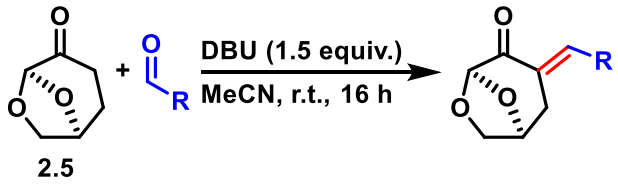
Scheme 2.33

Simultaneously to this, the Camp group exploited the ketone moiety in Cyrene™ **2.5** in an Aldol condensation reaction with aromatic aldehydes in the presence of strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile[140]. The reaction with 4-fluorobenzaldehyde **2.152** and Cyrene™ **2.5** at r.t. for 16 h afforded the desired product **2.153** at 61% (Scheme 2.34).



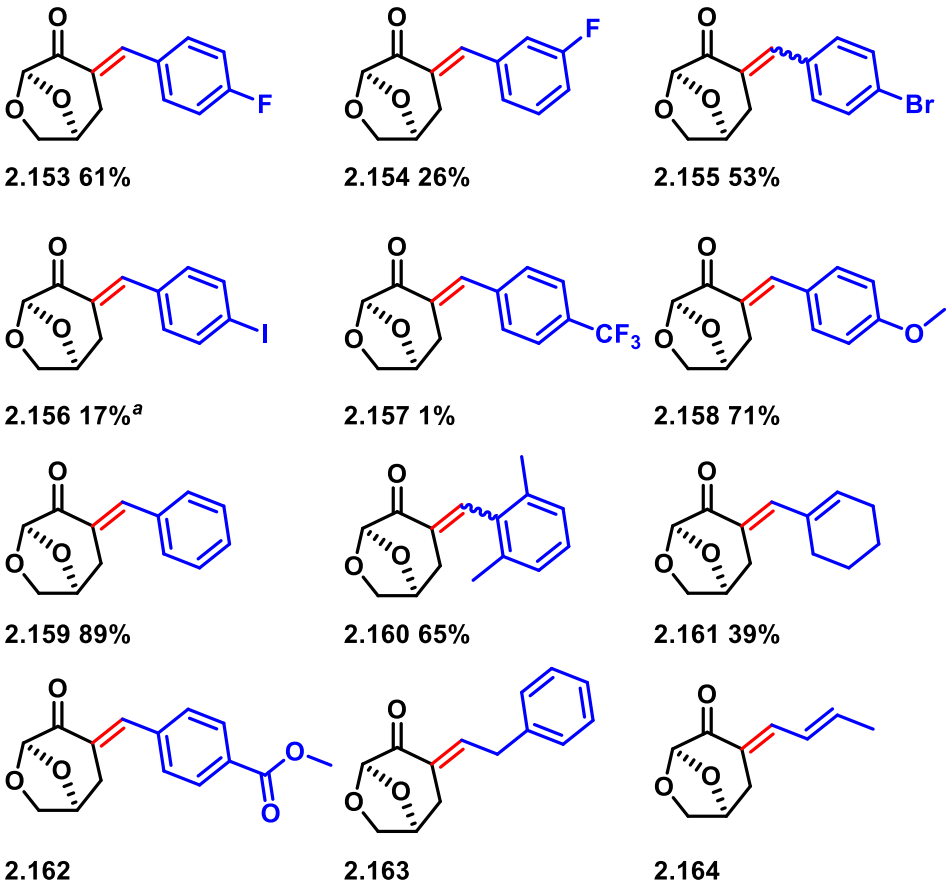
Scheme 2.34

3-Fluorobenzaldehyde did not react as well as the 4-fluoro isomer yielding only 26% (Scheme 2.35, Table 2.15 Entry **2.154**). 4-Bromobenzaldehyde reacted well with Cyrene™ **2.5** to produce the desired Aldol products in 53% while 4-iodobenzaldehyde reacted poorly, producing only 17% (Scheme 2.35, Table 2.15, Entries **2.155** and **2.156** respectively). Interestingly, a mixture of *E* and *Z* isomers was observed, in a 3:2 ratio respectively, for the reaction with 4-bromobenzaldehyde. A very poor yield was isolated when using 4-(trifluoromethyl)benzaldehyde at 1% (Scheme 2.35, Table 2.15, Entry **2.157**), however good yields were attained for both benzaldehyde and anisaldehyde (Scheme 2.35, Table 2.15, Entries **2.156** and **2.158**). Further investigations into the reaction using 4-(trifluoromethyl)benzaldehyde highlighted an additional product isolated in the purification step which will discussed *vide infra* (Section 0). Sterically hindered 2,6-dimethylbenzaldehyde reacted well while also producing both *E* and *Z* isomers in a ratio of 2:1, with a yield of 65% (Scheme 2.35, Table 2.15, Entry **2.160**). Moderate yield was isolated when using cyclohex-2-ene-1-carbaldehyde at 39% (Scheme 2.35, Table 2.15, Entry **2.161**). The reactions involving methyl 4-formylbenzoate, 2-phenylacetaldehyde and (*E*)-but-2-enal did not produce the desired enone (Table 2.15, Entries **2.162**-**2.164**).



Scheme 2.35

Table 2.15: Table of Aldol condensation products with Cyrene™



While Aldol condensation reactions can form both *E* and *Z* geometric isomers[141] it was found that only the *E*-isomer was formed in the reaction between Cyrene™ **2.5** and 4-fluorobenzaldehyde **2.152** through the investigation of 2D NMR spectra (Figure 2.10).

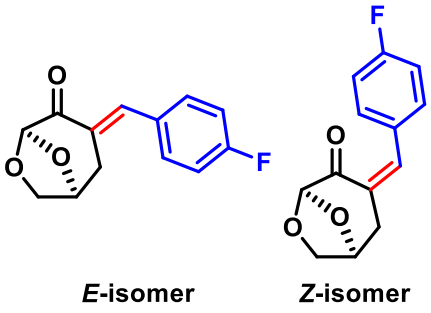


Figure 2.10: Structures of E *and* Z *isomer Aldol products*

In order to confirm whether the Aldol product was in the *E* or *Z* configuration a crystal of **2.154** was grown by layering (DCM/Hexane). X-ray analysis of the crystal showed only a single isomer of Aldol product was present, which was the *E*-isomer (Figure 2.11, Appendix A).

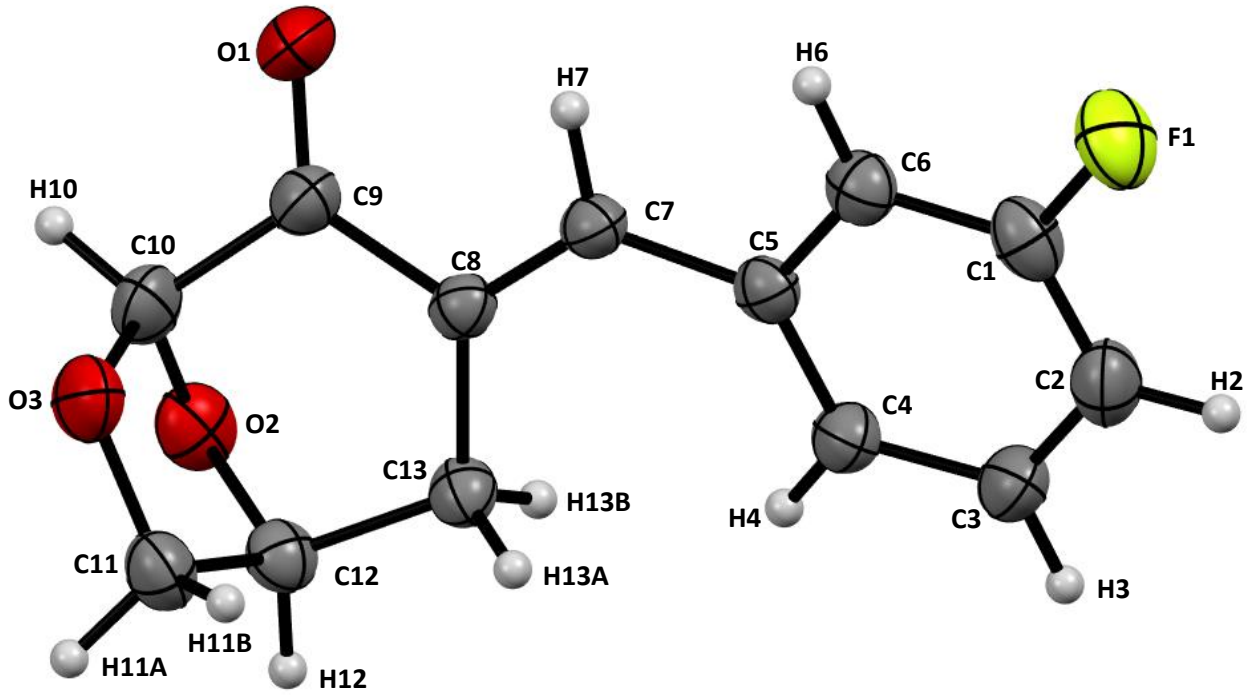


Figure 2.11: ORTEP plot of 2.154, ellipsoids at 50% probability

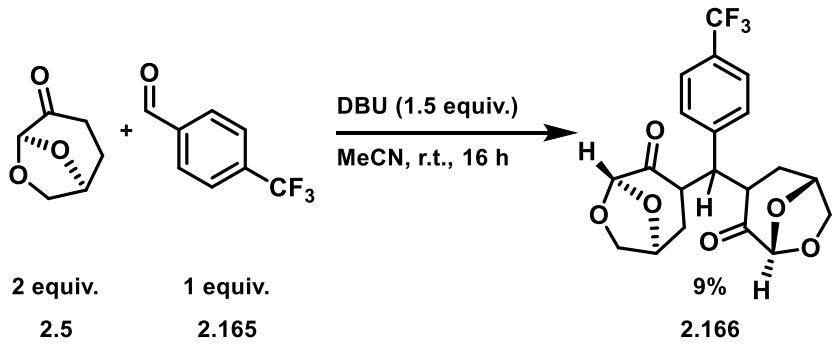
The bond lengths, Table 2.16, are comparable to those found in the literature[142]. The double bond between C7 and C8 is significantly shorter than that of the bond between C5 and C7, 1.352 Å and 1.468 Å respectively. The same can be said when comparing the carbonyl C9-O1 double bond with the C-O single bonds found in the Cyrene™ **2.5** fused ring system. Finally the C1-F1 has a bond length of 1.352 Å.

Table 2.16: Selected bond lengths for 2.154

Atom 1	Atom 2	Bond Length (Å)
C5	C7	1.468(4)
C7	C8	1.352(3)
O1	C9	1.215(4)
O3	C10	1.422(4)
O3	C11	1.440(4)
O2	C10	1.399(4)
O2	C12	1.436(3)
F1	C1	1.352(3)

2.3.4.2 Aldol/Michael cascade process

It was noticed that an additional compound was isolated during the purification of the Aldol condensation reaction between 4-(trifluoromethyl)benzaldehyde **2.165** and Cyrene™ **2.5**. In collaboration with Dr. Ben Greatrex and co-workers, the isolated compound was determined to be an Aldol/Michael cascade product where a molecule of Cyrene™ **2.5** further reacted with the desired Aldol condensation product to form a "dimer" product. In order to purposefully make the Aldol/Michael cascade product, the reaction between 4-(trifluoromethyl)benzaldehyde **2.165** and Cyrene™ **2.5** was repeated using 2 equivalents of Cyrene™ **2.5** (Scheme 2.36). This effort allowed the isolation of the dimer **2.166** although in a very poor yield of 9%.



Scheme 2.36

Complex 1D and 2D NMR spectra were analysed in order to determine the structure of the isolated compound. The aromatic region shows 2 broad peaks integrating to 2 protons each, this indicates there is a *para*-substituted aromatic ring in the compound, as expected. Interestingly, two singlets at 5.39 and 5.29 ppm can be identified for the protons sandwiched between the carbonyl and acetal moieties (Figure 2.12, highlighted Blue). The presence of two peaks signifies they are not in equal environments. Analysis of the 2D spectra identified the central proton as an apparent doublet at 3.28 ppm (Figure 2.12, highlighted Red). The corresponding ^{13}C peak for this proton is at 42.9 ppm and is confirmed to be a CH by DEPT 135 and DEPT 90. HMBC of this proton reveals correlations of this proton with both carbonyl carbons.

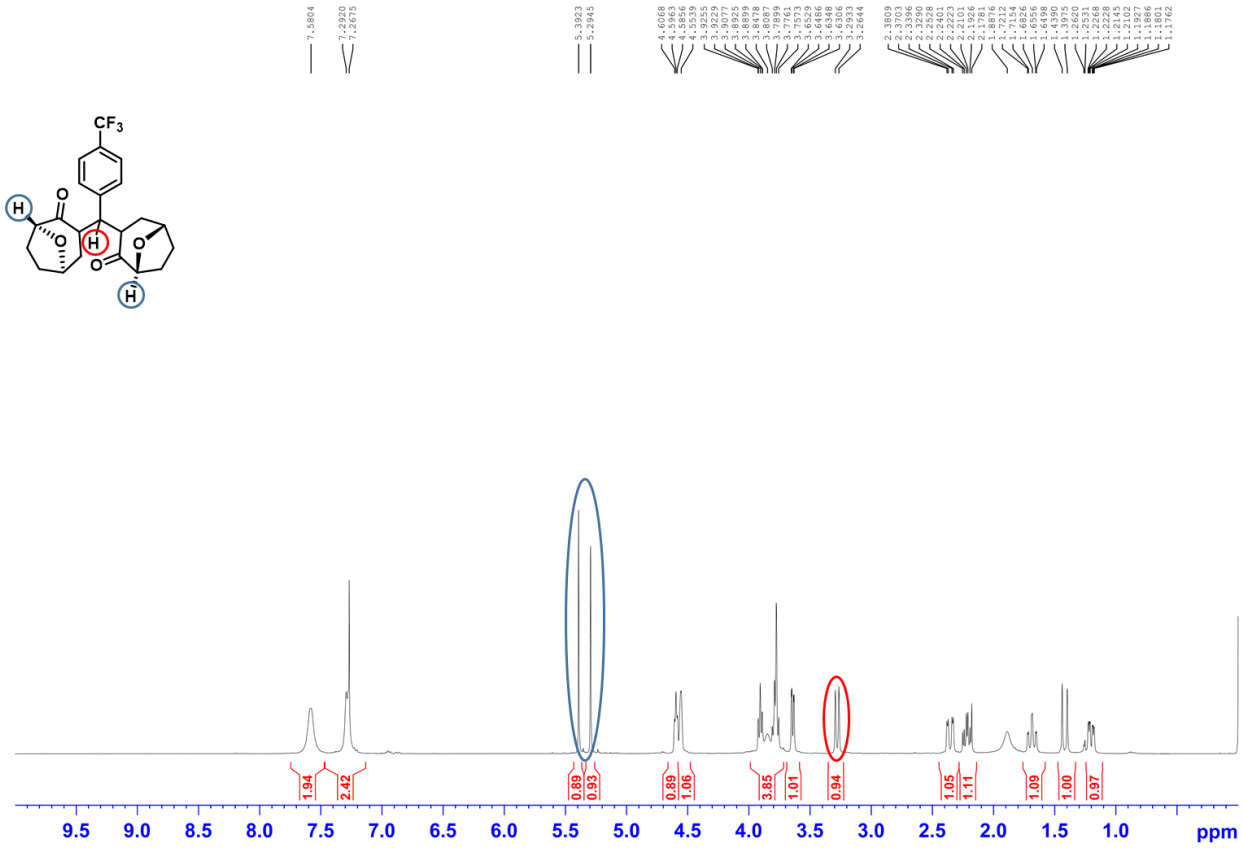
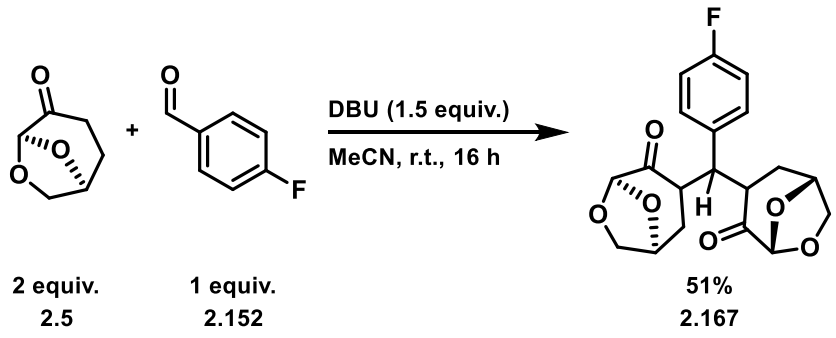


Figure 2.12: ^{1}H NMR spectrum of isolated dimer adduct 2.166

To determine whether this process could be repeated, 4-fluorobenzaldehyde **2.152** was subjected to the same reaction conditions of 2 equivalents of Cyrene™ **2.5** (Scheme 2.37). The desired dimer product **2.167** was isolated in a much better yield of 51%.



Scheme 2.37

The dimer structure is further confirmed by the analysis of the NMR data. Comparing the complex NMR spectra of the dimer adduct to the simpler NMR spectra for the Aldol condensation product, many similarities and differences can be identified (Figure 2.13). Both compounds contain 4 aromatic protons as expected, however 2 peaks can be identified for the proton sandwiched between the acetal and ketone moiety in the dimer adduct whereas only 1 peak is seen for **2.153**, showing that the dimer product does contain two Cyrene™ "units". Additionally, it can be seen that

the alkene proton at 7.61 ppm in **2.153** is not present in the dimer product. The central CH present in the dimer adduct is seen shifted upfield to 3.15 ppm in the 4-fluoro compound compared to the CF_3 compound due to the CF_3 moiety being more electronegative, thus deshielding the proton. Further evidence for the formation of **2.166** and **2.167** can be gathered from the IR spectra and mass spectrometry. Both compounds show carbonyl functionality with signals at around 1680 cm^{-1}, which is characteristic for ketone moieties. Additionally, analysis of the compounds by mass spectrometry indicates the proposed compounds are present, with the mass signals corresponding to $[M+H]^+$ adducts with *m/z* = 413.1202 for **2.166** (CF_3) and *m/z* = 363.1249 for **2.167** (4-F), $[M+Na]^+$ species were present.

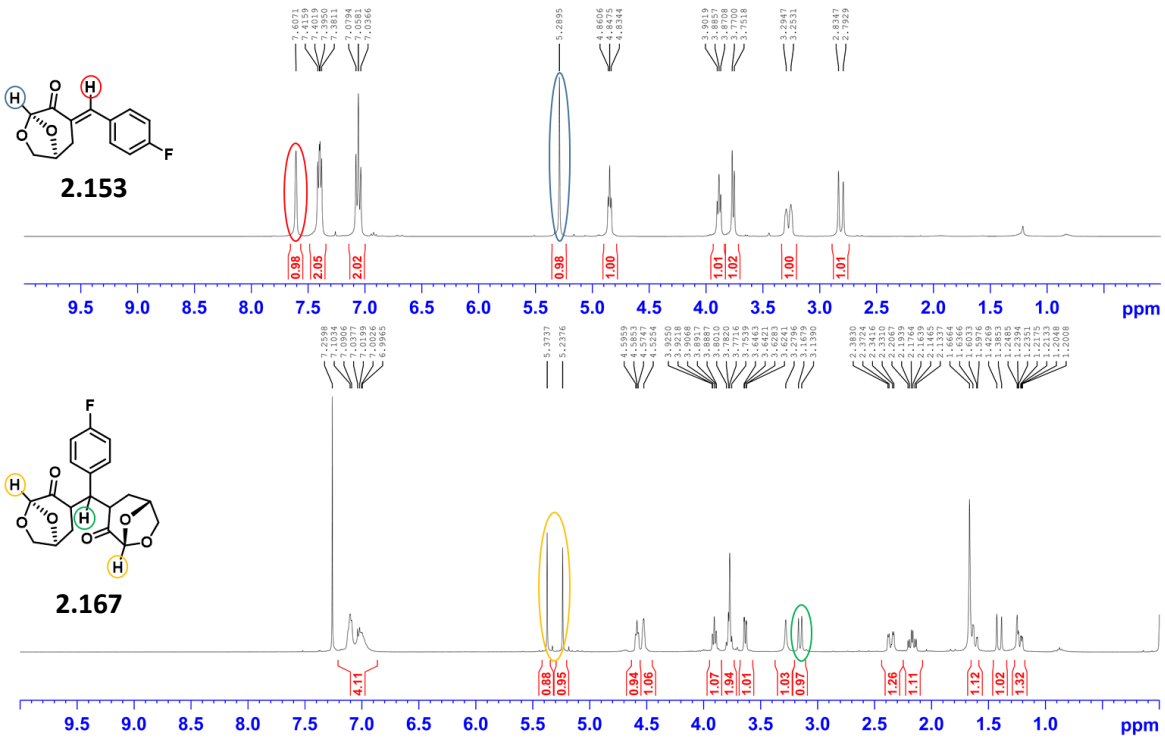


*Figure 2.13: Comparison of ^{1}H NMR of Aldol and dimer products for the reactions using 4-fluorobenzaldehyde **2.152***

2.4 Conclusions

Preliminary studies found that the synthesis of ureas from aryl isocyanates and amines in the bio-available solvent Cyrene™ would proceed as desired. Development of the work-up procedures for the reactions in Cyrene™ discovered that urea products would precipitate from the reaction mixture upon addition of water when using secondary amines. Isolation of products by this method did not require further purification by column chromatography, thus reducing waste produced, however, ureas synthesised from primary amines were found not to precipitate upon the addition of water to the reaction mixture.

A range of amines were reacted with phenyl isocyanate in the bio-available solvent Cyrene™ affording 16 examples in good to excellent yields. Cyclic and acyclic aliphatic amines were found to react well under the conditions developed while heteroaromatic, amino acid and hydroxylamine did not yield the desired products. Owing to the success of urea synthesis from phenyl isocyanate with various amines, the phenyl moiety was altered and a range or aryl isocyanates were reacted with pyrrolidine. Overall seven additional urea examples were synthesised in moderate to excellent yields.

Following the success of Cyrene™ in the synthesis of ureas, the synthesis of amides from acid chlorides with a range of amines, was investigated. Initial studies found that the product of the reaction between 4-fluorobenzoyl chloride with secondary amine pyrrolidine could not be isolated by precipitation. Instead an aqueous work-up and purification by column chromatography was required to isolate the reaction product in high yield. In order to reduce the waste produced by the work-up procedure, the reaction mixture was columned directly, removing the aqueous work-up step, although this reduced the yield of the reaction. It was found that reactions using primary amines aniline and benzylamine afforded products by the desired precipitation work-up method. Analysis of the Mol. E% of the work-up procedures determined that the isolation of compounds by precipitation was between 24-28 times more efficient than that of isolation by aqueous work-up and purification by column chromatography.

A series of acid chlorides were reacted with both aniline and benzylamine to afford twenty one examples in poor to excellent yields. Halogenated aromatic acid chlorides were found to react very well under the conditions and products were isolated easily by precipitation, as was electron rich aromatic acid chloride 3,4-dimethoxybenzoyl chloride. Heteroaromatic acid chlorides were also found to react under the reaction conditions and isolated by precipitation with the exception of the reaction between nicotinoyl chloride and benzylamine. Cyclic aliphatic acid chlorides were also good substrates for the reaction and work-up conditions. Unsubstituted benzoyl chloride, long chain

valeroyl chloride and 4-(dimethylamino)benzoyl chloride did not afford products under the desired reaction and work-up conditions with either of the amines used along with the dichloro heteroaromatic acid chloride and bis-acid chloride and their respective reactions with benzylamine. A small selection of additional primary amines were also reacted with 4-fluorobenzoyl chloride however this series provided no isolable products.

Next, a series of acid chlorides were reacted with the secondary amine pyrrolidine, the products did not precipitate but an additional six examples were isolated by direct column chromatography in good to very good yields. The reaction of several acid chlorides however did not afford the desired amides, either producing a complex mixture of products or returning amine starting material.

Utilising an Excel-based Mol. E% calculator that was developed in the group, the method for synthesising amides and isolation by precipitation was compared to similar methods for the synthesis of amides, including the synthesis of amides using pyrrolidine that was also. It was found that the method of synthesising amides and isolating by precipitation was roughly 55 times more efficient than standard methods which require aqueous work-up and purification by column chromatography.

Finally, the use of Cyrene™ as a solvent for the synthesis of carbamates was investigated by reacting aryl isocyanates with alcohols. Initial studies found that the reaction at room temperature required a week to afford good yields; an increase in temperature to 40 °C was sufficient to reduce the reaction time of 4-fluorophenyl isocyanate with isopropanol to 16 h. Two alcohols were initially investigated for the synthesis of carbamates, primary alcohol 4-fluorobenzyl alcohol and secondary alcohol isopropanol and were found to afford the desired products by precipitation when reacted with 4-fluorophenyl isocyanate. With optimised conditions in hand, a variety of aryl isocyanates were reacted with isopropanol and 4-fluorobenzyl alcohol, this afforded eight examples in good to excellent yields. Unsubstituted, *para*-halogenated and electron rich aryl isocyanates were all found to react well, affording the desired products with both alcohols by precipitation. Electron-withdrawing, *meta*- and *ortho*-substituted halogenated phenyl isocyanates and *para*-bromophenyl isocyanate were found not to be suitable substrates for the reaction and work-up conditions. In order to determine the substrate scope of the alcohols that can be used for the synthesis of carbamates in Cyrene™, a variety of alcohols were subjected to the reaction conditions, providing eleven examples in poor to excellent yields.

A study into the reaction rate of the synthesis of carbamates from aryl isocyanates and alcohols was performed whereby the reaction of 4-fluorophenyl isocyanate and isopropanol was performed in

several solvents and the substrate concentration was followed by ^{19}F NMR on a Spinsolve desktop NMR machine. This study determined that the rate of the reaction was fastest in DMF followed by DCM. The rate of reaction in Cyrene™ was slightly slower than in DCM and in THF was much slower than that of Cyrene™.

In order to probe the recyclability of Cyrene™, it was recovered from the reaction of 4-fluorophenyl isocyanate (5 mmol) and isopropanol, where the reaction product was isolated by precipitation, by washing with water and passing through a silica plug. The recycled solvent was then successfully reused in a second reaction between 3,4-dichlorophenyl isocyanate and 4-fluorobenzyl alcohol. Performing the standard work-up procedures afforded the desired product by precipitation without any loss of yield. This highlights the ability to reuse the Cyrene™ solvent without any detrimental effects to the subsequent reactions performed in it.

The use of Cyrene™ as a chiral scaffold has been previously reported whilst simultaneously being investigated in the Camp group. Aldol condensation reactions of Cyrene™ were performed in the presence of DBU in acetonitrile with a variety of aldehydes. Nine examples of Aldol condensation product were synthesised in very poor to very good yields. Crystal structure of the 4-fluoro adduct was used to determine the structure of the compound was the *E*-isomer. It was discovered that the reaction using 4-(trifluoromethyl)benzaldehyde afforded two different compounds and through extensive investigations of the NMR spectra it was determined to be a bis-addition product where the Aldol condensation product reacted further with another Cyrene™ molecule. Performing the reaction with 2 equivalents of Cyrene™ afforded the bis-addition product in greater yield.

In summary, conditions for the synthesis of ureas, amides and carbamates have been developed using the bio-available solvent Cyrene™. Isolation of products by precipitation has been shown to be much more efficient than standard work-up procedures for similar reactions. The use of Cyrene™ as a solvent in large scale reactions as well as solvent recycling has been demonstrated without compromising the reactions. Furthermore the use of Cyrene™ as a chiral scaffold has been presented.

2.5 Experimental

2.5.1 Equipment and reagents

Unless otherwise stated, reagents were used as supplied. Reagents were purchased from Alfa Aesar, Fluorochem, and Sigma Aldrich. Cyrene™ was provided by Circa Group Ltd.

NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz and ^{19}F 300 MHz) or a Bruker Avance 500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz and ^{19}F 376 MHz). Coupling constants are given in Hz.

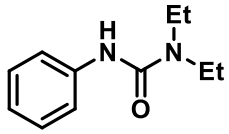
Accurate mass measurements were obtained from the IPOS Mass Spectrometry Service at the University of Huddersfield. Single crystal studies were recorded on a Bruker D8 Venture diffractometer with a Dual IμS Microfocus Sources using Mo and/or Cu radiation. The temperature of data collection was 100K.

Melting point ranges were determined in capillary tubes using a Stuart SMP10 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Nicolet 380 Spectrum Spotlight system equipped with a diamond probe ATR attachment (neat sample). TLC was performed on Merck TLC Aluminium sheets, silica gel 60 F_{254} using a range of eluent systems of differing polarity. Flash column chromatography separations were performed on Aldrich, 35-70μ, 60A silica gel or Fluorochem 40-63μ, 60A silica gel or purified using a Biotage® Isolera 4 Automated Purification System equipped with Biotage® Snap Ultra Biotage® HP-Sphere™ 25μm cartridges.

^{19}F{^{1}H} NMR spectra were recorded on a benchtop NMR instrument (Magritek, Spinsolve Carbon, 43 MHz) utilizing a permanent magnet in a Hallbach design[143], temperature stabilized at 28.5°C. The instrument works on a lock-free basis hence deuterated solvents are not required, although shimming, which is performed daily prior to insertion of the samples of interest, is performed on a H_2O:D_2O (1:9 v:v) mixture. Samples were prepared by adding 4-fluorophenyl isocyanate to a solution of isopropanol in the desired solvent in 5 mm NMR tubes immediately prior to NMR acquisition. Spectra were recorded using a 90° pulse with 0.819s FID acquisition time, and averaged over 4 scans ^{19}F{^{1}H}, a spectrum obtained in this way is shown in Fig S1; reagent concentration was obtained by integration over the range -113.1 to -117.1 ppm, -114.1 to -118.1 ppm for DMF, -113.8 to -117.8 ppm for THF, and -112.9 to -116.9 ppm for DCM. Reaction rates were extracted assuming second order kinetics from linear fits to graphs of inverse concentration vs time.

2.5.2 Chapter 2 compound experimental

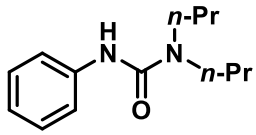
2.5.2.1 1,1-Diethyl-3-phenylurea 2.17[104]



To a stirred solution of diethylamine (52 µL, 0.50 mmol) in Cyrene™ (0.1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.50 mmol). The resultant mixture was stirred at r.t. for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulfate to give 1,1-diethyl-3-phenylurea (**2.17**, 92 mg, 96%) as a white solid.

mp. (°C) 79-81 [Lit. 84-85]; IR (neat): 2981, 2361, 1752, 1635, 1529 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, *J* = 7.2 Hz, 6H), 3.37 (q, *J* = 7.2 Hz, 4H), 6.55 (bs, 1H), 7.07-7.11 (m, 1H), 7.29-7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5, 42.0, 121.3, 124.1, 128.9, 137.8, 155.8; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{17}N_2O]^+$ 193.1335; found 193.1335.

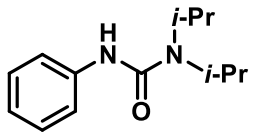
2.5.2.2 3-Phenyl-1,1-dipropylurea 2.18[104]



To a stirred solution of dipropylamine (69 µL, 0.50 mmol) in Cyrene™ (0.1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.50 mmol). The resultant mixture was stirred at r.t. for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulfate to give 1,1-dipropyl-3-phenylurea (**2.18**, 49 mg, 44%) as a white solid.

mp. (°C) 70-72 [Lit. 71]; IR (neat): 3314, 2953, 2871, 2362, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, *J* = 11.8 Hz, 6H), 1.64 (sex, *J* = 9.4 Hz, 4 H), 3.25 (t, *J* = 9.4 Hz, 4 H), 6.36 (bs, 1 H), 6.97-7.01 (m, 1 H), 7.23-7.27 (m, 2 H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 21.8, 49.4, 119.8, 122.7, 128.7, 139.3, 155.0; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{21}N_2O]^+$ 221.1648; found 221.648.

2.5.2.3 1,1-Diisopropyl-3-phenylurea 2.19[104]

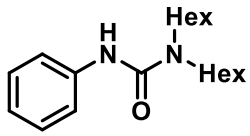


To a stirred solution of diisopropylamine (70 µL, 0.50 mmol) in Cyrene™ (0.1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.50 mmol). The resultant mixture was stirred at r.t. for 1 h. Water (5 mL)

was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulfate to give 1,1-diisopropyl-3-phenylurea (**2.19**, 68 mg, 62%) as a white solid.

mp. (°C) 119-121 [Lit. 113-115]; IR (neat): 3313, 2954, 2871, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (d, *J* = 8.6 Hz, 12 H), 3.94 (sept, *J* = 8.6 Hz, 2 H), 6.31 (bs, 1H), 6.96-6.99 (m, 1H), 7.23-7.26 (m, 2H), 7.35-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 45.5, 119.7, 122.5, 128.7, 139.4, 154.6; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{21}N_2O]^+$ 221.1648; found 221.1648.

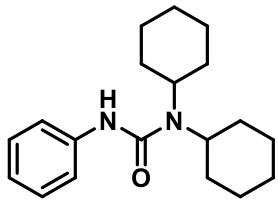
2.5.2.4 1,1-Dihexyl-3-phenylurea 2.21[104]



To a stirred solution of dihexylamine (117 µL, 0.50 mmol) in Cyrene™ (0.1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.50 mmol). The resultant mixture was stirred at r.t. for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulfate to give 1,1-dihexyl-3-phenylurea (**2.21**, 136 mg, 89%) as a yellow solid.

mp. (°C) 62-63; IR (neat): 3310, 2925, 2855, 1626, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87-0.96 (m, 6 H), 1.30 (br. s, 12 H), 1.56-1.60 (m, 4H), 3.26 (t, *J* = 9.5 Hz, 4H), 6.43 (bs, 1H), 6.96-7.00 (m, 1H), 7.22-7.26 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.6, 26.6, 28.6, 31.6, 47.7, 119.8, 122.6, 128.7, 139.4, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{19}H_{33}N_2O]^+$ 305.2587; found 305.2588.

2.5.2.5 1,1-Dicyclohexyl-3-phenylurea 2.23[104]

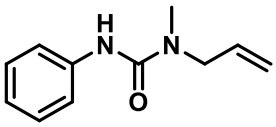


To a stirred solution of dicyclohexylamine (99 µL, 0.50 mmol) in Cyrene™ (0.1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.50 mmol). The resultant mixture was stirred at r.t. for 1 h. Water (5 mL) was added and the precipitate was filtered and washed with water. The residue was dried over anhydrous sodium sulfate to give 1,1-dicyclohexyl-3-phenylurea (**2.23**, 131 mg, 87%) as a white solid.

mp. (°C) 173-175 [Lit. 167-168]; IR (neat): 3321, 2924, 2850, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.17 (m, 2H), 1.24-1.38 (m, 4H), 1.64- 1.84 (m, 14H), 3.43-3.50 (m, 2H), 6.33 (br. s, 1 H), 6.96-6.99 (m, 1H), 7.23-7.27 (m, 2H), 7.34- 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 26.4, 31.9,

55.4, 119.6, 122.4, 128.7, 139.4, 154.9; HRMS (ESI) *m/z* Calcd for $[C_{19}H_{29}N_2O]^+$ 301.2274; found 301.2275.

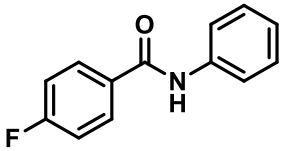
2.5.2.6 1-Allyl-1-methyl-3-phenylurea 2.24[104]



To a stirred solution of 1-allylmethylamine (48 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C was added phenyl isocyanate (55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 30 min. The solvent was removed by Büchner filtration and the filtrate was washed with water (60 mL). The residue was dissolved in EtOAc (20 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1-allyl-1-methyl-3-phenylurea (**2.24**, 68 mg, 71%) as a white solid.

mp. (°C) 73-75 [Lit. 73-76]; IR (neat): 3308, 1644, 1524, 1237, 1203, 991, 913, 747, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.01 (s, 3H), 3.97 (dt, *J* = 5.3 Hz, *J* = 1.6 Hz, 2H), 5.26 (t, *J* = 1.6 Hz, 1H), 5.27-5.29 (m, 1H), 5.83-5.91 (m, 1H), 6.38 (br.s, 1H) 7.00-7.03 (m, 1H), 7.25-7.29 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 34.6, 51.6, 117.0, 120.0, 122.9, 128.8, 133.5, 139.2, 155.5; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{14}N_2ONa]^+$ 213.0998; found 213.0991.

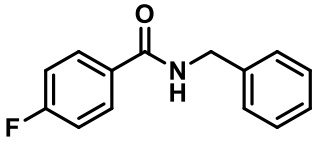
2.5.2.7 (4-Fluorophenyl)-1-pyrrolidinyl 2.49[51]



To a stirred solution of 4-fluorobenzoyl chloride (59 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give (4-fluorophenyl)-1-pyrrolidinyl (**2.49**, 87mg, 69%) as an off white solid.

mp. (^oC) 175-180 [Lit. 180 - 181]; IR (neat): 3350, 3062, 2928, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92-7.87 (m, 2H), 7.75 (br. s, 1H), 7.64-7.62 (d, *J* = 10 Hz, 2H), 7.40-7.36 (m, 2H), 7.26-7.15 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 116.2, 164.6, 163.7, 137.7, 131.2, 131.1, 129.5, 129.4, 129.2, 124.7, 120.2, 116.0, 115.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -107.36; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{10}FNO]^+$ 216.0819; found 216.0819.

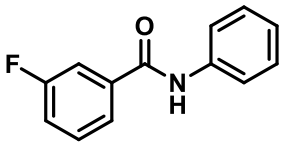
2.5.2.8 4-Fluoro-*N*-(phenylmethyl) 2.50[51]



To a stirred solution of 4-fluorobenzoyl chloride (59 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzylamine (55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give 4-fluoro-*N*-(phenylmethyl) (**2.50**, 93.1 mg, 81%) as a white solid.

mp. (°C) 140-145 [Lit. 143- 144]; IR (neat): 3317, 3066, 3032, 2931, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82-7.78 (m, 2H), 7.38-7.26 (m, 5H), 7.11-7.07 (m, 2H), 6.44 (br. s, 1H) 4.64-4.62 (m, *J* = 10 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 166.0, 163.5, 138.0, 130.6, 130.5, 129.4, 129.3, 128.8, 128.0, 127.7, 115.8, 115.5, 44.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -108.10; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{12}FNO]^+$ 230.0976; found 230.0978.

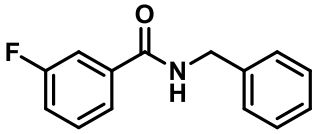
2.5.2.9 3-Fluoro-*N*-phenyl-benzamide 2.51[51]



To a stirred solution of 3-fluorobenzoyl chloride (61 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give 3-fluoro-*N*-phenyl-benzamide (**2.51**, 63 mg, 58%) as a white solid.

mp. (°C) 148-153; IR (neat): 3346, 3081, 2928, 2852, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (br. s, 1H), 7.64-7.58 (m, 4H), 7.50-7.44 (m, 1H), 7.41-7.37 (t, *J* = 15Hz, 2H), 7.28-7.23 (m, 2H), 7.20-7.16 (t, *J* = 10Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4-164.1, 161.6, 137.6, 137.3-137.2, 130.6-130.5, 129.2, 124.9, 122.4-122.4, 120.3, 119.0, 118.8, 114.7, 114.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -111.21; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{10}FNO]^+$ 216.0819; found 216.0826.

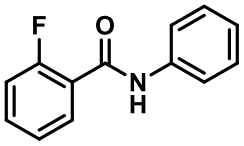
2.5.2.10 3-Fluoro-*N*-(phenylmethyl)-benzamide 2.52[51]



To a stirred solution of 3-fluorobenzoylchloride (61 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzylamine (55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give 3-fluoro-*N*-(phenylmethyl)-benzamide (**2.52**, 63.6 mg, 56%) as an off white solid.

mp. (^{o}C) 90-93; IR (neat): 3295, 3070, 3034, 2933, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.49 (m, 2H), 7.34-726 (m, 6H), 7.20-7.15 (m, 1H), 6.85 (br. s, 1H), 4.59-4.57 (d, *J* = 10 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3-166.2, 164.0, 161.5, 138.0, 136.7-136.0, 130.3-130.2, 128.8, 127.9-127.7, 122.5, 118.6, 118.4, 114.6, 114.4, 44.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -111.79; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{12}FNO]^+$ 230.0976; found 230.0979.

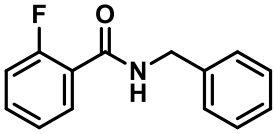
2.5.2.11 2-Fluoro-*N*-phenylbenzamide 2.53[51]



To a stirred solution of 2-fluorobenzoyl chloride (60 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give 2-fluoro-*N*-phenylbenzamide (**2.53**, 34.5 mg, 32%) as a white solid.

mp. (^{o}C) 94-98 [Lit.[46] 99]; IR (neat): 3376, 3065, 2981, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51-8.47 (br. d, *J* = 18, 1H), 8.17-8.13 (m, 1H), 7.68-7.66 (d, *J* = 10 Hz, 2H), 7.54-7.48 (m, 1H), 7.40-7.36 (t, *J* = 10 Hz, 2H), 7.32-7.26 (m, 1H), 7.19-7.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6, 161.4-161.3, 159.1, 137.7, 133.8-133.7, 132.2, 129.1, 125.1, 124.8, 121.5-121.4, 120.6, 116.3, 116.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.16; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{10}FNO]^+$ 216.0819; found 216.0825.

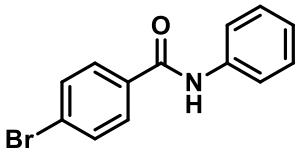
2.5.2.12 2-Fluoro-*N*-(phenylmethyl)benzamide 2.54[51]



To a stirred solution of 2-fluorobenzoyl chloride (60 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzyl amine (55 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give 2-fluoro-*N*-(phenylmethyl)benzamide (**2.54**, 95.2 mg, 83%) as a white solid.

mp. (°C) 39-40 Lit.[55]; IR (neat): 3306, 3085, 29279, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15-8.12 (m, 1H), 7.50-7.04 (m, 11H), 4.69-4.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3, 161.9, 159.4, 138.0, 133.4-133.3, 132.2-132.1, 128.8, 128.5, 127.7-127.6, 124.9-124.8, 121.0-120.1, 116.1-15.9, 44.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.42; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{12}FNO]^+$ 230.0976; found 229.0907.

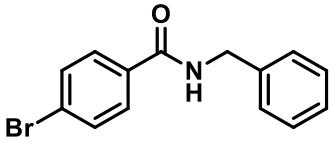
2.5.2.13 *N*-phenyl 4-bromobenzamide 2.55[51]



To a stirred solution of 4-bromobenzoyl chloride (110 mg, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give *N*-phenyl 4-bromobenzamide (**2.55**, 55 mg, 40%) as an off white solid.

mp. (°C) 178-181 [Lit.[47] 180 - 190]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8.4, 3H), 7.65-7.62 (m, 4H), 7.39 (t, *J*= 7.9, 2H), 7.18 (t, *J* = 7.4, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 137.6, 133.8, 132.1, 129.2, 128.6, 126.6, 124.8, 120.2; IR (neat): 3347, 3094, 3056, 2916, 1651 cm^{-1}; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{10}{}^{79}BrNO]^+$ 276.0019; found 276.0025.

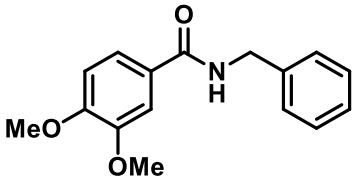
2.5.2.14 *N*-(4-bromobenzoyl)benzylamine 2.56[51]



To a stirred solution of 4-bromobenzoyl chloride (101.5 mg, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (71 µL, 0.51 mmol) and aniline (50 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give *N*-(4-bromobenzoyl)benzylamine (**2.56**, 69 mg, 69%) as an off white solid.

mp. (°C) 165-169 [Lit.[56] 160-162]; IR (neat): 3305, 3060, 3029, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67-7.65 (m, 2H), 7.57-7.55 (m, 1H), 7.38-7.29 (m, 5H), 4.64-4.62 (m, 2H); HRMS (ESI) *m/z* Calcd for $[C_{14}H_{13}{}^{79}BrNO]^{+}$ 290.0102; found 290.0171.

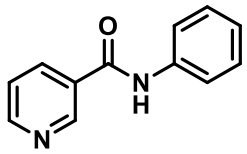
2.5.2.15 *N*-benzyl-3,4-dimethoxybenzamide 2.58[51]



To a stirred solution of 3,4-dimethoxybenzoyl chloride (100 mg, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzylamine (54 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to afford *N*-benzyl-3,4-dimethoxybenzamide (**2.58**, 101 mg, 86%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 1.9 Hz, 1H), 7.34 (dd, *J* = 1.9 Hz, *J* = 7.3 Hz, 1H), 7.28-7.22 (m, 5H), 7.06 (t, *J* = 5.5 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.5 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 167.1, 151.7, 148.8, 138.6, 128.6, 127.8, 127.4, 126.9, 119.7, 110.6, 110.2, 55.9, 55.9, 44.0; IR 3298, 2929, 2838, 1629, 1582, 1509 cm^{-1}; HRMS (*m/z*) cald. for $[C_{16}H_{17}NO_3K]^{+}$ 310.0840; found 310.0840.

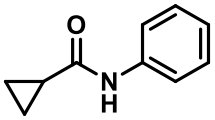
2.5.2.16 *N*-phenyl-3-Pyridinecarboxamide 2.59[51]



To a stirred solution of pyridine-3-carbonyl chloride (94mg, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (81 µL, 0.58 mmol) and aniline (48 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give *N*-phenyl-3-pyridinecarboxamide (**59**, 13 mg, 10%) as a white solid.

mp. (°C) Lit.[48] 116-119; IR (neat): 3295, 3139, 2981, 2928, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.10 (s, 1H), 8.79-8.78 (m,1H), 8.23-8.21 (m, 1H), 7.86 (br. s, 1H), 7.68-7.64 (m, 2H), 7.47-7.44 (m, 1H), 7.42-7.38 (m, 2H), 7.7.26-7.18 (m, 1H); HRMS (ESI) *m/z* Calcd for $[C_{12}H_{10}N_2O]^+$ 199.0866; found 199.0871.

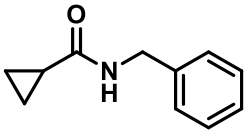
2.5.2.17 *N*-Phenylcyclopropanecarboxamide 2.67[51]



To a stirred solution of cyclopropancarbonyl chloride (45 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give *N*-phenylcyclopropanecarboxamide (**2.67**, 29 mg, 36%) as a white solid.

mp. (°C) 110-114 [Lit.[54] 110-111]; IR (neat): 3284, 3253, 3131, 2980, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (br. s, 1H), 7.52-7.50 (m, 2H), 7.31-7.26 (m, 2H), 7.10-7.06 (m, 1H), 1.53-1.52 (m, 1H), 1.09-1.05 (m, 2H), 0.84-0.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 138.2, 129.0, 124.0, 119.8, 15.7, 7.9; HRMS (ESI) *m/z* Calcd for $[C_{10}H_{11}NO]^+$ 162.0913; found 162.0916.

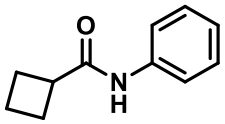
2.5.2.18 *N*-Benzylcyclopropanecarboxamide 2.68[51]



To a stirred solution of cyclopropanecarbonyl chloride (45 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzylamine (54 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to afford *N*-benzylcyclopropanecarboxamide (**2.68**, 56 mg, 64%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.26* (m, 5H), 5.85 (br. s, 1H), 4.47 (d, *J* = 5.7 Hz, 2H), 1.38-1.32 (m, 1H), 1.04-1.00 (m, 2H), 0.78-0.74 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 170.8, 138.5, 128.7, 127.9, 127.5, 43.9, 14.8, 7.3; IR 3291, 1630, 1560, 1452, 1110 cm^{-1}; HRMS (DualESI-TOFMS) *m/z* cald. for $[C_{11}H_{14}NO]^+$ 176.1070; found 176.1073.

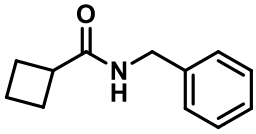
2.5.2.19 *N*-Phenylcyclobutanecarboxamide 2.69[51]



To a stirred solution of Cyclobutanecarbonyl chloride (57 µL, 0.5 mmol) in Cyrene™ (0.5 mL, 1 M) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and aniline (46 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to give *N*-phenylcyclobutanecarboxamide (**2.69**, 21 mg, 24%) as an off white solid.

mp. (^{o}C) 109-113 [Lit.[53] 112.5 - 113]; IR (neat): 3294, 3137, 2982, 2942, 2865, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.52 (m, 2H), 7.33-7.26 (m, 2H), 7.16-7.07 (m, 2H), 3.16 (p, J = 10.6 Hz, 1H), 2.42-2.35 (m, 2H), 2.26-2.18 (m, 2H), 2.06-1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 138.0, 129.0, 124.1, 119.7, 40.9, 25.3, 18.1; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{13}NO]^+$ 176.1075; found 176.1074.

2.5.2.20 *N*-Benzylcyclobutanecarboxamide 2.70[51]

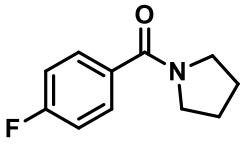


To a stirred solution of cyclobutanecarbonyl chloride (57 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and benzylamine (54 µL, 0.5 mmol). The resultant mixture was allowed to warm to r.t. over 1 h. Water (5 mL) was added and the mixture was stirred

for 2 h. The precipitate was filtered and washed with water. The residue was dissolved in EtOAc, dried over sodium sulphate and the solvent was removed under reduced pressure to afford *N*-benzylcyclobutanecarboxamide (**2.70**, 40 mg, 42%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26* (m, 5H), 5.59 (br. s, 1H), 3.03 (quin, *J* = 8.5 Hz, 1H), 2.37-2.27 (m, 2H), 2.20-2.12 (m, 2H), 2.03-1.83 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 174.8, 138.5, 128.7, 127.8, 127.5, 43.5, 39.9, 28.4, 18.2; IR 3290, 2930, 1631, 1520, 1450 cm^{-1}; HRMS (*m/z*) cald. for $[C_{123}H_{15}NOK]^+$ 228.0785; found 228.0787.

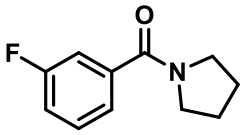
2.5.2.21 (4-Fluorophenyl)(pyrrolidin-1-yl)methanone 2.82[51]



To a stirred solution of 4-fluorobenzoyl chloride (59 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford (4-fluorophenyl)(pyrrolidin-1-yl)methanone (**2.82**,72 mg, 75%) as a colourless solid.

mp: 87-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.47 (m, 2H), 7.06-7.00 (m, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 3.38 (t, *J* = 6.6 Hz, 2H), 1.95-1.80 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.41 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 168.6, 163.4 (d, $J_{C\text{-}F}$ = 248 Hz), 133.2 (d, $J_{C\text{-}F}$ = 3 Hz), 129.4 (d, $J_{C\text{-}F}$ = 8 Hz), 115.2 (d, $J_{C\text{-}F}$ = 22 Hz), 49.7, 46.3, 26.4, 24.4; IR 3064, 2980, 2956, 2886, 1621, 1601, 1425 cm^{-1}; HRMS (*m/z*) cald. for $[C_{11}H_{13}FNO]^+$ 194.0976; found 194.0975.

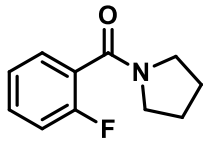
2.5.2.22 (3-Fluorophenyl)(pyrrolidin-1-yl)methanone 2.83[51]



To a stirred solution of 3-fluorobenzoyl chloride (61 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford (3-fluorophenyl)(pyrrolidin-1-yl)methanone (**2.83**, 73 mg, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 1H), 7.26-7.24 (m, 1H), 7.20-7.16 (m, 1H), 7.09-7.04 (m, 1H), 3.59 (t, *J* = 6.9 Hz, 2H), 3.38 (t, *J* = 6.5 Hz, 2H), 1.96-1.81 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.30 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 168.2 (d, J_{C-F} = 2 Hz), 162.4 (d, J_{C-F} = 246 Hz), 139.2 (d, J_{C-F} = 7 Hz), 130.0 (d, J_{C-F} = 8 Hz), 122.8 (d, J_{C-F} = 3 Hz), 116.7 (d, J_{C-F} = 21 Hz), 114.3 (d, J_{C-F} = 23 Hz), 49.5, 46.2, 26.4, 24.4; IR 3067, 2973, 2876, 1621, 1581, 1445 cm^{-1}; HRMS (*m/z*) cald. for $[C_{11}H_{13}FNO]^+$ 194.0976; found 194.0976.

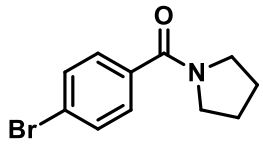
2.5.2.23 2-Fluoro-*N*-phenylbenzamide 2.84[51]



To a stirred solution of 2-fluorobenzoyl chloride (60 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford 2-fluoro-*N*-phenylbenzamide (**2.84**, 36 mg, 37%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.35 (m, 2H), 7.22-7.16 (m, 1H), 7.09 (t, *J* = 9.0 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.01-1.85 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.03 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 165.2, 158.3 (d, J_{C-F} = 246 Hz), 131.2 (d, J_{C-F} = 8 Hz), 128.9 (d, J_{C-F} = 4 Hz), 125.7 (d, J_{C-F} = 18 Hz), 124.5 (d, J_{C-F} = 3 Hz), 115.9 (d, J_{C-F} = 22 Hz), 47.9 (d, J_{C-F} = 4 Hz), 45.9, 25.9, 24.5; IR 2973, 2881, 1628, 1613, 1453, 1421 cm^{-1}; HRMS (*m/z*) cald. for $[C_{11}H_{13}FNO]^+$ 194.0976; found 194.0976.

2.5.2.24 4-Bromo-*N*-phenylbenzamide 2.85[51]

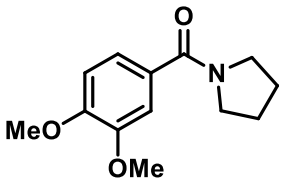


To a stirred solution of 4-bromobenzoyl chloride (110 mg, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford 4-bromo-*N*-phenylbenzamide (**2.85**, 64 mg, 50%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.52 (m, 2H), 7.41-7.39 (m, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 6.6 Hz, 2H), 1.99-1.84 (m, 4H); ^{13}C (100 MHz, $CDCl_3$): δ 168.6, 136.0, 131.5, 128.9, 124.1, 49.6, 46.3,

26.4, 24.4; IR 2970, 2874, 162, 1417 cm^{-1}; HRMS (*m/z*) cald. for $[C_{11}H_{13}{}^{79}BrNO]^+$ 254.0175; found 254.0176.

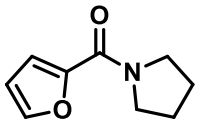
2.5.2.25 (3,4-Dimethoxyphenyl)(pyrrolidin-1-yl)methanone 2.86[51]



To a stirred solution of 3,4-dimethoxybenzoyl chloride (100 mg, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford (3,4-dimethoxyphenyl)(pyrrolidin-1-yl)methanone (**2.86**, 81 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06-7.02 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.81 (s, 6H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.41 (t, *J* = 6.4 Hz, 2H), 1.88-1.77 (m, 4H); ^{13}C (100 MHz, $CDCl_3$): δ 169.3, 150.2, 148.6, 129.5, 120.22, 110.9, 110.1, 55.9, 49.8, 46.3, 26.4, 24.4; HRMS (*m/z*) cald. for $[C_{13}H_{17}NO_3Na]^+$ 258.1101; found 258.1104.

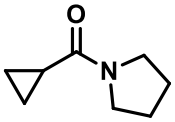
2.5.2.26 Furan-2-yl(pyrrolidin-1-yl)methanone 2.87[51]



To a stirred solution of furoyl chloride (49 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford furan-2-yl(pyrrolidin-1-yl)methanone (**2.87**, 64 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 0.7 Hz, *J* = 1.6 Hz, 1H), 7.01 (dd, *J* = 0.6 Hz, *J* = 3.5 Hz, 1H), 6.44 (dd, *J* = 1.7 Hz, *J* = 3.5 Hz, 1H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.60 (t, *J* = 6.9 Hz, 2H), 1.98-1.81 (m, 4H); ^{13}C (100 MHz, $CDCl_3$): δ 158.1, 148.7, 144.0, 115.7, 111.3, 47.8, 47.0, 26.6, 23.7; IR 3486, 3110, 2971, 2877, 1611, 1479, 1413 cm^{-1}; HRMS (*m/z*) cald. for $[C_9H_{11}NO_2Na]^+$ 188.0682; found 188.0683.

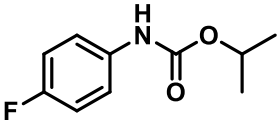
2.5.2.27 Cyclopropyl(pyrrolidin-1-yl)methanone 2.88[51]



To a stirred solution of cyclopropanecarbonyl chloride (45 µL, 0.5 mmol) in Cyrene™ (0.5 mL) at 0 °C were added triethylamine (77 µL, 0.55 mmol) and pyrrolidine (42 µL, 0.5 mmol) and the resultant mixture was stirred at r.t. for 1 h. The solution was purified by flash chromatography column on silica gel (30% EtOAc in hexane → 70% EtOAc in hexane) to afford cyclopropyl(pyrrolidin-1-yl)methanone (**2.88,** 11 mg, 16%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, *J* = 6.8 Hz, 2H), 3.45 (t, *J* = 6.9 Hz, 1H), 1.98 (quin, *J* = 6.6 Hz, 2H), 1.85 (quin, *J* = 6.8 Hz, 2H), 1.64-1.58 (m, 1H), 1.00-0.97 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 170.1, 46.5, 46.0, 26.1, 24.5, 12.5, 7.3; IR 3438, 1615, 1451 cm^{-1}; HRMS (DualESI-TOFMS) *m/z* Calcd. for $[C_8H_{14}NO]^+$ 140.1070; found 140.1071.

2.5.2.28 Isopropyl (4-fluorophenyl)carbamate 2.95



Method A: To a stirred solution of isopropanol (38 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at r.t. for 16h. Water (5 mL) was added to the reaction and the mixture was allowed to stir for 1h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford isopropyl (4-fluorophenyl)carbamate (**2.95**, 55 mg, 61%) as a colourless solid.

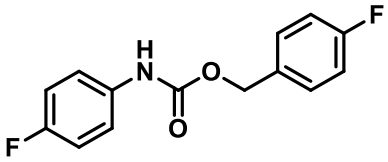
Method B: To a stirred solution of isopropanol (38 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford isopropyl (4-fluorophenyl)carbamate (**2.95**, 81 mg, 82%) as a colourless solid.

Method C: To a stirred solution of isopropanol (380 µL, 5 mmol) in Cyrene™ (5 mL) was added 4-fluorophenyl isocyanate (570 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (50 mL) was added to the reaction and the mixture was allowed to stir

for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford isopropyl (4-fluorophenyl)carbamate (**2.95**, 930 mg, 94%) as a colourless solid.

mp: 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.32 (m, 2H), 7.00-6.96 (m, 2H), 6.67 (br. s, 1H), 5.01 (sept, *J* = 6.2 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.88 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 158.9 (d, $J_{C\text{-}F}$ = 240 Hz), 153.5, 134.1, 120.3, 115.6 (d, $J_{C\text{-}F}$ = 22 Hz), 68.9, 22.1; IR (neat) 3333, 2981, 1690, 1531, 1506 cm^{-1}.

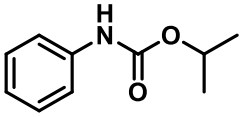
2.5.2.29 4-Fluorobenzyl (4-fluorophenyl)carbamate 2.97



To a stirred solution of 4-fluorobenzyl alcohol (55 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 4-fluorobenzyl (4-fluorophenyl)carbamate (**2.97**, 103 mg, 78%) as a colourless solid.

mp: 104-106 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ 8.82 (br. s, 1H), 7.60-7.55 (m, 2H), 7.54-7.50 (m, 1H), 7.43-7.38 (m, 1H), 7.23-7.19 (m, 1H), 7.18-7.14 (m, 1H), 7.10-7.02 (m, 2H), 5.23 (s, 2H); ^{19}F NMR [376 MHz, $(CD_3)_2CO$]: δ -119.99 (s, 1F), -122.15 (br. s, 1F); ^{13}C [100 MHz, $(CD_3)_2CO$]: δ 161.0 (d, $J_{C\text{-}F}$ = 245 Hz), 158.8 (d, $J_{C\text{-}F}$ = 239 Hz), 153.3, 135.5, 130.9 (d, $J_{C\text{-}F}$ = 4 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8 Hz), 124.3 (d, $J_{C\text{-}F}$ = 4 Hz), 123.8 (d, $J_{C\text{-}F}$ = 15 Hz), 120.4 (d, $J_{C\text{-}F}$ = 8 Hz), 120.0 (br. s), 115.2 (d, $J_{C\text{-}F}$ = 23 Hz), 115.0 (d, $J_{C\text{-}F}$ = 22.4 Hz), 60.0 (d, $J_{C\text{-}F}$ = 4 Hz); IR (neat) 3308, 2955, 1701, 1610, 1525, 1507 cm^{-1}; HRMS (Dual ESI) *m/z* Calcd for $[C_{14}H_{11}F_2NO_2]^+$ 264.0831; found 264.0828.

2.5.2.30 Isopropyl phenylcarbamate 2.98

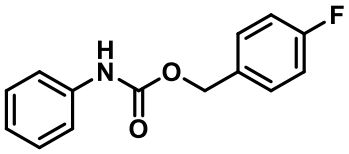


To a stirred solution of isopropanol (38 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added phenyl isocyanate (54 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over

sodium sulfate and the solvent removed under reduced pressure to afford isopropyl phenylcarbamate (**2.98**, 55 mg, 61%) as a colourless solid.

mp: 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.70 (br. s, 1H), 5.03 (sept, *J* = 6.2 Hz, 1H), 1.30 (d, *J* = 6.2, 6H); ^{13}C (100 MHz, $CDCl_3$): δ 153.3, 138.1, 129.0, 123.2, 118.6, 68.7, 22.1; IR (neat) 3313, 2981, 2935, 1696, 1597, 1531 cm^{-1}.

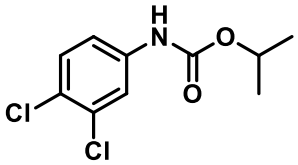
2.5.2.31 4-Fluorobenzyl phenylcarbamate 2.99



To a stirred solution of 4-fluorobenzyl alcohol (54 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added phenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 4-fluorobenzyl phenylcarbamate (**2.99**, 78 mg, 64 %) as a colourless solid.

mp: 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 6H), 7.17-7.06 (m, 3H), 6.81 (br. s, 1H), 5.28 (s, 2H); ^{19}F NMR [376 MHz, $(CD_3)_2CO$]: δ -117.99 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 161.1 (d, $J_{C\text{-}F}$ = 247 Hz), 153.2, 137.7, 130.9 (d, $J_{C\text{-}F}$ = 4 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8 Hz), 129.1, 124.2 (d, $J_{C\text{-}F}$ = 4 Hz), 123.6, 123.2 (d, $J_{C\text{-}F}$ = 15 Hz), 118.7 (br. s), 115.5 (d, $J_{C\text{-}F}$ = 21 Hz), 60.9; IR (neat) 3296, 2953, 1697, 1594, 1522, 1491 cm^{-1}; HRMS (Dual ESI) *m/z* Calcd for $[C_{14}H_{13}FNO_2]^+$ 246.0925; found 246.0921.

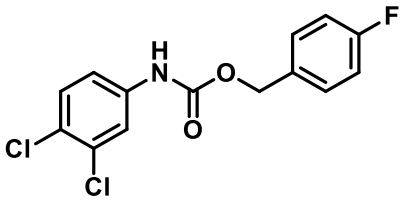
2.5.2.32 Isopropyl (3,4-dichlorophenyl)carbamate 2.100



To a stirred solution of isopropanol (38 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 3,4-dichlorophenyl isocyanate (94 mg, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford isopropyl (3,4-dichlorophenyl)carbamate (**2.100**, 99 mg, 80 %) as a colourless solid.

mp: 235-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (br. s, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.18 (dd, *J* = 2.4 Hz, *J* = 8.7 Hz, 1H), 6.76 (br. s, 1H), 5.01 (sept, *J* = 6.2 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 6H); ^{13}C (100 MHz, $CDCl_3$): δ 152.9, 137.7, 132.8, 130.5, 126.3, 120.2, 117.8, 69.4, 22.0; IR (neat) 3267, 2981, 1693, 1641, 1581, 1521 cm^{-1}.

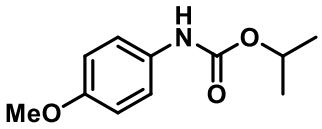
2.5.2.33 4-Fluorobenzyl (3,4-dichlorophenyl)carbamate 2.101



To a stirred solution of 4-fluorobenzyl alcohol (55 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 3,4-dichlorophenyl isocyanate (94 mg, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 4-fluorobenzyl (3,4-dichlorophenyl)carbamate (**2.101**, 117 mg, 74 %) as a colourless solid.

mp: 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (br. s, 1H), 7.43 (td, *J* = 1.6 Hz, *J* = 7.5 Hz, 1H), 7.38-7.33 (m, 2H), 7.20-7.14 (m, 2H), 7.10 (t, *J* = 9.1 Hz, 1 Hz), 6.74 (br. s, 1H), 5.27 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -117.90 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 161.2 (d, $J_{C\text{-}F}$ = 247 Hz), 152.8, 137.2, 132.9, 131.0 (d, $J_{C\text{-}F}$ = 4 Hz), 130.7 (d, $J_{C\text{-}F}$ = 8 Hz), 130.6, 126.8, 124.3 (d, $J_{C\text{-}F}$ = 4 Hz), 122.8 (d, $J_{C\text{-}F}$ = 15 Hz), 120.3, 117.8, 115.6 (d, $J_{C\text{-}F}$ = 21 Hz), 61.4; IR (neat) 3329, 2980, 1703, 1587, 2639 cm^{-1}.

2.5.2.34 Isopropyl (4-methoxyphenyl)carbamate 2.102

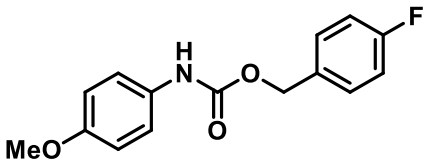


To a stirred solution of isopropanol (38 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-methoxyphenyl isocyanate (54 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford isopropyl (4-methoxyphenyl)carbamate (**2.102**, 55 mg, 61%) as a colourless solid.

mp: 57-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.70 (br. s, 1H), 5.03 (sept, *J* = 6.2 Hz, 1H), 1.30 (d, *J* = 6.2, 6H); ^{13}C (100 MHz, $CDCl_3$): δ 155.8,

153.7, 131.3, 120.6, 114.2, 68.5, 55.5, 22.1; IR (neat) 3308, 2988, 2931, 1694, 1532, 1512 cm^{-1}; HRMS (Dual ESI) *m/z* Calcd for $[C_{11}H_{16}N_2O_3]^+$ 210.1125; found 210.1127.

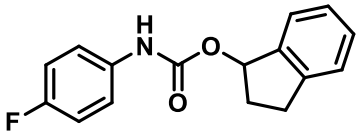
2.5.2.35 4-Fluorobenzyl (4-methoxyphenyl)carbamate 2.103



To a stirred solution of 4-fluorobenzyl alcohol (55 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-methoxyphenyl isocyanate (65 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 4-fluorobenzyl (4-methoxyphenyl)carbamate (**2.103**, 100 mg, 73 %) as a colourless solid.

mp: 228-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.41 (m, 1H), 7.35-7.28 (m, 3H), 7.13 (d, *J* = 0.9 Hz, *J* = 7.5 Hz, 1H), 6.81 (br. s, 1H), 5.28 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -117.99 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 161.1 (d, $J_{C\text{-}F}$ = 247 Hz), 153.2, 137.7, 130.9 (d, $J_{C\text{-}F}$ = 4 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8 Hz), 129.1, 124.2 (d, $J_{C\text{-}F}$ = 4 Hz), 123.6, 123.2 (d, $J_{C\text{-}F}$ = 15 Hz), 118.7 (br. s), 115.5 (d, $J_{C\text{-}F}$ = 21 Hz), 60.9; IR (neat) 2394, 2961, 2934, 2834, 1607, 1555, 1505 cm^{-1}; HRMS (Dual ESI) *m/z* Calcd for $[C_{15}H_{15}FNO_3]^+$ 276.1030; found 276.1042.

2.5.2.36 2,3-Dihydro-1*H*-inden-1-yl (4-fluorophenyl)carbamate 2.115

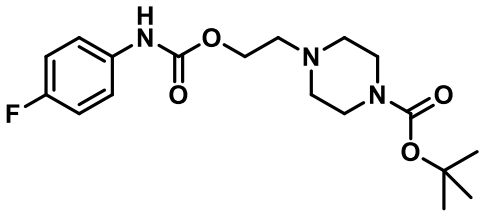


To a stirred solution of 1-indanol (55 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 2,3-dihydro-1*H*-inden-1-yl (4-fluorophenyl)carbamate (**2.115**, 113 mg, 83%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.35-7.23 (m, 4H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.78 (br. s, 1H), 6.24 (dd, *J* = 3.6 Hz, *J* = 6.9 Hz, 1H), 3.15-3.08 (m, 1H), 2.93-2.86 (m, 1H), 2.57-2.50 (m, 1H), 2.21-1.14 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.54 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 159.0 (d,

$J_{C\text{-}F}$ = 241 Hz), 153.8, 144.4, 140.9, 134.0, 129.1, 126.8, 125.6, 124.9, 120.4, 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 79.4, 32.4, 30.2.

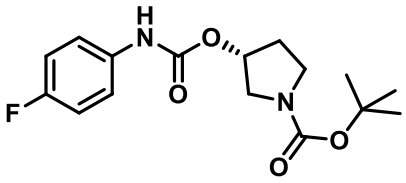
2.5.2.37 *tert*-Butyl 4-(2-(((4-fluorophenyl)carbamoyl)oxy)ethyl)piperazine-1-carboxylate 2.116



To a stirred solution of *tert*-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (115 mg, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford *tert*-butyl 4-(2-(((4-fluorophenyl)carbamoyl)oxy)ethyl)piperazine-1-carboxylate (**2.116**, 148 mg, 81%) as a white solid.

mp: 212-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.29 (m, 3H), 6.96-6.92 (m, 2H), 4.24 (t, *J* = 5.6 Hz, 2H), 3.41 (t, *J* = 4.9 Hz, 4H), 2.63 (t, *J* = 5.6 Hz, 2H), 2.43-2.41 (m, 4H), 1.42 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.60 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 158.9 (d, $J_{C\text{-}F}$ = 241 Hz), 154.7, 153.7, 134.0, 120.4, 115.6 (d, $J_{C\text{-}F}$ = 22 Hz), 79.8, 61.9, 57.1, 53.1, 43.4 (d, $J_{C\text{-}F}$ = 89 Hz), 28.4; IR (neat) 3292, 2980, 1716, 1652, 1633, 1609, 1539, 1509 cm^{-1}.

2.5.2.38 *tert*-Butyl (*R*)-3-(((4-fluorophenyl)carbamoyl)oxy)pyrrolidine-1-carboxylate 2.117

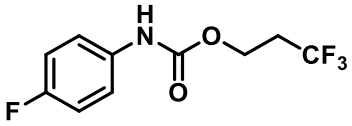


To a stirred solution of *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (94 mg, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under

reduced pressure to afford *tert*-butyl (*R*)-3-(((4-fluorophenyl)carbamoyl)oxy)pyrrolidine-1-carboxylate (**2.117**, 100 mg, 62%) as a white solid.

mp: 237-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.26 (m, 3H), 6.99 (t, J = 7.8 Hz, 2H), 5.31 (br. s, 1H), 3.56-3.37 (m, 4H), 2.09 (br. s, 2H), 1.48-1.46 (m, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.52 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 158.9 (d, $J_{C\text{-}F}$ = 237 Hz), 154.6 (d, $J_{C\text{-}F}$ = 11 Hz), 153.1, 134.1, 120.3, 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 79.8, 74.2 (d, $J_{C\text{-}F}$ = 101 Hz), 51.8 (d, $J_{C\text{-}F}$ = 60 Hz), 43.9 (d, $J_{C\text{-}F}$ = 15 Hz), 31.4 (d, $J_{C\text{-}F}$ = 95 Hz), 28.5; IR (neat) 3333, 2981, 2896, 1726, 1678, 1609, 1540, 1506 cm^{-1}.

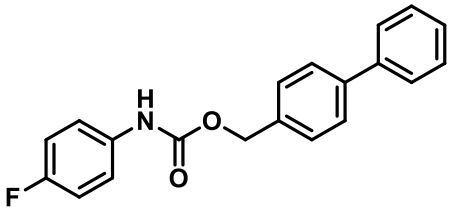
2.5.2.39 3,3,3-Trifluoropropyl (4-fluorophenyl)carbamate 2.118



To a stirred solution of 3,3,3-trifluoropropan-1-ol (44 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford 3,3,3-trifluoropropyl (4-fluorophenyl)carbamate (**2.118**, 60 mg, 48%) as a white solid.

mp: 256-257 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (br. s, 2H), 7.03-6.98 (m, 2H), 6.76 (br. s, 1H), 4.39 (t, J = 6.2 Hz, 2H), 2.55-2.47 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.87 (s, 3F), -119.04 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 159.2 (d, $J_{C\text{-}F}$ = 241 Hz), 153.0, 133.4, 125.8 (q, $J_{C\text{-}F}$ = 275 Hz), 120.6 (br. s), 115.8 (d, $J_{C\text{-}F}$ = 23 Hz), 58.0, 33.6 (q, $J_{C\text{-}F}$ = 29 Hz); IR (neat) 3326, 1703, 1611, 1532, 1508 cm^{-1}.

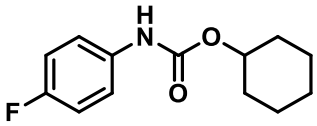
2.5.2.40 [1,1'-Biphenyl]-4-ylmethyl (4-fluorophenyl)carbamate 2.119



To a stirred solution of [1,1'-biphenyl]-4-ylmethanol (85 mg, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford [1,1'-biphenyl]-4-ylmethyl (4-fluorophenyl)carbamate (**2.119**, 137 mg, 85%) as a white solid.

mp: 135-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.59 (m, 4H), 7.49-7.44 (m, 4H), 7.40-7.35 (m, 3H), 7.03-6.99 (m, 2H), 6.80 (br. s, 1H), 5.25 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.32 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 159.1 (d, $J_{C\text{-}F}$ = 241 Hz), 153.6, 141.0 (d, $J_{C\text{-}F}$ = 81 Hz), 140.4 (d, $J_{C\text{-}F}$ = 93.2 Hz), 134.9, 133.8, 128.9, 127.5, 127.4 (d, $J_{C\text{-}F}$ = 14 Hz), 127.3 (d, $J_{C\text{-}F}$ = 26 Hz), 127.2 (d, $J_{C\text{-}F}$ = 23 Hz), 120.5 (br. s), 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 66.9; IR (neat) 3308, 1698, 1541, 1509 cm^{-1}.

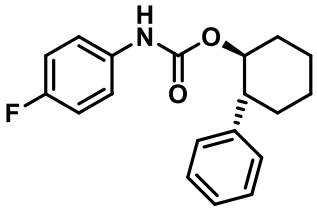
2.5.2.41 Cyclohexyl (4-fluorophenyl)carbamate 2.120



To a stirred solution of cyclohexanol (53 µL, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford cyclohexyl (4-fluorophenyl)carbamate (**2.120**, 88 mg, 74%) as a white solid.

mp: 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (br. s, 2H), 6.99-6.95 (m, 2H), 6.79 (br. s, 1H), 4.76-4.72 (m, 1H), 1.92-1.89 (m, 2H), 1.74-1.71 (m, 2H), 1.56-1.23 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.94 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 158.8 (d, $J_{C\text{-}F}$ = 240 Hz), 153.5, 134.2 (d, $J_{C\text{-}F}$ = 2 Hz), 120.3 (br. s), 115.6 (d, $J_{C\text{-}F}$ = 22 Hz), 73.7, 31.9, 25.4, 23.8; IR (neat) 3351, 2951, 2861, 1696, 1609, 1523, 1511 cm^{-1}.

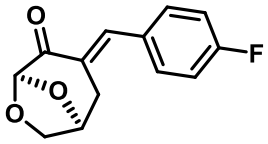
2.5.2.1 (1S,2R)-2-phenylcyclohexyl (4-fluorophenyl)carbamate 2.123



To a stirred solution of (1S,2R)-2-phenylcyclohexan-1-ol (88 mg, 0.5 mmol) in Cyrene™ (0.5 mL) was added 4-fluorophenyl isocyanate (57 µL, 0.5 mmol) and the reaction was stirred at 40 °C for 16 h. Once the reaction cooled to r.t. water (5 mL) was added to the reaction and the mixture was allowed to stir for 1 h before the precipitate was filtered and washed with water. The residue was then dissolved in EtOAc, dried over sodium sulfate and the solvent removed under reduced pressure to afford (1*S*,2*R*)-2-phenylcyclohexyl (4-fluorophenyl)carbamate (**2.123**, 131 mg, 84%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.13 (m, 7H), 6.92 (t, *J* = 8.6 Hz, 2H), 6.42 (br. s, 1H), 5.02-4.96 (m, 1H), 2.74-2.67 (m, 1H), 2.31-2.28 (m, 1H)1.98-1.79 (m, 3H), 1.58-1.36 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -119.84 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 158.9 (d, $J_{C\text{-}F}$ = 241 Hz), 153.3, 143.3, 133.9, 128.5, 127.5, 126.5, 120.5 (br.), 115.5 (d, $J_{C\text{-}F}$ = 22 Hz), 77.0 (br. s), 49.9, 34.6, 32.7, 25.9, 24.8.

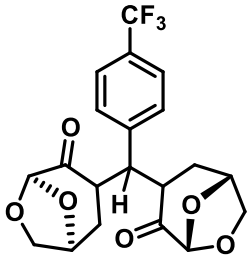
2.5.2.2 (1*S*,5*R*)-3-(4-Fluorobenzoyl)-6,8-dioxabicyclo[3.2.1]octan-4-one 2.153



To a stirred solution of Cyrene™ (103 µL, 2 mmol) and 4-fluorobenazaldehyde (107 µL, 2 mmol) in acetonitrile (1 mL, 2M) was added DBU (245 µL, 3 mmol) at r.t. The resultant mixture was stirred at r.t. for 16 h. Water (10 mL) and ethyl acetate (10 mL) was then added to the mixture and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were then dried over sodium sulfate and the solvent was removed under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (hexane:ethyl acetate, 9:1) to afford the *title compound* (**2.153**, 61 mg, 61%) as a yellow solid.

mp. 78-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.57 (s, 1H), 7.39-7.35 (m, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 5.26 (s, 1H), 4.82 (t, *J* = 5.3 Hz, 1H), 3.87-3.84 (m, 1H), 3.74-3.72 (m, 1H), 3.26-2.22 (m, 1H), 2.79 (d, *J* = 16.7 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.5 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): 189.6, 163.1 (d, $J_{C\text{-}F}$ = 250 Hz), 138.5, 132.5 (d, $J_{C\text{-}F}$ = 34 Hz), 130.9 (d, $J_{C\text{-}F}$ = 3 Hz), 127.8 (d, $J_{C\text{-}F}$ = 7 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 100.9, 72.4, 68.4, 34.4; IR (neat) 2957, 2922, 2853 cm^{-1}; HRMS (ESI) *m/z* Calcd. for [$C_{13}H_{11}FO_3$] 234.0692; found 234.0692.

2.5.2.3 (1S,1'S,5R,5'R)-3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(6,8-dioxabicyclo[3.2.1]octan-4-one) 2.166

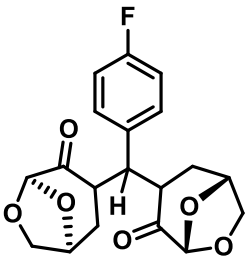


To a stirred solution of Cyrene (410 µL, 4 mmol) in acetonitrile (1 mL, 2M) was added 4-trifluoromethylbenzaldehyde (273 µL, 2 mmol) and DBU (449 µL, 3 mmol). The mixture was stirred at r.t. for 24 h after which water (25 mL) and EtOAc (25 mL) were added. The aqueous phase was washed with EtOAc (3 × 25 mL) and the combined organic extracts were dried over sodium sulfate

before the solvent was removed under reduced pressure. The crude product was purified using a Biotage Isolera 4 (snap Ultra 10g cartridge, EtOAc in hexane, 5% → 50%) to afford the *title compound* (**2.166**, 75 mg, 9%) as a colourless oil which solidified.

mp: 227-228 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.51 (m, 2H), 7.29-7.26 (m, 2H), 5.38 (s, 1H), 5.31 (s, 1H), 4.59-4.56 (m, 1H), 3.88 (t, *J* = 6.1 Hz, 1H), 3.80-3.75 (m, 2H), 3.62 (dd, *J* = 1.6 Hz, *J* = 7.2 Hz, H), 3.28 (d, *J* = 11.6 Hz, 1H), 3.10 (dd, *J* = 4.2 Hz, *J* = 16.5 Hz, 1H), 2.34 (td, *J* = 4.2 Hz, *J* = 16.5 Hz, 1H), 2.20 (td, *J* = 5.0 Hz, *J* = 12.1 Hz, 1H), 1.72-1.65 (m, 1H), 1.41 (m, *J* = 16.7 Hz, 1H), 1.25-1.16 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.45 (s, 3F); ^{13}C (100 MHz, $CDCl_3$): δ 145.1, 143.6, 131.0 (br. S), 129.6 (d, *J* = 32 Hz), 127.0, 125.4 (2 × C), 122.7, 103.8, 101.4, 96.6, 94.7, 73.7, 72.1, 68.3, 68.0, 42.9, 39.3, 32.0, 30.4; IR 3402, 2901, 2360, 2341, 1682, 1618, 1323 cm^{-1}; HRMS (DualESI-TOFMS) *m/z* Calcd. for $[C_{20}H_{19}F_3O_6Na]^+$ 435.1026; found 435.1028.

2.5.2.4 (1S,1'S,5R,5'R)-3,3'-((4-fluorophenyl)methylene)bis(6,8-dioxabicyclo[3.2.1]octan-4-one) 2.167



To a stirred solution of Cyrene (820 µL, 8 mmol) in acetonitrile (2 mL, 2M) was added 4-fluorobenzaldehyde (430 µL, 4 mmol) and DBU (987 µL, 6 mmol). The mixture was stirred at r.t. for 24 h after which water (50 mL) and EtOAc (50 mL) were added. The aqueous phase was washed with EtOAc (3 × 25 mL) and the combined organic extracts were dried over sodium sulfate before the solvent was removed under reduced pressure. The crude product was purified using a Biotage Isolera 4 (snap Ultra 25g cartridge, EtOAc in hexane, 5% → 50%) to afford the *title compound* (**2.167**, 740 mg, 51%) as a colourless oil which solidified.

mp: 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.00 (m, 4H), 5.37 (s, 1H), 5.24 (s, 1H), 4.60-4.57 (m, 1H), 4.52 (br. s, 1H), 3.92-3.39 (m, 1H), 3.80-3.75 (m, 2H), 3.64 (dd, *J* = 1.7 Hz, *J* = 7.2 Hz, 1H), 3.28 (br. s, 1H), 3.15 (d, *J* = 11.6 Hz, 1H), 2.36 (dd, *J* = 4.2 Hz, *J* = 16.6 Hz, 1H), 2.17 (td, *J* = 5.1 Hz, *J* = 12.0 Hz, 1H), 1.67-1.60 (m, 1H), 1.41 (d, *J* = 16.6 Hz, 1H), 1.25-1.20 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.56 (s, 1F); ^{13}C (100 MHz, $CDCl_3$): δ 161.8 (d, $J_{C\text{-}F}$ = 244 Hz), 144.5, 134.9 (d, $J_{C\text{-}F}$ = 3 Hz), 132.1, 128.2, 116.3, 114.8, 104.4, 101.4, 96.6, 94.8, 73.7, 72.1, 68.3, 68.0, 42.2, 39.4, 32.0, 30.5; IR

3380, 2963, 2898, 1681, 1507, 1223 cm^{-1}; HRMS (DualESI-TOFMS) *m/z* Calcd. for $[C_{19}H_{19}FO_6Na]^+$ 385.1058; found 385.1062.

2.5.3 Solvent recycling

Solvent recycling was performed on a large scale reaction between 4-fluorophenyl isocyanate and isopropanol as mentioned previously (Section 2.3.3.3). This was done by precipitating the product by addition of water to the reaction mixture. Once filtered, the aqueous waste was extracted with ethyl acetate (3 × 10 mL) and the combined extracts were dried over sodium sulfate. Ethyl acetate was selectively removed under reduced pressure to give a yellow oil which was passed through a silica plug (ethyl acetate/hexane, 1:9). Cyrene™ containing fractions were combined and solvent selectively removed under reduced pressure to afford pure Cyrene™ in 65% yield.

Chapter 3: References

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Chapter 4: Appendices

4.1 Appendix A: Crystallographic Data

Figure 4.1: Crystal data and structure refinement for (1*S*,5*R*)-3-((E)-3-fluorobenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one **2.154**

Bond precision: C-C = 0.0038 A Wavelength=1.54178

Cell:	a=5.0830(4)	b=11.4757(8)	c=9.6596(6)
	alpha=90	beta=104.080(4)	gamma=90
Temperature:	150 K		

	Calculated	Reported
Volume	546.53(7)	546.53(7)
Space group	P 21 P 21	
Hall group	P 2yb P 2yb	
Moiety formula	C13 H11 F O3 ?	
Sum formula	C13 H11 F O3	C13 H11 F O3
Mr	234.22	234.22
Dx,g cm-3	1.423	1.423
Z	2	2
Mu (mm-1)	0.946	0.946
F000	244.0	244.0
F000'	244.88	
h,k,lmax	6,14,12	6,14,12
Nref	2240[1179]	2042
Tmin,Tmax	0.893,0.954	0.770,0.880
Tmin'	0.804	

Correction method= # Reported T Limits: Tmin=0.770 Tmax=0.880 AbsCorr = MULTI-SCAN

Data completeness= 1.73/0.91 Theta(max)= 74.542 R(reflections)= 0.0378(1925)

wR2(reflections)= 0.1055(2042)

S = 1.137 Npar=154

Table 4.1: Bond lengths (Å) for (1S,5R)-3-((E)-3-fluorobenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one ***2.154***

Atom 1	Atom 2	Bond Length (Å)
F1	C1	1.352(3)
O1	C9	1.215(4)
O2	C10	1.399(4)
O2	C12	1.436(3)
O3	C10	1.422(4)
O3	C11	1.440(4)
C1	C2	1.369(4)
C1	C6	1.383(4)
C2	C3	1.391(4)
C2	H2	0.9500
C3	C4	1.384(4)
C3	H3	0.9500
C4	C5	1.394(3)
C4	H4	0.9500
C5	C6	1.402(4)
C5	C7	1.468(4)
C6	H6	0.9500
C7	C8	1.352(3)
C7	H7	0.9500
C8	C9	1.486(3)
C8	C13	1.512(3)
C9	C10	1.532(3)
C10	H10	1.0000
C11	C12	1.514(4)
C11	H11A	0.9900
C11	H11B	0.9900
C12	C13	1.527(3)
C12	H12	1.0000
C13	H13A	0.9900
C13	H13B	0.9900

*Table 4.2: Bond Angles (°) for (1S,5R)-3-((E)-3-fluorobenzylidene)-6,8-dioxabicyclo[3.2.1]octan-4-one **2.154***

Atom 1	Atom 2	Atom 3	Angle (°)
C10	O2	C12	101.9(2)
C10	O3	C11	106.0(2)
F1	C1	C2	118.7(3)
F1	C1	C6	118.3(3)
C2	C1	C6	123.0(3)
C1	C2	C3	118.0(3)
C1	C2	H2	121.0
C3	C2	H2	121.0
C4	C3	C2	120.6(3)
C4	C3	H3	119.7
C2	C3	H3	119.7
C3	C4	C5	121.0(3)
C3	C4	H4	119.5
C5	C4	H4	119.5
C4	C5	C6	118.4(2)
C4	C5	C7	125.1(3)
C6	C5	C7	116.4(2)
C1	C6	C5	119.1(3)
C1	C6	H6	120.5
C5	C6	H6	120.5
C8	C7	C5	130.3(3)
C8	C7	H7	114.8
C5	C7	H7	114.8
C7	C8	C9	116.1(2)
C7	C8	C13	126.4(2)
C9	C8	C13	117.6(2)
O1	C9	C8	124.9(3)
O1	C9	C10	120.5(3)
C8	C9	C10	114.5(2)
O2	C10	O3	107.3(2)
O2	C10	C9	109.9(2)
O3	C10	C9	106.4(2)
O2	C10	H10	111.0
O3	C10	H10	111.0
C9	C10	H10	111.0
O3	C11	C12	103.8(2)
O3	C11	H11A	111.0

4.2 Appendix B: Mol. E% Calculations

4.2.1 Overview of Mol. E% calculations for the dehydrative Mizoroki-Heck project

Scheme No	Scheme Name	Reaction In	Reaction Out	Solvents	Solvents (No Water)	Workup & Purification	W&P (No Water)	Moles In	Moles In (No Water)	Moles Out	MolE% (No Water)	MolE (No Water)	MolE (Full)	MolE% (Reaction Only)	MolE% (Full)
1	1-bromination (22a)	21.8	8.3	133	133	61224	61224	61379	61379	8.3	0.01%	1.35E-04	1.35E-04	**38.0%**	**0.01%**
2	2-bromination (22b)	12.3	5.7	230	230	12967	203	13209	446	5.7	1.29%	1.29E-02	4.35E-04	**46.7%**	**0.04%**
3	3-bromination (22c)	10.5	2.5	195	94	20631	20631	20836	20735	2.5	0.01%	1.19E-04	1.18E-04	**23.4%**	**0.01%**
4	4-bromination (22d)	5.0	0.7	44	44	2145	2145	2194	2194	0.7	0.03%	3.37E-04	3.37E-04	**14.9%**	**0.03%**
5	5-bromination (22e)	1.9	0.3	0	0	3245	3134	3247	3136	0.3	0.01%	9.09E-05	8.78E-05	**15.3%**	**0.01%**
6	1-styrene (20a)	2.0	0.6	26	26	28	28	57	57	0.6	1.13%	1.13E-02	1.13E-02	**31.7%**	**1.13%**
7	2-styrene (20b)	13.4	5.8	0	0	51989	43665	52002	43678	5.8	0.01%	1.33E-04	1.12E-04	**43.4%**	**0.01%**
8	3-styrene (20c)	1.1	0.2	4	4	1202	142	1207	147	0.2	0.15%	1.48E-03	1.81E-04	**19.7%**	**0.02%**
9	4-styrene (20d)	1.2	0.3	9	9	3034	3034	3044	3044	0.3	0.01%	9.76E-05	9.76E-05	**25.0%**	**0.01%**
10	5-styrene (20e)	2.0	0.6	88	88	0	0	90	90	0.6	0.62%	6.24E-03	6.24E-03	**27.7%**	**0.62%**
11	2001 Fu (21)	2.9	0.7	10	10	6663	6663	6676	6676	0.7	0.01%	1.01E-04	1.01E-04	**23.5%**	**0.01%**
12	Method 2	1.6	0.3	88	57	1662	1108	1752	1167	0.3	0.03%	2.77E-04	1.85E-04	**20.4%**	**0.02%**
13	2012 Xiao (25)	9.2	1.4	60	60	9527	1203	9596	1272	1.4	0.11%	1.10E-03	1.46E-04	**15.3%**	**0.01%**
14	2010 Bedekar (24)	5.1	0.7	108	108	10054	3118	10167	3230	0.7	0.02%	2.12E-04	6.75E-05	**13.4%**	**0.01%**
15	2015 Tolman A 23)	11.0	4.2	468	468	303	205	782	684	4.2	0.61%	6.14E-03	5.37E-03	**38.1%**	**0.54%**
16	2015 Tolman B (23)	1.0	0.2	4	4	1164	107	1169	112	0.2	0.14%	1.42E-03	1.36E-04	**15.8%**	**0.01%**

4.2.2 Mol. E% calculator example using data for the synthesis of amides

MolE Calculator

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Date Published: March 2018

This spreadsheet presents molar efficiency calculations and estimates the MolE% of synthesis processes.

The *Overview* worksheet is read-only, presents a summary of all the calculations. The *Scheme Description* worksheet allows the user to write a few more details about the sources of the calculations. The next three worksheets *(Reaction, Reaction Solvents* and *Workup & Purification)* are the main input sheets of the calculator. The user enter the required information in the red-shaded cells, whereas the white cells are read-only and present all the results. Finally, the two *Libraries* are populated with the most common solvents and reagents used. However, users can freely add or alter their contents.

A maximum of 30 different schemes can be supported using one copy of the calculator. A maximum of 100 different solvents/reagents can be added in the two libraries. The user should make sure that the contents of the libraries have been sorted, after having added all the new entries.

The calculator is based on the work presented in: F. I. McGonagle, H. F. Sneddon, C. Jamieson and A. J. B. Watson, *ACS Sustainable Chem. Eng.* , 2014, **2**, 523–532

1	This worksheet is an overview of all the schemes entered. You cannot alter the content of the cells in this worksheet.																
2	Reaction Out	Solvents	Solvents (No Water)	Workup & Purification	W&P (No Water)	Moles In	Moles In (No Water)	Moles Out	Substrate Mass	Reagents Mass	Solvents Mass (Non Aq)	Aqueous Mass	Product Mass	MolE% (No Water)	MolE (No Water)	MolE (Full)	MolE% (Reaction Only)	MolE% (Full)
3	0.5	5	5	8615	5841	8622	5847	0.5	72.3	163.5	625.0	0.0		0.008%	7.78E-05	5.28E-05	**29.4%**	**0.0053%**
4	0.4	5	5	5325	5325	5331	5331	0.4	72.3	163.5	625.0	0.0		0.007%	7.03E-05	7.03E-05	**24.2%**	**0.0070%**
5	0.4	5	5	277	0	284	6	0.4	72.3	174.5	625.0	0.0		5.601%	5.60E-02	1.27E-03	**23.2%**	**0.1268%**
6	0.4	5	5	277	0	284	6	0.4	72.3	181.5	625.0	0.0		6.301%	6.30E-02	1.43E-03	**26.1%**	**0.1427%**
7	7.6	389	389	68272	57173	68687	57588	7.6	969.4	3633.7	625.0	0.0		0.013%	1.32E-04	1.11E-04	**29.7%**	**0.0111%**
8	0.5	389	389	14622	14622	15014	15014	0.5	226.6	525.9	28440.0	0.0		0.003%	3.00E-05	3.00E-05	**15.0%**	**0.0030%**
9	0.6	90	90	24244	22025	24348	22128	0.6	639.2	1896.9	28440.0	0.0		0.003%	2.85E-05	2.59E-05	**4.7%**	**0.0026%**
10	2.3	624	624	31354	24694	31990	25331	2.3	500.1	1534.2	6468.3	0.0		0.009%	9.20E-05	7.29E-05	**19.5%**	**0.0073%**
11	7.8	390	390	67195	65530	67619	65954	7.8	1720.3	4626.0	53040.0	0.0		0.012%	1.18E-04	1.15E-04	**22.9%**	**0.0115%**

	Scheme	Abbreviation	Details
2	1	Amide Pyrrol Aq	Amide synthesis in Cyrene using 4-fluorobenzoyl chloride and pyrrolidine - Aq w/u followed by column
3	2	Amide Pyrrol Col	Amide synthesis in Cyrene using 4-fluorobenzoyl chloride and pyrrolidine - straight column
4	3	Amide Aniline ppt	Amide synthesis in Cyrene using 4-fluorobenzoyl chloride and aniline - Aq precipitation
5	4	Amide Benzyl ppt	Amide synthesis in Cyrene using 4-fluorobenzoyl chloride and benzylamine - Aq precipitation
6	5	DMF-1	H. Kurouchi, K. Kawamoto, H. Sugimoto, S. Nakamura, Y. Otani and T. Ohwada, J. Org. Chem., 2012, 77, 9313-9328.
7	6	DMF-2	Lee, B. D;. Li, Z.; French, K. J.; Zhuang, Y.; Xia, Z.; Smith, C. D. J. Med. Chem. 2004, 47, 1413–1422.
8	7	THF-1	Konishi, M.; Tsuchida, K.; Sano, K.; Kochi, T.; Kakiuchi, F. J. Org. Chem.2017, 82, 8716–8724.
9	8	CH2Cl2-1	Reddy, M. D.; Blanton, A. N.; Watkins, E. B. J. Org. Chem. 2017, 82, 5080–5095.
10	9	CH2Cl2-2	Li, W.; Wu, X.-F. J. Org. Chem. 2014, 79, 10410–10416.

1	Add the name of a reagent in the first column and the quantities of reactants used in *mmol* in the red shaded cells, by inserting L next to the limiting reactant. Insert the yield percentage in the corresponding row.																			
2	**Scheme No**		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
3	**Scheme Name**		**Amide Pyrrol Aq**		**Amide Pyrrol Col**		**Amide Aniline pp**		**Amide Benzyl pp**		**DMF-1**		**DMF-2**		**THF-1**		**CH2Cl2-1**		**CH2Cl2-2**	
4	**Total Moles In**		1.55		1.55		1.55		1.55		25.60		3.00		13.50		11.98		34.00	
5	**Total Moles Out**		0.46		0.38		0.36		0.41		7.60		0.45		0.63		2.331		7.8	
6	**Total Mass In**		163.50		163.50		174.51		181.52		3633.66		525.91		1896.90		1534.18		4626.02	
7	**Substrate In**		72.29		72.29		72.29		72.29		969.44		226.56		639.18		500.10		1720.25	
8	**Yield**		91%		75%		72%		81%		95%		45%		21%		70%		78%	
9	Name	Molecular Weight	Reagents Used (in mmol)																	
10	4-Fluorobenzyl chloride	144.6	L	0.50	L	0.50	L	0.50	L	0.50								3.66		11.00
11	Triethylamine	101.2		0.55		0.55		0.55		0.55		8.80				6.00		4.99		13.00
12	Pyrrolidine	71.1		0.50		0.50														
13	Aniline	93.1						0.50												
14	Benzylamine	107.2								0.50										
15	Phenylethylamine	121.2									L	8.00								
16	Chloroformate	201.6										8.80								
17	N-(2-Aminophenyl)-acetamide	150.2															L	3.33		
18	2-Bromoaniline	172.0																	L	10.00
19	(4'-Aminophenyl)-2,2'-(4'-hydroxyphenyl)-propane	227.3																		
20	1-Benzyl-2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4-ylamine	275.4												1.00						
21	4-Fluoro-3-(trifluoromethyl)benzoyl chloride	226.6											L	1.00						
22	Sodium hydride	24.0												1.00						
23	5,7-Dichloroquinolin-8-amine	213.1													L	3.00				
24	3-Fluorobenzyl chloride	144.6														4.50				

1	**Insert the quantities of solvents used in the Orange Cells. Select the solvent from the drop-down list in Column A and the input type (moles, mass, volume) in Column B.**																			
2	**Scheme No**			**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
3	**Scheme Name**			**Amide Pyrrol Aq**		**Amide Pyrrol Co**		**mide Aniline pp**		**Amide Benzyl pp**		**DMF-1**		**DMF-2**		**THF-1**		**CH2Cl2-1**		**CH2Cl2-2**	
4	**Used Moles (in *mmol*)**			5		5		5		5		389		389		90		624		390	
5	**Used Moles w/o water (in *mmol*)**			5		5		5		5		389		389		90		624		390	
6	**Water Mass**			0		0		0		0		0		0		0		0		0	
7	**Solvent Mass**			625		625		625		625		625		28440		28440		6468		53040	
8	Name	MW	Input Type	Solvents Used																	
9	Cyrene	128.13	mL	1	5	1	5	1	5	1	5										
10	DMF	73.1	mL									30	389	30	389						
11	DCM	84.96	mL															40	624	25	390
12	NMP	99.13	mL																		
13	THF	72.11	mL													10	90				

1	Select the reagent from the drop-down list in Column A and the input type (moles, mass, volume) in Column B. Then, for each reagent, add the quantity used in the orange column of each																					
2	**Scheme No**				**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
3	**Scheme Name**				**Amide Pyrrol Aq**		**Amide Pyrrol Co**		**mide Aniline pp**		**mide Benzyl pp**		**DMF-1**		**DMF-2**		**THF-1**		**CH2Cl2-1**		**CH2Cl2-2**	
4	**Used Moles (in *mmol*)**				8615		5325		277		277		68272		14622		24244		31354		67195	
5	**Used Moles w/o water (in *mmol*)**				5841		5325		0		0		57173		14622		22025		24694		65530	
6	**Water (Mass)**				50000		0		5000		5000		200000		0		40000		120000		30000	
7	**Other Reagents (Mass)**				487250		441650		0		0		4648200		1606250		1775050		1988393		4579480	
8	Name	Input Type	ρ (g/mL)	MW (g/mol)	Solvents Used																	
9	EtOAc	mL	0.902	88.11	300	3071	250	2559					3150	32247			430	4402	645	6603	275	2815
10	Water	mL	1	18.02	50.0	2775			5	277	5	277	200	11099			40	2220	120	6659	30	1665
11	Hexanes	mL	0.6606	86.18	250	1916	250	1916					1500	11498			1608	12326	1505	11536		
12	Silica Gel	g	-	60.08	51	849	51	849					800	13316	110	1831	300	4993	333	5543	1000	16644
13	MgSO4	g	-	120.37	1	4													7	55	10	83
14	Na2SO4	g	-	142.04									16	113			6	42				
15	DCM	mL	1.326	84.96													8	117	40	624	30	468
16	NaHCO3	g	-	84													2	23	4	45		
17	HCl	g	1.49	36.46															2	41		
18	NaCl	g	-	58.44													7	121	14	246	11	185
19	Pentane	mL	0.626	72.15																	5225	45334
20	DMF	mL	0.948	73.1											15	195						
21	CHCl3	mL	1.489	119.37											990	12349						

1	**The Solvents Library includes all the solvents that can be used in the *Reaction Solvents* worksheet. The user can edit this list and add/update its values. However, they should make sure that the list is sorted from A to Z after finishing adding all new entries and before using it.**

	Symbol	Name	Density (g/mL)	Molecular Weight (g/mol)
3	Ac2O	Acetic anhydride	1.082	102.09
4	Acetone	Acetone	0.7845	58.8
5	AcOH	Acetic acid	1.049	60.05
6	Benzene	Benzene	0.8765	78.11
7	CCl4	Carbon tetrachloride	1.5867	153.81
8	CHCl3	Chloroform	1.489	119.37
9	Chlorobenzene	Chlorobenzene	1.11	112.56
10	Cyrene	Cyrene	1.25	128.13
11	DCE	1,2-Dichloroethane	1.253	98.95
12	DCM	Dichloromethane	1.326	84.96
13	Diethylether	Diethylether	0.713	74.12
14	Diglyme	Diglyme	0.937	134.18
15	Dioxane	1,4-Dioxane	1.033	88.11
16	DMA	*N,N*-Dimethylacetamide	0.937	87.12
17	DMAc	Dimethylacetamide	0.937	87.12
18	DME	Dimethoxyethane	0.8683	90.12
19	DMF	Dimethylformamide	0.948	73.1
20	DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone	1.064	128.18
21	DMSO	Dimethyl sulfoxide	1.1004	78.13
22	Ethylene glycol	Ethylene glycol	1.1132	62.07
23	EtOAc	Ethyl Acetate	0.902	88.11
24	EtOH	Ethanol	0.7893	46.07
25	Heptane	*n*-Heptane	0.6795	100.21
26	Hexanes	Hexanes	0.6606	86.18
27	*i*-PrOH	Isopropanol	0.786	60.1
28	Me-THF	2-Methyltetrahydrofuran	0.854	86.13
29	MeCN	Acetonitrile	0.786	41.05
30	MeOH	Methanol	0.792	32.04
31	*n*-BuOAc	*n*-Butylacetate	0.8825	116.16
32	Nitromethane	Nitromethane	1.1371	61.04
33	NMP	*N*-Methyl-2-pyrrolidone	1.028	99.13
34	Pentane	Pentane	0.626	72.15
35	Petrol	Petrolium ether (35 °C - 60 °C)	0.653	82.2
36	Pyridine	Pyridine	0.9819	79.1
37	Sulfolane	Sulfolane	1.261	120.17
38	t-BuOH	tert-Butyl alcohol	0.775	74.12
39	THF	Tetrahydrofuran	0.8892	72.11
40	Toluene	Toluene	0.87	92.14
41	Water	Water	1	18.02
42	Xylenes	Xylenes	0.864	106.16

1	The Reagents Library includes all the reagents that can be used in the *Workup & Purification* worksheet. The user can edit this list and add/update its values. However, they should make sure that the list is sorted from A to Z after finishing adding all new entries and before using it.			
2	Symbol	Name	Density (g/mL)	Molecular Weight (g/mol)
3	Ac2O	Acetic anhydride	1.082	102.09
4	Acetone	Acetone	0.7845	58.8
5	AcOH	Acetic acid	1.049	60.05
6	Aluminum oxide	Aluminum oxide	-	101.96
7	Benzene	Benzene	0.8765	78.11
8	CCl4	Carbon tetrachloride	1.5867	153.81
9	CHCl3	Chloroform	1.489	119.37
10	Chlorobenzene	Chlorobenzene	1.11	112.56
11	Cyrene	Cyrene	1.25	128.13
12	DCE	1,2-Dichloroethane	1.253	98.95
13	DCM	Dichloromethane	1.326	84.96
14	Diethylether	Diethylether	0.713	74.12
15	Diglyme	Diglyme	0.937	134.18
16	DMA	*N,N*-Dimethylacetamide	0.937	87.12
17	DMAc	Dimethylacetamide	0.937	87.12
18	DME	Dimethoxyethane	0.8683	90.12
19	DMF	Dimethylformamide	0.948	73.1
20	DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone	1.064	128.18
21	DMSO	Dimethyl sulfoxide	1.1004	78.13
22	Ethylene glycol	Ethylene glycol	1.1132	62.07
23	EtOAc	Ethyl Acetate	0.902	88.11
24	EtOH	Ethanol	0.7893	46.07
25	HCl	Hydrochloric acid	1.49	36.46
26	Heptane	*n*-Heptane	0.6795	100.21
27	Hexanes	Hexanes	0.6606	86.18
28	*i*-PrOH	Isopropanol	0.786	60.1
29	MeCN	Acetonitrile	0.786	41.05
30	MeOH	Methanol	0.792	32.04
31	Me-THF	2-Methyltetrahydrofuran	0.854	86.13
32	MgSO4	MgSO4	-	120.37
33	Na2SO4	Sodium sulfate	-	142.04
34	NaCl	Sodium chloride	-	58.44
35	NaHCO3	Sodium bicarbonate	-	84
36	NaOH	sodium hydroxide	-	40
37	*n*-BuOAc	*n*-Butylacetate	0.8825	116.16
38	Nitromethane	Nitromethane	1.1371	61.04
39	NMP	*N*-Methyl-2-pyrrolidone	1.028	99.13
40	Pentane	Pentane	0.626	72.15
41	Petrol	Petrolium ether (35 °C - 60 °C)	0.653	82.2
42	Pyridine	Pyridine	0.9819	79.1
43	Silica Gel	Silica Gel	-	60.08
44	Sulfolane	Sulfolane	1.261	120.17
45	*t*-BuOH	tert-Butyl alcohol	0.775	74.12
46	THF	Tetrahydrofuran	0.8892	72.11
47	Toluene	Toluene	0.87	92.14
48	Water	Water	1	18.02
49	Xylenes	Xylenes	0.864	106.16

Approximations use for methods lacking specific details

1. 100 g SiO_2 per 1.0 mmol (up to 10 mmol): 50 g SiO_2 per 1.0 mmol (up to 10 mmol) using automated purification system
2. 1.0 L solvent for first 1.0 mmol and then 500 mL solvent for each mmol thereafter (up to 10 mmol) for column chromatography: 0.5 L solvent and then 250 mL solvent for each mmol thereafter (up to 10 mmol) using automated purification system
3. 10.0 g silica gel for a "silica plug" or "filtered through silica" (up to 10 mmol)
4. 5.0 mL per 1.0 mmol for recrystallization (up to 10 mmol)
5. drying agent ($MgSO_4$ or Na_2SO_4) 2.0 g per 1 mmol

4.3 Publications

4.3.1 Recyclable glucose-derived palladium(0) nanoparticles as *in situ*-formed catalysts for cross-coupling reactions in aqueous media

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Recyclable glucose-derived palladium(0) nanoparticles as *in situ*-formed catalysts for cross-coupling reactions in aqueous media†

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In situ-generated, glucose-derived palladium(0) nanoparticles were shown to be convenient and effective catalysts for aqueous Mizoroki–Heck, Sonogashira and Suzuki–Miyaura cross-coupling reactions. The addition of only 4–10 mol% glucose to the reaction mixture lead to a significant increase in yield of the desired products in comparison to processes that omitted the renewable sugar. Interestingly, the Mizoroki–Heck reaction was observed to proceed in good yield even as the reaction reached acidic pH levels. Extensive analysis of the size and morphology of the *in situ*-formed palladium nanoparticles using advanced analytical techniques showed that the zero valent metal was surrounded by hydrophilic hydroxyl groups. The increased aqueous phase affinity afforded by these groups allowed for facile recycling of the catalyst.

Introduction

Palladium-catalysed cross-coupling reactions are some of the most powerful methods for the creation of new carbon–carbon bonds due to their high selectivity, functional group tolerance and regio-/stereoselectivity.[1] Many industries, including the pharmaceutical and agrochemical industries, have made extensive use of palladium mediated cross-couplings for the synthesis of added-value compounds.[2] In order to work effectively these processes often require toxic and expensive additives, which leads to unnecessary waste, expense and cost to the environment. One area of catalysis that addresses some of the limitations of traditional palladium-mediated bond formation is the use of palladium nanoparticles (PdNPs).[3] The rapid increase in the use of metal nanoparticles for catalysis is due to the fact that they have a good reactivity/selectivity profile,[4] require low catalyst loadings and are recoverable and recyclable.[5] Traditionally, palladium(0) nanoparticles (Pd^0NP) are formed *via* reduction of a palladium(II) precatalyst in the presence of a nanoparticle support and capping agents.[6] Once isolated, Pd^0NPs can then be used as efficient catalysts for bond formation under standard cross-coupling conditions.[7] Two key drawbacks to the use of nanoparticles in palladium catalysis are the cost associated with the synthesis, isolation and purification of the nanoparticles[8] and the use of toxic additives, capping reagents and excess reagents that lead to a decrease in the activity and recyclability of the catalyst.[9] The *in situ* formation of catalytically active PdNPs using a renewable reductant without the addition of capping agents would overcome many of these issues. Whilst it has been established that simple monosaccharides such as glucose,[10] fructose,[11] sucrose,[11] other biomass (cellulose/starch/beet juice/lignan)[12,13] and even whole plants[14] can reduce metal salts and form metal nanoparticles (MNPs),[15,16] very little research has been conducted on the ability of *in situ* formed nanoparticles to catalyse carbon–carbon bond forming reactions (Fig. 1).[17,18] Recently Nacci *et al.* showed that the addition of a reducing sugars to palladium-catalysed Ullmann couplings in the presence of TBAOH resulted in the formation of the desired symmetric biaryl products.[17a] In addition, we have shown that sugar derived palladium nanoparticles are viable catalysts for Suzuki–Miyaura cross-coupling reactions of aryl iodides and boronic acids in isopropanol.[17c] Despite the important role of monosaccharides in transition metal catalysis, where they have been mainly used as ligands,[19] their effect on cross-coupling processes is poorly understood. Herein, we harness renewable sugars for the *in situ* formation and stabilisation of palladium(0) nanoparticles in aqueous solutions, which allowed for the development of a variety of palladium-mediated cross-coupling reactions as well as facial recycling of the catalyst.

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† Electronic supplementary information (ESI) available: Nanoparticle characterisation (TEM, EDS-TEM, XPS, DLS, q-Nano and NanoSight data), experimental procedures, and $^1H/^{13}C\{^1H\}$ NMR data for all compounds. See DOI: 10.1039/c5ra25712c

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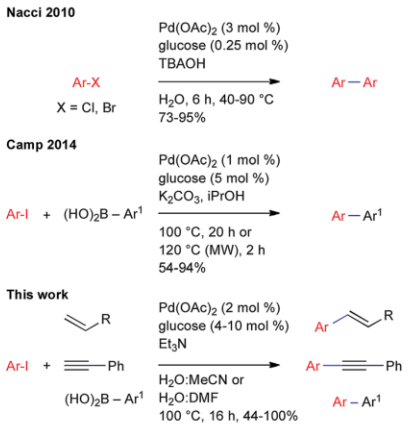
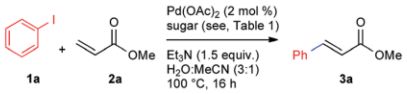


Fig. 1 Use of renewable sugars in palladium-catalysed coupling reactions.

Results and discussion

Initial investigations were aimed at establishing the catalytic viability of the sugar-derived palladium nanoparticles under aqueous conditions[20] and to gain an increased understanding of the role of the reducing sugar in the overall process. Due to its extensively studied mechanism and synthetic importance, the Mizoroki–Heck reaction was chosen as an archetypal transformation.[21] Importantly, aqueous conditions were investigated that should allow for increased recyclability of the catalysts and overall greener processes (*vide infra*).[22] Two key variables that needed to be examined were the choice of reducing sugar and the ratio of sugar to palladium. Thus, the coupling of iodobenzene (**1a**) with methyl acrylate (**2a**) in the presence of $Pd(OAc)_2$, a reducing sugar and triethylamine in water : acetonitrile (3 : 1) at 100 °C was used to probe the feasibility of the process (Table 1).[23] Whilst fructose,[24] cellulose,[25] sucrose[26] and glucose[27] all have the ability to reduce palladium(II) pre-catalysts to palladium(0), the yield of product obtained from the *in situ* generated nanoparticles varied significantly (Table 1, entries 1–4). Of the four sugars tested, fructose has the highest reduction potential and gives the smallest average particle size when used to form metal nanoparticles.[11] Despite these facts, fructose gave the lowest yield of product and actually inhibited the reaction when compared with control experiments (Table 1, entry 1 *vs.* 5). The PdNPs formed employing cellulose as the reductant also gave a low yield (Table 1, entry 2). Sucrose, which is hydrolysed under the reaction conditions to form a 1 : 1 mixture of fructose and glucose,[28] gave a moderate yield of the desired product after stirring for 16 h at 100 °C (Table 1, entry 3). Nearly quantitative yield of (*E*)-methyl-cinnamate (**3a**) was obtained when glucose was used as the reducing sugar (Table 1, entry 4). Control experiments in which the sugar, base and palladium were omitted all showed significantly lower product production than the glucose system (Table 1, entry 4 *vs.* 5–8). The observed benefit of glucose to the process is most likely due to the fact that it allows enough of the palladium surface to be

Table 1 Sugar-derived palladium(0) nanoparticles as catalysts for the Mizoroki–Heck reaction



Entry	Sugar	Pd/sugar ratio	Yield[a] (%)
1	Fructose	1 : 2	2
2	Cellulose	1 : 10[b]	21
3	Sucrose	1 : 2	58
4	Glucose	1 : 2	97
5	—	1 : 0	18
6[c]	—	1 : 0	12
7[c]	Glucose	1 : 2	6
8[c,d]	Glucose[e]	—	0
9	Glucose	1 : 1	70
10	Glucose	1 : 3.5	50
11	Glucose	1 : 4	42
12[f]	Glucose	1 : 2	20

[a] Isolated yield. [b] A 1 : 10 weight to weight ratio of palladium acetate to cellulose was used. [c] No Et_3N was added. [d] No palladium was added. [e] 4 mol% glucose was added. [f] PdNPs were preformed and isolated.

accessible for catalysis whilst preventing catalyst poisoning *via* aggregation (*vide supra*). Having established the benefits of glucose in the Mizoroki–Heck reaction, the ratio of sugar to palladium was examined (Table 1, entries 9–11). A 1 : 2 ratio of palladium to sugar was found to give the highest yield of **3a**. Excess sugar may prevent the surface of the catalyst from being solvent exposed, whilst too little results in increased aggregation of the palladium(0) and deactivation of the catalyst. It was also found that a reaction time of 16 h was required for completion of the process at 100 °C.[29] Additionally, experiments showed that the *in situ* formed palladium nanoparticles gave a significantly better yield of **3a** than ones that were preformed and isolated prior to addition to the reaction (Table 1, entry 4 *vs.* 12).[11,30] This is most likely due to the surface of the nanoparticle being coated with a layer of organic material, which can block many of the catalytic sites.

Next the pH of the reaction was monitored as a function of time (Fig. 2). To accomplish this, a series of reaction between iodobenzene (**1a**) and methyl acrylate (**2a**) under the standard condition were run for set amounts of time and the pH was determined. After the pH measurement was made, the crude reaction mixture was worked-up and purified according to the general procedure to obtain the isolated yields. A plot of pH *vs.* time *vs.* yield revealed that the reaction proceeds in good yield even at acidic pH (increasing from 30–97% as the pH decrease from 4.52–2.66). Unfortunately, complete removal of base from the system gave only a small amount of the desired product (Table 1, entry 7). These results are in contrast to other pH dependency studies that established a pH range of 9–11.5 to be optimal for palladium-catalysed cross-coupling reactions.[31] It is likely that the role of the sugar at basic pH levels is to act as a ligand for the palladium catalyst, as proposed by Jain *et al.* for the use of mannose,[19g] and that the reaction proceeds through

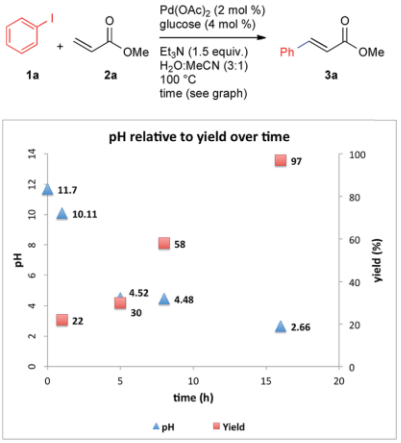
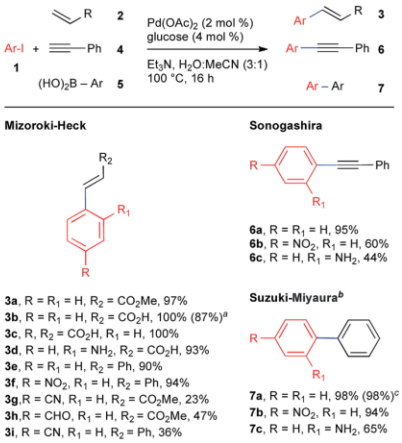


Fig. 2 Comparison of pH *vs.* time *vs.* yield of the PdNP mediated reaction.

Table 2 Substrate and reaction scope



[a] Sodium erythorbate (4 mol%) was used in place of glucose. [b] Ar–I (1.0 equiv.), $(HO)_2B$–Ph (1.5 equiv.), glucose (10 mol%), $Pd(OAc)_2$ (2 mol%), Cs_2CO_3 (2.0 equiv.), DMF : H_2O (10 : 1), 100 °C, 16 h. [c] Ph–Br (1.0 equiv.) was used.

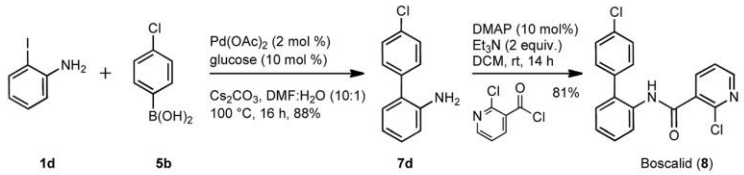
a standard Mizoroki–Heck mechanism.[32] As the solution becomes acid, it is possible that the sugar is then responsible for reducing the palladium(II) species to the catalytically active palladium(0) complex.[27] These observations could have important implications for the development of Pd(0) mediated, base-free carbon–carbon bond forming reactions under acidic conditions.

In order to assess the catalytic ability of the *in situ* formed PdNPs with respect to both reaction type and substrate scope a variety of substituted aryl iodides were interrogated. Three palladium mediated carbon–carbon bond forming reactions, the Mizoroki–Heck, Sonogashira and Suzuki–Miyaura were investigated (Table 2). Unprotected arenes with both electron donating and withdrawing substituents were examined in an attempt to mitigate the use of protecting groups.[33] Several features of the sugar derived palladium nanoparticle methodology are noteworthy. It was shown that both electron withdrawing groups, such as carboxylic acid and nitro moieties, as well as basic functionality, such as anilines were well tolerated in the Mizoroki–Heck reaction between aryl iodides **1** and various alkenes **2** to give styrene derivatives **3a–i**. Substitution at both the 2- and 4-positions of the iodobenzene ring was found to be compatible with the cross-coupling procedure. Interestingly, it was also shown that sodium erythorbate, a common food additive, could be used to afford a viable catalytic system for the synthesis of (*E*)-3-phenyl-2(*E*)-propenoic acid (**3b**), though in a slightly reduced yield. The sugar derived palladium nanoparticles were also efficient catalysts for the Sonogashira and Suzuki–Miyaura reactions under aqueous conditions. Coupling of aryl iodides **1** and phenyl acetylene (**4**) gave disubstituted alkynes **6a–c** in moderate to good yield. Additionally, the Suzuki–Miyaura reaction between aryl iodides **1** and phenyl boronic acid (**5**) gave biaryls **7a–c** in good to excellent yields under slightly modified conditions. In contrast to our recently reported methods in isopropanol,[17c] aryl bromides also coupled efficiently in a DMF : H_2O (10 : 1) solvent system to afford biphenyl (**7a**) in excellent yield. Unfortunately, the use of arylbromides and aryl chlorides in the Mizoroki–Heck and Sonogashira cross-coupling reactions only gave the desired products in 2–8% yield.[29] In contrast to a recent related study, the nitro moiety was not reduced under the reaction conditions and cleanly afford the cross-coupled products **3f**, **6b**, and **7b**.[19g]

Building upon our substrate scope study, we turned our attention to the synthesis of the important agrochemical Boscalid (**8**).[34] Thus, reaction of 4-chlorophenylboronic acid (**5b**) with 2-iodoaniline (**1d**) under the standard conditions gave the desired biaryl **7d**. Amidation of aniline **7d** afforded the fungicide in good overall yield. Boscalid has been the target of a number of synthetic approaches.[35] Due to the fact that unprotected anilines are well tolerated under the reaction conditions, this method provides a nearly two-fold increase in molar efficiency[36,37] compared to a standard protocol[38] (Scheme 1).

Characterisation of *in situ*-formed palladium(0) nanoparticles

A number of analytical techniques were used to confirm the formation of the glucose-derived palladium nanoparticles as well as to establish their size, morphology, surface characteristics and oxidation state. Transmission Electron Microscopy (TEM) analysis indicated that the palladium nanoparticles were semi-crystalline, approximately 5–20 nm in size and exist in a variety of conformations and morphologies, including spheres and prisms (Fig. 3a and b).[29] In addition, EDS-TEM was used to determine that the surface of the nanoparticles is decorated with carbon and oxygen molecules (Fig. 3c). Thus, the lighter amorphous material at the periphery most likely contains the sugar residues, which served as both the reductant and stabiliser of the palladium nanoparticles. This sugar



Scheme 1 Synthesis of Boscalid (**8**) using *in situ* formed palladium nanoparticles.

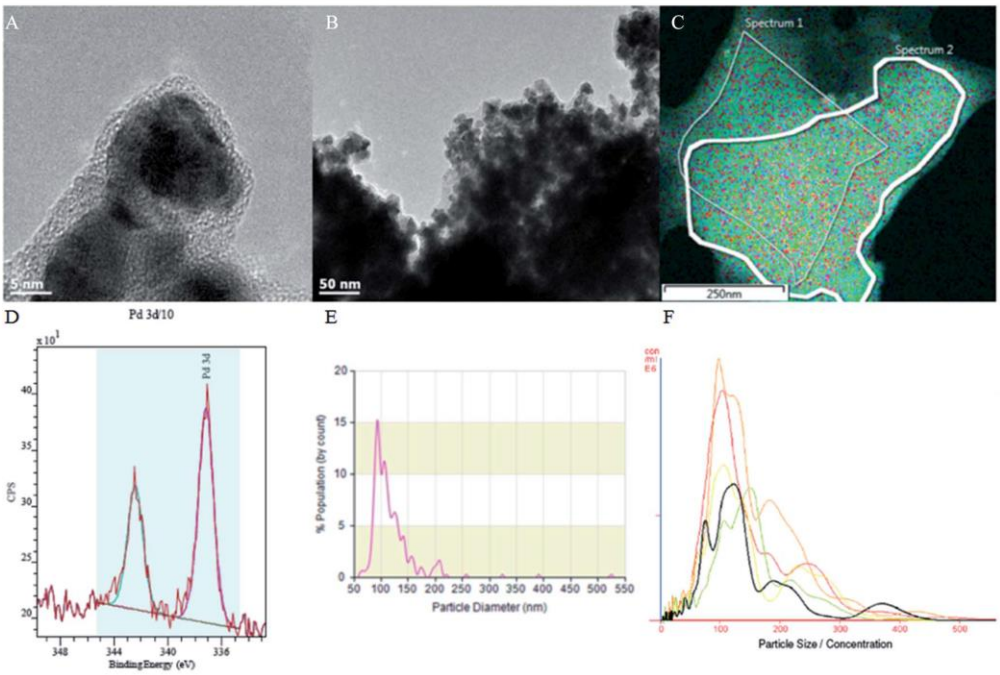


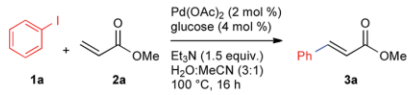
Fig. 3 Structural and surface characterisation of the sugar–PdNPs. (a and b) typical TEM image of sugar-derived palladium nanoparticles (c) EDS-TEM map of the nanoparticles showing the nanoparticles surrounded by a hydrophilic hydroxyl shell; palladium (green), oxygen (red), and carbon (blue) (d) XPS analysis (e) scanning ion occlusion sensing analysis (f) nanoparticle tracking analysis.

coating provides a hydrophilic environment around the palladium catalyst. XPS analysis determined that the individual nanoparticles were predominately in the palladium(0) oxidation state. Analysis of the sugar-derived nanoparticles suspended in water at room temperature by nanoparticle tracking analysis (NTA), scanning ion occlusion sensing (SIOS) and dynamic light scattering (DLS) analysis showed that the nanoparticles aggregate into larger clusters of around 100 nm. This average particle size in solution is significantly greater than the small particles identifiable by TEM analysis. Similar levels of aggregation have been observed in related sugar-derived palladium nanoparticles.[39]

Recycling of the palladium nanoparticle catalysts

To exploit the hydrophilic nature of the palladium catalysts we investigated the recyclability of the *in situ* formed catalyst in an aqueous solvent. Importantly, the hydrophilic surface of the renewable sugar derived PdNP should help keep the catalyst in the aqueous layer during extraction by an organic solvent. To probe this hypothesis the recyclability of the *in situ* formed palladium nanoparticles was investigated *via* a series of reactions between iodobenzene (**1a**) and methyl acrylate (**2a**, Table 3). After the initial reaction was performed under the standard conditions, diethylether was added and the solution was subjected to centrifugation. The organic layer was isolated, the solvent was removed under reduced pressure and the residue was purified *via* flash chromatography. To the aqueous layer were added the substrates (**1a** and **2a**), acetonitrile (1 mL) and triethylamine (1.5 equiv.). No additional palladium or glucose was added at this stage. Importantly, it was not necessary to wash the aqueous mixture to remove excess salts or base.[40] This study showed that the *in situ* formed palladium nanoparticles were recyclable for up to three additional cycles without significant loss of catalytic activity. A fifth reaction catalysed by the same palladium(0) nanoparticles gave the product in 61% yield. A similar, though more substantial, drop-off in reactivity was reported for the recycling of sugar-derived

Table 3 Recyclability of the *in situ*-formed palladium nanoparticle catalysts



1a 2a 3a

Entry	Pd/sugar ratio	Yield[b] (%)	Notes
1	1 : 2	97	
2[a]	—	92	1st recycle
3[a]	—	92	2nd recycle
4[a]	—	82	3rd recycle
5[a]	—	61	4th recycle

[a] Et_3N (1.5 equiv.) was added after each cycle, but no additional palladium or glucose. [b] Isolated yield.

catalysts in the Ullmann reaction.[17a] The decrease in yield in our system is most likely caused by the low level of sugar residue on the surface of the nanoparticles at this point in the reaction, which lead to increased aggregation of the palladium(0) and deactivation. Similar results were observed in our initial stoichiometry study (see, Table 1, entries 4 *vs.* 9). Thus, it may be necessary to add glucose at various points of the reaction in order to improve the recyclability of the catalyst. Efforts are currently ongoing in our laboratory to study the effect of continuous glucose addition on the overall yield of the process.

Conclusion

In summary, the ability of simple sugars to both form and stabilise recyclable, catalytically active palladium(0) nanoparticles was demonstrated for a variety of synthetically important carbon–carbon bond forming reactions. Additionally, the sugar coating on the surface of the palladium not only prevented aggregation and deactivation *via* palladium black formation, but also allowed for facial recycling of the *in situ* formed catalyst. Only a catalytic amount of palladium and a small amount of sugar are required in the C–C bond forming reactions, which can be run under aqueous conditions. This *in situ* catalyst formation method compares favorably to other recyclable bio-derived palladium nanoparticles catalyst as it mitigates the requirement to perform and isolate the palladium nanoparticles.[29] We believe that our study provides the groundwork for a simple technology that opens up exciting opportunities for the development of a variety of catalytic systems in which the reducing potential of renewable sugars is harnessed for the generation, stabilisation and turnover of catalytically active metal nanoparticles – sugar-powered catalysis.

Experimental section

General procedures

Mizoroki–Heck. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol%) and glucose (4 mol%). Water/acetonitrile (3 : 1, 0.2 M) was added followed by triethylamine (1.2 equiv.), iodobenzene (1.0 equiv.) and methyl acrylate (1.2 equiv.). The vial was sealed and the resultant mixture was heated at 100 °C for 16 h. The mixture was cooled to rt and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol/EtOAc, 15 : 1) to afford the desired cross-coupled product.

Sonogashira. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol%) and glucose (4 mol%). Water/acetonitrile (3 : 1, 0.2 M) was added followed by triethylamine (1.2 equiv.), phenyl acetylene (1.0 equiv.) and iodobenzene (1.0 equiv.). The vial was sealed and the mixture was heated to 100 °C for 16 h. The mixture was cooled and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol/EtOAc, 9 : 1) to afford the desired cross-coupled product.

Suzuki–Miyaura. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol%) and glucose (10 mol%). Water/DMF (1 : 10, 0.2 M) was added followed by cesium carbonate (2.0 equiv.), iodobenzene (1.0 equiv.) and phenylboronic acid (1.5 equiv.). The vial was sealed and the mixture was heated to 100 °C for 16 h. The mixture was cooled and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol/EtOAc, 30 : 1) to afford the desired cross-coupled product.

Conflict of interest

The authors declare no competing financial interest.

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Synthesis J. E. Camp et al. Feature

Dehydrative Cross-Coupling of 1-Phenylethanol Catalysed by Palladium Nanoparticles Formed in situ Under Acidic Conditions

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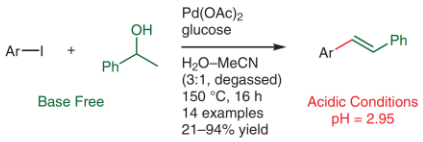

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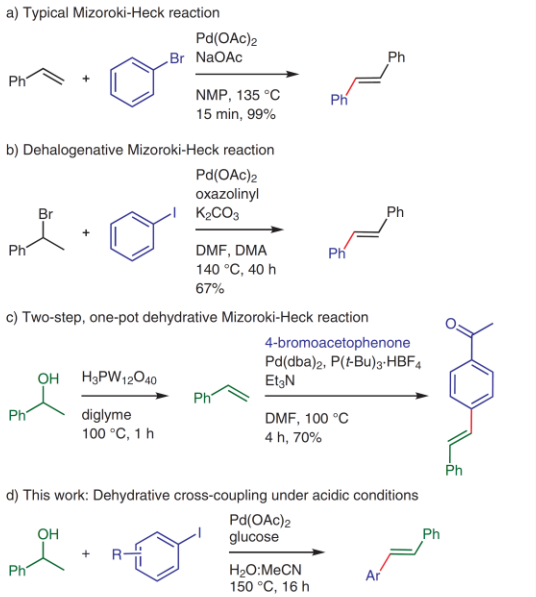
Abstract A dehydrative cross-coupling of 1-phenylethanol catalysed by sugar derived, in situ formed palladium(0) nanoparticles under acidic conditions is realised. The acidic conditions allow for use of alcohols as a feedstock in metal-mediated coupling reactions via their in situ dehydration and subsequent cross-coupling. Extensive analysis of the size and morphology of the palladium nanoparticles formed in situ showed that the zero-valent metal was surrounded by hydrophilic hydroxyl groups. EDX-TEM imaging studies using a prototype silicon drift detector provided insight into the problematic role of molecular oxygen in the system. This increased understanding of the catalyst deactivation allowed for the development of the cross-coupling methodology. A 250-12,000 fold increase in molar efficiency was observed when compared to related two-step protocols that use alternative feedstocks for the palladium-mediated synthesis of stilbenes. This work opens up a new research area in which the active catalyst is formed, stabilised and regenerated by a renewable sugar.

Key words glucose, nanoparticles, catalysis, dehydrative heck, palladium

Palladium-mediated cross-coupling reactions are some of the most powerful methods for the controlled formation of carbon–carbon bonds.[1] Of these, the Mizoroki–Heck reaction, is the method of choice for the formation of aryl–alkenyl bonds from the reaction of aryl halides and alkenes.[2] Since its initial development in the 1970s, the Mizoroki–Heck reaction has been optimised in terms of catalyst,[3] solvent[4] and reaction parameters[5] in order to address limitations of the methodology and expand its substrate scope (Scheme 1a).[6] Two factors that have remained relatively unexamined are the addition of an exogenous base[7] and the use of alkenes as the feedstock.[8] For related palladium-catalysed processes, the elimination of exogenous base has been shown to broaden their scope and increase overall sustainability.[9] In one of the rare instances of using an alternative feedstock in the Mizoroki–Heck reaction, Saiyed and Bedekar showed that benzylbromides, in the presence of excess base, could be used in a domino process to form stilbenes (Scheme 1b).[8a,10] Importantly, this work eliminated the need to preform and isolate the reactive alkene intermediate. In addition, Colbon et al. recently showed that aryl alcohols could be used in a two-step, one-pot process for the in situ generation and reaction of styrenes to form stilbenes (Scheme 1c).[11]



Scheme 1 Comparison of feedstocks in the Mizoroki–Heck reaction

Biographical Sketches

Dr. Jason E. Camp is currently a Senior Lecturer in the Department of Chemical Sciences at the University of Huddersfield, working on the use of green solvents in organic synthesis as well as on sugar-powered catalysis protocols. Dr. Camp received his Bachelor of Science degree in Biochemistry from the University of California, Davis in June 2000. During his undergraduate studies he conducted research as an UCEAP Undergraduate Research Fellow supervised by Prof. Geoffrey T. Crisp (University of Adelaide, Australia) and completed an honours project with the support of Prof. Alan L Balch (UC Davis). Following graduate studies with Prof. Robert Williams at Colorado State University he completed his PhD in 2007 under the supervision of Prof. Steven M. Weinreb at The Pennsylvania State University before undertaking postdoctoral research with Prof. Donald Craig (2008-2009) at Imperial College London. Following his postdoctoral work, he was appointed as a lecturer at both the University of Nottingham (2009-2013) and Queen Mary University of London (2013-2014).

Thomas Bousfield is currently finishing his PhD at The University of Huddersfield, which has focused on the development of sugar-powered catalysis methods as well as the use of Cyrene as a green solvent. During his PhD, Thomas was awarded COST Short Term Scientific Mission funding to work with Prof. Wim Thielemans at the University of KU Leuven. He obtained a MChem degree from Loughborough University, during which time he worked with Dr Marc Kimber on the synthesis of *N*-allenyl amides, ureas, carbamates and sulfonamides.

Dr. Jay Dunsford is currently a chemist at the National Nuclear Laboratory, UK. He completed his BSc and PhD at Cardiff University. His doctoral research with Prof. Kingsley Cavell focused on the synthesis of expanded ring NHC carbene complexes and their use in catalytic processes. He then undertook post-doctoral research with Dr Jason Camp at the University of Nottingham followed by Dr Michael Ingelson at the University of Manchester.

James Adams is currently finishing his BBSRC funded PhD at The University of Manchester, which resulted in two publications and a prestigious SCI scholarship (2015). He obtained a First Class MSci degree in chemistry from The University of Nottingham. During his undergraduate studies he participated in numerous research projects, which resulted in three publications. James was the recipient of six different undergraduate awards, including the GSK Medal for Outstanding Work in Medicinal Chemistry (2013) and the BP Achievement Award (2012).

Dr. Joshua Britton earned his MSci at Nottingham University, UK and his PhD jointly at Flinders University and The University of California, Irvine under Colin L. Raston and Gregory A. Weiss, respectively, in the area of continuous-flow synthesis and biocatalysis. He then undertook post-doctoral studies at MIT with Prof. Tim Jamison, which focused on the advancing of multi-step continuous-flow synthesis of active pharmaceutical ingredients. After post-doctoral studies, he co-founded Synthase, a biotechnology company focused on the continuous-flow synthesis of pharmaceuticals and high-value chemicals using biocatalysis and organic synthesis.

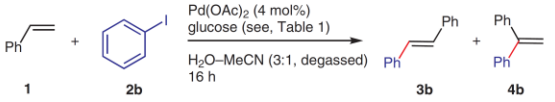
Dr. Michael Fay received his BSc degree from the University of Leicester in 1994 followed by an MSc from the University of Warwick in 1996 and a PhD from the University of Sheffield in 2001. He has been at the University of Nottingham since 2000, where he is currently a Senior Research Fellow responsible for the operation of transmission electron microscopes in the Nanoscale and Microscale Research Centre

Dr. Athanasios Angelis-Dimakis received his undergraduate diploma in Chemical Engineering from the National Technical University of Athens in Greece in 2005. He completed his PhD in Chemical Engineering in 2011 at the same university and then carried out an EU funded post-doctoral research on the life cycle assessment of innovative and eco-efficient technologies. In 2015, he joined the Centre for Environmental Policy at Imperial College London, to participate in a project, funded by Climate KIC and lead by Covestro AG, on enabling carbon dioxide reutilization between industries. In May 2016, he was appointed as a Lecturer in Chemical Engineering at the University of Huddersfield. His research interests include industrial symbiosis, urban mining, and assessment of the performance of novel green processes using various indicators; including the molar efficiency of chemical processes.

This was accomplished by first reacting the aryl alcohol with a catalytic amount of acid followed by the addition of excess base under Mizoroki–Heck reaction conditions. During the course of our study, Sinha and co-workers used an ionic liquid for the dehydrative-Heck cross-coupling of benzylic alcohols with aryl halides[12] to form potential anti-cancer compounds.[13] This methodology was further extended to include a double dehydrative-Heck process for the synthesis of lead compounds against Alzheimer's disease.[14] Aryl alcohol 1-phenylethanol (PE) is currently made on an industrial scale as the byproduct of the reaction of ethylbenzene hydroperoxide to form propylene oxide.[15] The majority of the alcohol is then dehydrated to form styrene.[16] Whilst styrene is a highly useful reagent, it is inherently unstable and precautions must be taken to prevent rapid exothermic polymerization.[17] Importantly, the International Agency for Research on Cancer recently classified styrene in Group 2A 'probably carcinogenic to humans'.[18] Therefore, there are key safety, economic and green drivers to develop cross-coupling methods that can eliminate the issues associated with bulk styrene. Previously, it was shown that the addition of reducing sugars, such as glucose, to palladium-mediated cross-coupling reactions leads to increased yields as well as facile catalyst recycling and increased metal remediation.[19–21] Herein, we report a dehydrative cross-coupling of 1-phenylethanol with aryl iodides catalysed by palladium nanoparticles formed in situ under base-free, acidic conditions in which the reducing sugars form, stabilise and regenerate the active catalyst (Scheme 1d).

The Mizoroki–Heck reaction between iodobenzene and styrene to form stilbene was used to assess the feasibility of the removal of base (Table 1). It was found that merely removing the base from the previously reported reaction conditions did not afford any of the desired products (Table 1, entries 1 vs. 2).[18] In order to eliminate the competing oxidation of palladium by molecular oxygen[22] (see below), the solvents were degassed with nitrogen.[23]

Table 1 Development of the Mizoroki–Heck Cross-Coupling under Acidic Conditions



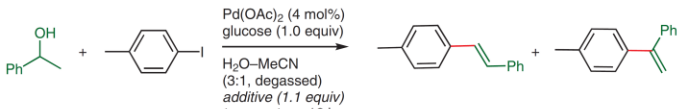
1 2b 3b 4b

Entry	Pd/sugar ratio	Temp. (°C)	Yield (%)[b]	Notes
1	1:2	100	97[a]	Ref.[18]
2	1:2	100	00	
3	1:2	150	05	
4	1:10	150	41	
5	1:25	150	97	pH 2.95
6	1:50	150	40	
7	1:100	150	33	

[a] Et_3N (1.5 equiv) was added
[b] **3b**/**4b** were isolated in a ratio of >90:10.

Heating a solution of styrene (**1**) and iodobenzene (**2b**) to 150 °C for 16 h, in the presence of $Pd(OAc)_2$ and glucose, gave alkenes **3b**/**4b** as a 94:6 mixture in excellent yield (Table 2, entry 5). The regiochemical distribution is in line with previously reported high-temperature Mizoroki–Heck cross-coupling reactions.[24,25] The final pH of this solution was determined to be 2.95. Additionally, it was found that the ratio of sugar to palladium had a substantial effect on the yield of the product, with a 1:25 ratio being optimal (Table 2, entries 3–7).

Table 2 Optimization of the Dehydrative Cross-Coupling Reaction



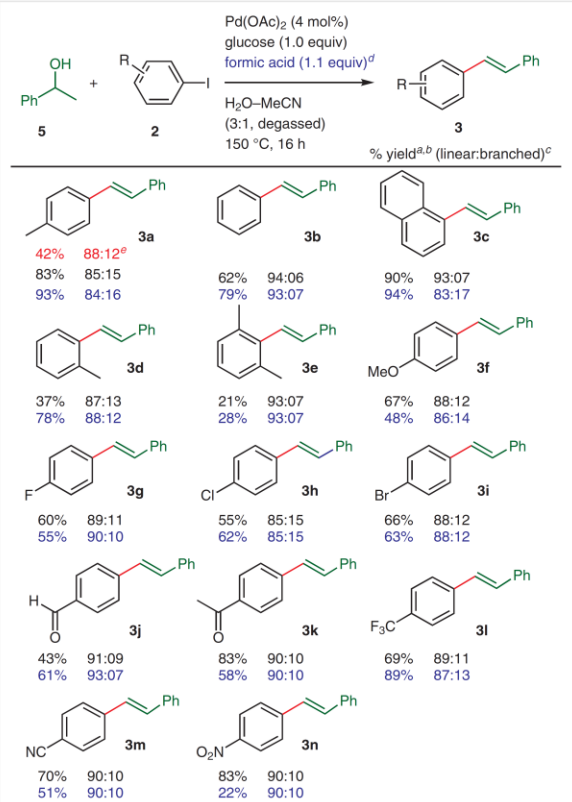
5 2a 3a 4a

Entry	Temp (°C)	Additive	Ratio **3**/**4**	Yield (%)
1	130	–	85:15	27
2	140	–	84:16	53
3	150	–	85:15	83
4	150	HCl	87:13	57[a]
5	150	H_2SO_4	87:13	16[a]
6	150	formic acid	83:17	22[b]
7	150	formic acid	84:16	93[a]

[a] 1.1 equiv of additive.
[b] 0.1 equiv formic acid used.

With a better understanding of the acidic cross-coupling reaction in hand, the dehydrative cross-coupling of 1-phenylethanol (**5**) with 4-iodotoluene (**2a**) was investigated (Table 2 and Table S3). It was found that the reaction gave the highest yield when 2 equivalents of alcohol **5** and 1 equivalent of glucose were used at 150 °C for 16 h (Table 2, entry 3). The product alkenes were isolated as a 85:15 mixture of linear **3a** to branched isomers **4a**. The equivalent of glucose is required to both reduce the palladium and stabilise the in situ formed nanoparticles (see below). To facilitate the dehydration of 1-phenylethanol (**5**), acidic additives were screened (Table 2, entries 5–8). The addition of strong acids led to a decreased yield of alkenes **3a**/**4a** (Table 2, entries 5 and 6). In contrast, the addition of 1.1 equivalents of formic acid resulted in an increase in yield of the desired product to 93%, but had no effect on the isomeric ratio. In contrast, the addition of 10 mol% of formic acid gave a deceased yield (Table 2, entry 7 vs. 6). Unfortunately, neither 4-bromotoluene nor 4-chlorotoluene afforded any of the desired cross-coupled products and only the starting materials were isolated. A comparison of the molar efficiency (Mol. E%)[26,27] of this protocol versus related two-step protocols that use alcohols or carboxylic acids for the palladium-mediated synthesis of stilbenes showed a 250–12,000 fold increase in efficiency.[23] Importantly, we have previously shown that palladium nanoparticles formed in situ can readily be recycled without significant loss of catalytic reactivity, which would mitigate the relatively high catalyst loading required in this protocol.[19]

To assess the generality of these conditions, the reaction of 1-phenylethanol (**5**) with a variety of aryl iodides **2** was investigated. As there was some ambiguity in the initial study with regard to the use of formic acid in the dehydrative cross-coupling process, the substrate scope investigation was conducted in both its presence and absence (Scheme 2). For comparison, base-free Mizoroki–Heck cross-coupling reactions were also conducted to gain further insights into the dehydrative process (Table S2). Whilst the products were isolated as a mixture of regioisomers **3**/**4**, the ratio of branched to linear was generally >85:15. The reactions of 4-iodotoluene and iodobenzene with 1-phenylethanol (**5**) in the presence of 4 mol% palladium acetate and 1 equivalent of glucose proceeded in good yields to form stilbenes **3a** and **3b**, respectively. For these substrates, a substantial increase in yield was observed upon the addition of formic acid. The products of the reaction of 1-iodonaphthalene, **3c**, were formed in good yield under the standard reaction conditions. The addition of formic acid to the reaction of 2-iodotoluene resulted in an increased yield of stilbene **3d**. In contrast, the addition of formic acid had little effect on the formation of the more sterically hindered adduct **3e**. Electron-rich substrate, 4-iodoanisole, was tolerated well under the reaction conditions. Iodobenzenes with electron-withdrawing groups afforded the desired cross-coupled adducts **3g**–**n** in good to excellent yields. In general, formic acid had either a beneficial or negligible effect on the dehydrative cross-coupling reaction, except in cases where additional reactions may have occurred.



Scheme 2 Substrate scope and role of formic acid in the dehydrative cross-coupling reaction. [a] Isolated yield. [b] Reaction conditions: aryliodide (1.0 equiv), 1-phenylethanol (2.0 equiv), $Pd(OAc)_2$ (4 mol %), glucose (1.0 equiv), H_2O/MeCN (3:1, degassed), 150 °C, 16 h. [c] Linear/branched selectivity was determined by ^1H NMR spectroscopy. [d] Reaction conditions: aryliodide (1.0 equiv), 1-phenylethanol (2.0 equiv), $Pd(OAc)_2$ (4 mol %), glucose (1.0 equiv), formic acid (1.1 equiv) H_2O/MeCN (3:1, degassed), 150 °C, 16 h. [e] Styrene (1.0 equiv) was used in place of 1-phenylethanol.

For example, the nitro group of (*E*)-4-nitro-*trans*-stilbene **3n** could have been reduced under the reaction conditions,[28] whereas the nitrile moiety of **3m** could have been hydrolysed in the presence of formic acid. Iodoarenes that contained basic nitrogen centres, such as 4-iodoaniline and 3-iodopyridine, did not give any of the desired cross-coupled products **3**/**4** under the optimised conditions. This result is in contrast to the related work by Liotta and coworkers,[7a] who found that basic-nitrogen-containing substrates were required for exogenous base-free Suzuki–Miyaura reactions and furthermore highlights the importance of the acidic conditions in our dehydrative cross-coupling protocol.

Transmission electron microscopy (TEM) analysis indicated that nanoparticles were formed when the palladium(II) pre-catalyst was subjected to the standard reaction conditions. The less dense amorphous matter at the periphery of the nanoparticles most likely contains the sugar residues (Figure 1a).[23] Analysis of the sugar-derived nanoparticles suspended in water at room temperature showed that the nanoparticles aggregate into larger clusters of around 100 nm (Figure 1b).[23] XPS analysis revealed that the palladium was present only in the zero oxidation state (Figure 1c).[23] A prototype EDX-TEM silicon drift detector was used to determine the amount of carbon and oxygen on the surface of the nanoparticles that were formed in both the absence and presence of oxygen (Figure 1d and Figure 1e, respectively).[23] It was found that there was a statistically significant decrease in the amount of carbon and oxygen on the surface of the nanoparticles that were formed in the presence of oxygen, 5%, versus those that were formed in the absence of oxygen, 37% (Figure 1f).[23] This difference in surface coverage is significant because if too little carbon and oxygen are present on the surface of the metal then the catalyst is unreactive (cf. Table 1). To our knowledge, this is the first time that a EDX-TEM silicon drift detector has been used to probe the difference in reactivity between in situ formed catalysts.

Our mechanistic hypothesis for the dehydrative cross-coupling reaction is predicated on the accepted mechanism for the classical Mizoroki–Heck process[2,29] as well as on the wealth of information on both the formation of metal nanoparticles[20,30] from reducing sugars and the synthesis of gluconic acid from glucose (Scheme 3).[31] Initially, the palladium(II) precatalyst is reduced by glucose to generate palladium(0) nanoparticles (Pd^0NP) with concomitant formation of gluconic acid.[19–21] The formation of gluconic acid was confirmed by analysis of a truncated reaction by mass spectrometry. After this initial oxidation, the gluconic acid can undergo a series of further palladium(II) mediated oxidations to eventually afford carbon dioxide and water, whilst simultaneously releasing additional reducing equivalents.[32] It is the sequential oxidation of the glucose in combination with the generation of one equivalent of hydrogen iodide

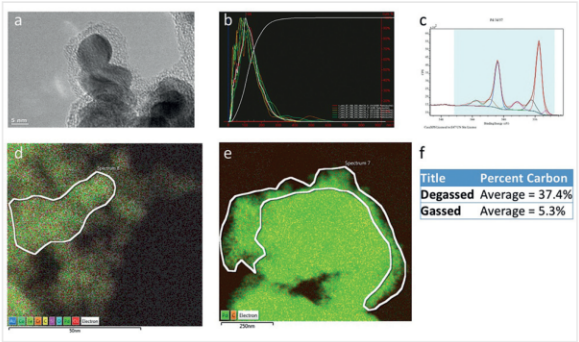
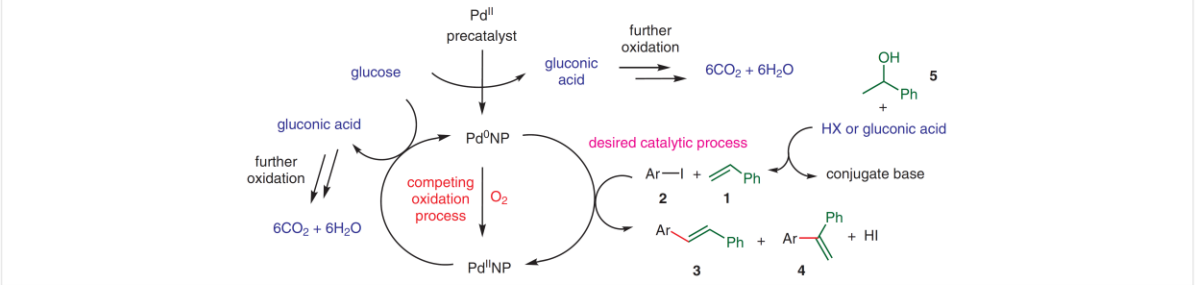


Figure 1 (a) TEM analysis (b) Nanosight analysis (c) XPS analysis (d) EDX-TEM analysis of palladium-nanoparticles formed in the absence of molecular oxygen (e) EDX-TEM analysis of palladium-nanoparticles formed in the presence of molecular oxygen (f) Percentage of carbon on the surface of palladium-nanoparticles formed in both the absence and presence of oxygen.

per catalytic cycle that makes the aqueous solution acidic, with a final pH 2.95. The acids generated in situ promote the dehydration of 1-phenylethanol (**5**) to styrene (**2**). Under the thermal conditions the in situ formed Pd^0NPs may be attacked by the arylating agent **1** to form a soluble anionic complex.[33] This species completes the desired Mizoroki–Heck reaction to form cross-coupled products **3**/**4**, with concomitant generation of a palladium(II) species. The active palladium(0) catalyst can be regenerated via reduction of the palladium(II) species by glucose or an oxidized derivative of glucose. A competing oxidation process involving molecular oxygen can short-circuit the catalytic cycle by converting the Pd^0NPs into a non-catalytically active palladium(II) species, which would then have to be reduced to re-enter the catalytic cycle. In aerated solvents we believe that the molecular oxygen outcompetes the iodobenzene for the Pd^0NP catalyst, leading to recovery of the starting material. It is believed that an increased temperature of 150 °C is needed to promote the requisite ring-opened conformation of glucose.[34]

In conclusion, a novel palladium-catalysed dehydrative cross-coupling protocol for the conversion of 1-phenylethanol into disubstituted alkenes was developed. The ability to



Scheme 3 Proposed mechanism for the dehydrative cross-coupling reaction

run the process under acidic conditions and use a secondary aryl alcohol as starting material significantly expands the scope and synthetic utility of the Mizoroki–Heck reaction. The high yields of cross-coupled products were achieved in an aqueous system, without the need to preform and isolate the catalyst, through the simple addition of a renewable reducing sugar. Mol.E% calculations showed that the direct dehydrative cross-coupling of 1-phenylethanol was significantly more efficient than previously reported two-step protocols. This work opens up exciting opportunities for the use of reducing sugars to power catalytic reactions, sugar-powered catalysis.

Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. Acetonitrile and water were degassed by bubbling nitrogen through the solvent at reflux for 1 h. Solvents used for column chromatography were of technical grade. For purification procedures using column chromatography, silica gel (60–120) mesh was used. Thin-layer chromatography was carried out using Merck Kieselgel silica gel 60 F254 plates (0.2 mm) and visualisation was achieved using UV light followed by dipping in a potassium permanganate solution and heating. All reactions were performed in a Biotage 5 mL microwave vial with Teflon coated cap.

^{1}H NMR and ^{13}C NMR were recorded with a Bruker AV400 (400 MHz) spectrometer, Bruker AV(III)400 (400 MHz) spectrometer, Bruker DPX400 (400 MHz) spectrometer or JOEL EX270 (270 MHz) spectrometer at ambient temperature using $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm), $(CD_3)_2CO$ (2.05 ppm) or CD_3OD (3.31 ppm) as the solvent. Chemical shift values are expressed as parts per million (ppm) and *J* values are in Hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet or combination thereof, br.s: broad singlet or m: multiplet. Solution IR spectra were recorded with a Perkin Elmer 1600 series FTIR-spectrophotometer. Mass spectra were determined with a Bruker MicroTOF mass spectrometer. pH measurements were recorded with a Philip Harris digital pH meter using a pH 7 standard buffer.

Transmission Electron Microscopy (TEM): TEM analysis was performed with a JEOL2100F field-emission gun microscope operating at 200 kV and equipped with a Gatan Orius camera. The Pd(0) nanoparticles were dispersed in water using an ultrasound bath and a suspension (3.5 µL) was deposited onto a holey carbon grid (Agar Scientific), which had previously been exposed to a low-temperature O_2/Ar plasma for five seconds in a Fischione Model 1020 Plasma Cleaner to make them hydrophilic. TEM image simulations was carried out using spherical aberration coefficient (*Cs*) = 1 mm.

EDX Transmission Electron Microscopy (EDX-TEM): EDX analysis was performed with a prototype Oxford Instruments Light Element 100 mm silicon drift detector with a JEOL 2100F operating at 200kV and the Aztec software. All spectra are acquired from regions not containing amorphous carbon supporting film. Cr, Fe and Co signals can originate from scatter from the polepiece and holder; Au signal can originate from scatter from the sample holder; Cu signal from the TEM supporting grid has been de-convolved from the quantification.

Nanoparticle Tracking Analysis (NTA): NTA was performed with a Nanosight LM10-HS instrument equipped with an electron multiplication charge coupled device camera mounted on an optical microscope system to track light scattered by particles that are present in a focused (80 µm) beam generated by a single-mode laser diode with a 60 mW blue laser illumination (405 nm). The solution containing the palladium(0) nanoparticles in a concentration of between 10^7 and 10^9 particles/mL was injected in a sample chamber of 0.5 mL size from which a volume of 120×80×20 microns was visualised under the microscope. The sample concentration was adjusted to ensure statistically significant number of particles under analysis. The Brownian motion of the nanoparticles was tracked at 30 frames/s. NTA 2.2 software was used to evaluate the mean square displacements of each visible particle (calibration 166 nm/pixel) and from the Strokes–Einstein equation the particle sizes were determined. All experiments were performed without filtering to ensure measurement of all particles.[35]

Dynamic Light Scattering (DLS): DLS experiments were performed with a Malvern Zetasizer ZS equipped with a He-Ne (633 nm, 5 mW) laser and an Avalanche photodiode detector at an angle of 173°. All DLS data were processed using Dispersion Technology Software (Malvern Instruments). All experiments were performed without filtering to ensure measurement of all particles.[36]

X-ray Photoelectron Spectroscopy (XPS): XPS spectra were recorded with a Kratos AXIS ULTRA with a monochromated Al Kα X-ray source (1486.6 eV) operated at 15mA emission current and 12kV anode potential – 180 W. Hybrid (magnet/electrostatic) optics (300×700 µm aperture), hemispherical analyser, multichannel plate and delay line detector (DLD) with a take-off angle of 90° and an acceptance angle of 30°. All scans were acquired under charge neutralisation conditions using a low-energy electron gun within the field of magnetic lens. Survey scans were taken with a pass energy of 80 eV and high-resolution scans with a pass energy of 20 eV. Data analysis was carried out using CASAXPS software with Kratos sensitivity factors to determine atomic % values from the peak areas.

Scanning Ion Occlusion Sensing (SIOS): SIOS measurements were carried out with a qNano instrument (Izon Science Ltd., Christchurch, NZ). A standard electrolyte buffer (SEB) of 0.1 M KCl, 10 mM Tris buffer, 0.01% Triton X-100, and 3 mM EDTA, pH 8.0, filtered through a 0.22 µm filter was used in all experiments. The membrane was wetted prior to sampling by applying a voltage (typically 0.3 V) and manually stretching the pore open (typically with a jaw stretch of 5 mm). Once a stable background current achieved, the fluid in the top half of the cell was replaced with a solution of the palladium(0) nanoparticles in the SEB (30–70 µL). The magnitude and duration of changes in the current signal were collected at a sampling frequency of 50 kHz. The instrument was calibrated using a solution of polystyrene particles (3000 series, 100 nm) in SEB.[37]

(*E*)-1-Methylstilbene[38] (3a) and 1-Methyl-4-(1-phenylvinyl)benzene[39] (4a)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and 4-iodotoluene (170 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methylstilbene (**3a**) and 1-Methyl-4-(1-phenylvinyl)benzene (**4a**, 80 mg, ratio 88:12, 42% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the

mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methylstilbene (**3a**) and 1-methyl-4-(1-phenylvinyl)benzene (**4a**, 63 mg, ratio 85:15, 83% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methylstilbene (**3a**) and 1-methyl-4-(1-phenylvinyl)benzene (**4a**, 71 mg, ratio 84:16, 93% combined yield) as a white solid.

(*E*)-1-Methylstilbene (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.4 Hz, 2 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.26 (m, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 7.13 (d, *J* = 16.4 Hz, 1 H), 7.08 (d, *J* = 16.5 Hz, 1 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5 (2 × C), 134.6, 129.4 (2 × C), 128.7 (2 × C), 128.6, 127.7, 127.4, 126.5 (2 × C), 126.4 (2 × C), 21.3.

IR ($CHCl_3$): 3020, 2915, 1593, 1508, 1493, 1448, 969, 803, 706 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{15}H_{14}]^+$: 194.1090; found: 194.1087.

1-Methyl-4-(1-phenylvinyl)benzene (4a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 5 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 5.44 (d, *J* = 1.1 Hz, 2 H), 5.41 (d, *J* = 1.2 Hz, 2 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 141.7, 138.6, 137.5, 128.9 (2 × C), 128.3 (2 × C), 128.2 (2 × C), 128.1 (2 × C), 127.6, 113.7, 21.2.

(*E*)-Stilbene[40] (3b), 1,1-Diphenylethene[41] (4b)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added iodobenzene (87 µL, 0.78 mmol) and styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-stilbene (**3b**) and 1,1-diphenylethene (**4b**, 136 mg, ratio 94:6, 97% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and iodobenzene (44 µL, 0.39 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-stilbene (**3b**) and 1,1-diphenylethene (**4b**, 44 mg, ratio 94:6, 62% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), iodobenzene (44 µL, 0.39 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-stilbene (**3b**) and 1,1-diphenylethene (**4b**, 55 mg, ratio 93:7, 79% combined yield) as a white solid.

(*E*)-Stilbene (3b) and 1,1-Diphenylethene (4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 4 H), 7.45–7.39 (m, 5.57 H), 7.35–7.31 (m, 2 H), 7.18 (s, 2 H), 5.54 (s, 0.26 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (stillbene) = 137.4, 128.8, 127.7, 126.6.

IR ($CHCl_3$): 3021, 2915, 1494, 1451, 983, 808, 688 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $C_{14}H_{12}$: 180.0934; found: 180.0932.

(*E*)-1-Styrylnaphthalene[42] (3c) and 1-(1-Phenylethenyl)naphthalene[43] (4c)

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and 1-iodonaphthalene (57 µL, 0.78 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-styrylnaphthalene (**3c**) and 1-(1-phenylethenyl)naphthalene (**4c**, 45 mg, ratio 93:17, 90% combined yield) as a colourless oil.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), 1-iodonaphthalene (57 µL, 0.78 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-styrylnaphthalene (**3c**) and 1-(1-phenylethenyl)naphthalene (**4c**, 85 mg, ratio 83:17, 94% combined yield) as a colourless oil.

(*E*)-1-Styrylnaphthalene (3c)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.3 Hz, 1 H), 7.93–7.88 (m, 2 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 7.1 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 2 H), 7.58–7.50 (m, 3 H), 7.43 (t, *J* = 7.7 Hz, 3 H), 7.34–7.31 (m, 1 H), 7.18 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 135.1, 133.8, 131.8, 131.4, 128.8 (2 × C), 128.7, 128.1, 127.8, 126.7 (2 × C), 126.1, 125.9, 125.8, 125.7, 123.8, 123.5.

IR ($CHCl_3$): 3056, 2928, 2852, 1493, 1263, 959, 774, 734, 692 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{18}H_{14}]^+$: 230.1090; found: 230.1089.

1-(1-Phenylethenyl)naphthalene (4c)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.84 (m 2 H), 7.77–7.75 (m, 1 H), 7.51–7.48 (m, 1 H), 7.44–7.41 (m, 2 H), 7.34–7.30 (m, 3 H), 7.27–7.24 (m, 3 H), 5.98 (d, *J* = 1.4 Hz, 2 H), 5.39 (d, *J* = 1.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 141.1, 139.8, 133.7, 131.9, 128.4 (2 × C), 128.2, 128.0, 127.7, 127.2, 126.6 (2 × C), 126.4, 125.9, 125.7, 125.4, 116.3.

(*E*)-2-Methylstilbene[44] (3d) and 1-Methyl-2-(1-phenylvinyl)benzene[45] (4d)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 2-iodotoluene (99 µL, 0.78 mmol) and styrene (99 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-2-methylstilbene (**3d**) and 1-methyl-2-(1-phenylvinyl)benzene (**4d**, 71 mg, ratio 88:12, 47% combined yield) as a colourless oil.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and 2-iodotoluene (50 µL, 0.39 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-2-methylstilbene (**3d**) and 1-methyl-2-(1-phenylvinyl)benzene (**4d**, 28 mg, ratio 87:13, 37% combined yield) as a colourless oil.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), 2-iodotoluene (50 µL, 0.39 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-2-methylstilbene **3d** and 1-methyl-2-(1-phenylvinyl)benzene **4d** (59 mg, ratio 88:12, 78% combined yield) as a colourless oil.

(*E*)-2-Methylstilbene (3d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.1 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 3 H), 7.37–7.23 (m, 5 H), 7.06 (d, *J* = 16.2 Hz, 1 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 136.5, 135.9, 130.5, 130.1, 128.8 (2 × C), 127.7, 127.6, 126.64 (2 × C), 126.61, 126.3, 125.4, 20.0.

IR ($CHCl_3$): 3023, 2923, 1540, 1494, 959, 756, 711 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{15}H_{14}]^+$: 194.1090; found: 194.1088.

1-Methyl-2-(1-phenylvinyl)benzene (4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 9 H), 5.77 (d, *J* = 1.3 Hz, 1 H), 5.22 (d, *J* = 1.3 Hz, 1 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 136.5, 130.5, 130.1, 128.8 (2 × C), 127.7, 127.6, 126.64 (2 × C), 126.61, 126.3, 125.4, 20.0.

(*E*)-2,6-Dimethylstilbene[46] (3e) and 1,3-Dimethyl-2-(1-phenylvinyl)benzene[46] (4e)

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and 2-iodo-1,3-dimethylbenzene (57 µL, 0.39 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-2,6-dimethylstilbene (**3e**) and 1,3-dimethyl-2-(1-phenylvinyl)benzene (**4e**, 17 mg, ratio 93:7, 21% combined yield) as a colourless oil.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), 2-iodo-1,3-dimethylbenzene (57 µL, 0.39 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-2,6-dimethylstilbene (**3e**) and 1,3-dimethyl-2-(1-phenylvinyl)benzene (**4e**, 23 mg, ratio 93:7, 28% combined yield) as a colourless oil.

(*E*)-2,6-Dimethylstilbene (3e)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.9 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 1 H), 7.17–7.11 (m, 4 H), 6.64 (d, *J* = 16.8 Hz, 1 H), 2.40 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 137.0, 136.3 (2 × C), 134.0, 128.7 (2 × C), 127.7 (2 × C), 127.6, 127.0, 126.8, 126.3 (2 × C), 21.1 (2 × C).

IR ($CHCl_3$): 3023, 2922, 2853, 1595, 1464, 968, 766, 690 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{16}H_{16}]^+$: 208.1247; found: 208.1248.

(*E*)-4-Methoxystilbene[47] (3f) and 1-Methoxy-4-(1-phenylvinyl)benzene[47] (4f)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and 4-iodoanisole (183 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methoxystilbene (**3f**) and 1-methoxy-4-(1-phenylvinyl)benzene (**4f**, 152 mg, ratio 84:16, 93% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodoanisole (91 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by

flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methoxystilbene (**3f**) and 1-methoxy-4-(1-phenylvinyl)benzene (**4f**, 64 mg, ratio 88:12, 67% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodoanisole (91 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-methoxystilbene (**3f**) and 1-methoxy-4-(1-phenylvinyl)benzene (**4f**, 43 mg, ratio 86:14, 48% combined yield) as a white solid.

(*E*)-1-Methoxystilbene (3f)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 3 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.28–7.22 (m, 2 H), 7.10 (d, *J* = 16.3 Hz, 1 H), 7.00 (d, *J* = 16.3 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 137.7, 130.2, 128.7 (2 × C), 128.2, 127.7 (2 × C), 127.2, 126.6, 126.3 (2 × C), 114.1 (2 × C), 55.3.

IR ($CHCl_3$): 3022, 3002, 2933, 2836, 1600, 1508, 1266, 1028, 811, 686 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{15}H_{14}O]^+$: 210.1039; found: 210.1039.

(*E*)-4-Fluorostilbene[44] (3g) and 1-Fluoro-4-(phenylvinyl)benzene[43] (4g)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 4-fluoroiodobenzene (90 µL, 0.78 mmol) and styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-fluorostilbene (**3g**) and 1-fluoro-4-(1-phenylvinyl)benzene (**4g**, 83 mg, ratio 94:6, 54% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and 4-fluoroiodobenzene (45 µL, 0.39 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-fluorostilbene (**3g**) and 1-fluoro-4-(1-phenylvinyl)benzene (**4g**, 60 mg, ratio 89:11, 60% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), 4-fluoroiodobenzene (45 µL, 0.39 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-fluoro-*trans*-stilbene (**3g**) and 1-fluoro-4-(1-phenylvinyl)benzene (**4g**, 42 mg, ratio 90:10, 55% combined yield) as a white solid.

(*E*)-4-Fluorostilbene (3g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 4 H), 7.39 (t, *J* = 7.6 Hz, 2 H), 7.29 (t, *J* = 7.30 Hz, 1 H), 7.12–7.02 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (d, *J* = 246.3 Hz), 137.2, 133.5 (d, *J* = 3.4 Hz), 128.7, 128.5 (d, *J* = 2.4 Hz), 128.0 (d, *J* = 8.0 Hz), 127.7, 127.5, 126.5, 115.6 (d, *J* = 21.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.2 (s, 1 F).

IR ($CHCl_3$): 3022, 2923, 2851, 1592, 1504, 1226, 999, 822, 751 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $C_{14}H_{12}F$: 198.0839; found: 198.0835.

(*E*)-1-Chloro-4-styrylbenzene[40] (3h), 1-Chloro-4-(1-phenylvinyl)benzene[41] (4h)

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-chloroiodotoluene (93 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-chloro-4-styrylbenzene (**3h**) and 1-chloro-4-(1-phenylvinyl)benzene (**4h**, 46 mg, ratio 85:15, 55% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-chloroiodotoluene (93 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-chloro-4-styrylbenzene (**3h**) and 1-chloro-4-(1-phenylvinyl)benzene (**4h**, 52 mg, ratio 85:15, 62% combined yield) as a white solid.

(*E*)-1-Chloro-4-styrylbenzene (3h)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.4 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.40–7.27 (m, 5 H), 7.12–7.03 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 135.9, 133.2, 129.3, 128.9 (2 × C), 128.8 (2 × C), 127.9, 127.7 (2 × C), 127.4, 126.6 (2 × C).

IR ($CHCl_3$): 3055, 2987, 2928, 1558, 1540, 1264, 730, 701, 669 cm^{-1}.

GCMS (EI): *m*/*z* calcd. for $[C_{14}H_{11}Cl]^+$: 214.1; found: 214.0.

1-Chloro-4-(1-phenylvinyl)benzene (4h)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m 10 H), 5.47 (s, 1 H), 5.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 141.02, 140.0, 133.6, 129.6 (2 × C), 128.4 (2 × C), 128.3 (2 × C), 128.2 (2 × C), 237.9, 114.7.

(*E*)-4-Bromostilbene[48] (3i) and 1-(4-Bromophenyl)-1-phenylethene[49] (4i)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodobromobenzene (221 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-bromo-stilbene (**3i**) and 1-bromo-4-(1-phenylvinyl)benzene (**4i**, 176 mg, ratio 86:14, 87% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodobromobenzene (110 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-bromostilbene (**3i**) and 1-bromo-4-(1-phenylvinyl)benzene (**4i**, 67 mg, ratio 88:12, 66% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodobromobenzene (110 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-bromostilbene (**3i**) and 1-bromo-4-(1-phenylvinyl)benzene (**4i**, 64 mg, ratio 88:12, 63% combined yield) as a white solid.

(*E*)-4-Bromostilbene (3i)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.46 (m, 4 H), 7.40–7.34 (m, 4 H), 7.30–7.25 (m, 1 H), 7.07 (dd, *J* = 16.4 Hz, *J* = 28.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 136.3, 131.8, 129.4, 128.8, 128.0, 127.9, 127.4, 126.6, 121.3.

IR ($CHCl_3$): 3025, 2921, 2852, 1485, 1072, 964, 840, 688 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{14}H_{11}Br]^+$: 258.0039; found: 258.0029.

(*E*)-4-Styrylbenzaldehyde[50] (3j) and 4-(1-Phenylvinyl)benzaldehyde[43] (4j)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and 4-iodobenzaldehyde (170 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-styrylbenzaldehyde (**3j**) and 4-(1-phenylvinyl)benzaldehyde (**4j**, 63 mg, ratio 90:10, 39% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodobenzaldehyde (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-styrylbenzaldehyde (**3j**) and 4-(1-phenylvinyl)benzaldehyde (**4j**, 35 mg, ratio 91:9, 43% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodobenzaldehyde (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-styrylbenzaldehyde (**3j**) and 4-(1-phenylvinyl)benzaldehyde (**4j**, 50 mg, ratio 93:7, 61% combined yield) as a white solid.

(*E*)-4-Styrylbenzaldehyde (3j)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.00 (s, 1 H), 7.87 (d, *J* = 8.2 Hz, 2 H), 7.66 (d, *J* = 8.1 Hz, 2 H), 7.55 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.34–7.25 (m, 2 H), 7.15 (t, *J* = 16.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6, 143.4, 136.6, 135.3, 132.2, 130.3, 128.9, 128.5, 127.3, 126.9 (2 × C).

IR ($CHCl_3$): 3028, 2820, 2729, 1692, 1590, 1209, 1166, 968, 816, 759, 688 cm^{-1}.

HRMS (Dual ESI): *m*/*z* calcd. for $[C_{15}H_{13}O]^+$: 209.0961; found: 209.0961.

(*E*)-1-(4-Styrylphenyl)ethan-1-one[48] (3k) and 1-(4-(1-Phenylvinyl)phenyl)ethan-1-one[51] (4k)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) and 4-iodotoluene (170 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-(4-styrylphenyl)ethan-1-one (**3k**) and 1-(4-(1-phenylvinyl)phenyl)ethan-1-one (**4k**, 78 mg, ratio 93:7, 45% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give

(*E*)-1-(4-styrylphenyl)ethan-1-one (**3k**) and 1-(4-(1-phenylvinyl)phenyl)ethan-1-one (**4k**, 50 mg, ratio 90:10, 83% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-(4-styrylphenyl)ethan-1-one (**3k**) and 1-(4-(1-phenylvinyl)phenyl)ethan-1-one (**4k**, 50 mg, ratio 90:10, 58% combined yield) as a white solid.

(*E*)-1-(4-Styrylphenyl)ethan-1-one (3k)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, 2 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 7.54 (d, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.33–7.29 (m, 1 H), 7.26–7.22 (m, 1 H), 7.14 (d, *J* = 16.4 Hz, 1 H), 2.61 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 136.7, 136.0, 131.5, 128.9 (2 × C), 128.8 (2 × C), 128.3, 127.5, 126.8 (2 × C), 126.5 (2 × C), 26.6.

IR ($CHCl_3$): 3010, 2922, 2853, 1673, 1633, 1410, 1356, 1260, 999, 843, 753, 688, 610 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{16}H_{14}O]^+$: 222.1039; found: 222.1039.

(*E*)-4-Trifluoromethylstilbene[40] (3l) and 1-(1-Phenylvinyl)-4-trifluoromethylbenzene[41] (4l)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 4-iodobenzotrifluoride (114 µL, 0.78 mmol) and styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-trifluoromethylstilbene (**3l**) and 1-(1-phenylvinyl)-4-(trifluoromethyl)benzene (**4l**, 172 mg, ratio 87:13, 89% combined yield) as a white solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and 4-iodobenzotrifluoride (57 µL, 0.78 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-trifluoromethylstilbene (**3l**) and 1-(1-phenylvinyl)-4-(trifluoromethyl)benzene (**4l**, 67 mg, ratio 89:11, 69% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) and glucose (70 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol), 4-iodobenzotrifluoride (57 µL, 0.78 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-trifluoromethylstilbene (**3l**) and 1-(1-phenylvinyl)-4-(trifluoromethyl)benzene (**4l**, 86 mg, ratio 87:13, 89% combined yield) as a white solid.

(*E*)-4-Trifluoromethylstilbene (3l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.59 (m, 4 H), 7.55 (d, *J* = 7.04 Hz, 2 H), 7.41 (t, *J* = 7.48 Hz, 2 H), 7.33 (t, *J* = 7.28 Hz, 1 H), 7.21 (d, *J* = 16.4 Hz, 1 H), 7.13 (d, *J* = 16.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 136.6, 131.2, 129.7, 129.4, 129.1, 128.8, 127.1, 126.8, 126.6, 125.7 (q, 2 × C), 122.9, 123.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.4 (s, 3 F).

IR ($CHCl_3$): 3028, 2928, 2854, 1612, 1450, 1321, 1164, 1105, 1066, 843, 756, 692 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{15}H_{11}F_3]^+$: 248.0807; found: 248.0809.

1-(1-Phenylvinyl)-4-(trifluoromethyl)benzene (4l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.2 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 2 H), 7.39–7.32 (m, 5 H), 5.58 (s, 1 H), 5.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 140.6, 128.8, 128.6 (2 × C), 128.4 (2 × C), 128.2 (2 × C), 128.1, 126.8, 126.6, 125.2 (q, 2 × C), 115.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.5 (s, 3 F).

(*E*)-4-Styrylbenzonitrile[40] (3m) and 4-(1-Phenylvinyl)benzonitrile[45] (4m)

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-styrylbenzonitrile (**3m**) and 4-(1-phenylvinyl)benzonitrile (**4m**, 56 mg, ratio 90:10, 70% combined yield) as a white solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodotoluene (85 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-4-styrylbenzonitrile (**3m**) and 4-(1-phenylvinyl)benzonitrile (**4m**, 41 mg, ratio 90:10, 51% combined yield) as a white solid.

(*E*)-4-Styrylbenzonitrile (3m)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–55 (m, 6 H), 7.44 (t, *J* = 7.4 Hz, 2 H), 7.37–7.33 (m, 1 H), 7.24 (d, *J* = 16.4 Hz, 1 H), 7.11 (d, *J* = 16.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 136.3, 132.5 (2 × C), 132.4, 128.9 (2 × C), 128.7, 126.93 (2 × C), 126.88 (2 × C), 126.7, 119.1, 110.6.

IR ($CHCl_3$): 3023, 2920, 2854, 2223, 1600, 1503, 972, 823, 756, 689 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{15}H_{11}N]^+$: 205.0886; found: 205.0890.

(*E*)-4-Nitro-stilbene[52] (3n) and 1-Nitro-4-(1-phenylvinyl)benzene[45] (4n)

Method 1: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodonitrobenzene (194 mg, 0.78 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added styrene (87 µL, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-nitrostilbene (**3n**) and 1-nitro-4-(1-phenylvinyl)benzene (**4n**, 159 mg, ratio 92:8, 90% combined yield) as a yellow solid.

Method 2: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodonitrobenzene (97 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. was added 1-phenylethanol (97 mg, 0.79 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-nitrostilbene (**3n**) and 1-nitro-4-(1-phenylvinyl)benzene (**4n**, 62 mg, ratio 90:10, 83% combined yield) as a yellow solid.

Method 3: To a stirred solution of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), glucose (70 mg, 0.39 mmol) and 4-iodonitrobenzene (97 mg, 0.39 mmol) in degassed acetonitrile / degassed water (1:3, 4 mL) at r.t. were added 1-phenylethanol (97 mg, 0.79 mmol) and formic acid (33 µL, 0.87 mmol). The vial was sealed and the mixture was heated at 150 °C for 16 h. The mixture was cooled to r.t. and water (10 mL) and dichloromethane (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 5%) to give (*E*)-1-nitrostilbene (**3n**) and 1-nitro-4-(1-phenylvinyl)benzene (**4n**, 19 mg, ratio 90:10, 22% combined yield) as a yellow solid.

(*E*)-1-Nitrostilbene (3n)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.8 Hz, 2 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 2 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.36–7.32 (m, 1 H), 7.28 (d, *J* = 16.3 Hz, 2 H), 7.15 (d, *J* = 16.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 143.9, 136.2, 133.3, 128.9 (2 × C), 128.8, 127.0 (2 × C), 126.9 (2 × C), 126.3, 124.2 (2 × C).

IR ($CHCl_3$): 3089, 2920, 1593, 1569, 1505, 1336, 1105, 849, 692 cm^{-1}.

HRMS (APPI): *m*/*z* calcd. for $[C_{14}H_{11}NO_2]^+$: 225.0784; found: 225.0778.

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Supporting Information

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Synthesis of ureas in the bio-alternative solvent Cyrene†

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Cyrene as a bio-alternative solvent: a highly efficient, waste minimizing protocol for the synthesis of ureas from isocyanates and secondary amines in the bio-available solvent Cyrene is reported. This method eliminated the use of toxic solvents, such as DMF, and established a simple work-up procedure for removal of the Cyrene, which led to a 28-fold increase in molar efficiency *versus* industrial standard protocols.

Introduction

Ureas are an important class of compound that have been exploited in a number of fields, such as pharmaceuticals, agrochemicals and materials science. In the pharmaceutical sector the utility of ureas can be observed in the variety of biological activities that they exhibit.[1] For example, ureas are found in anti-malaria compounds,[2] hepatitis C protease inhibitors,[3] HIV-protease inhibitors,[4] anti-obesity therapeutics,[5] anticancer agents,[6] antibiotics,[7] anticonvulsants[8] and antimicrobials[9] (Fig. 1). Furthermore, ureas themselves are increasingly exploited as catalysts,[10] ligands,[11] reagents,[12] solvents[13] and substrates[14] for a multitude of synthetic transformations.

Due to their importance a variety of methods have been developed for the synthesis of ureas,[15] with a recent emphasis on developing greener, more sustainable processes.[16,17] One of the most common ways to synthesize ureas is from the reaction of isocyanates with amines. For example, a series of phenyl isocyanates **1** was reacted with *N*-aryl-*NH*-piperazine **2** to give a series of ureas **3** that was screened for inhibition of platelet-derived growth factor receptor phosphorylation (Fig. 2, eqn (1)).[18] In this typical example using DMF as solvent, a variety of ureas **3** were formed in good yields, though extended reaction times and extensive work-up/purification procedures needed to be employed. Whilst this reaction can be carried out in a variety of different solvents/reaction media, nearly 80% of the reactions in the literature use DMF or halogenated solvents.[19] There are strong environmental, safety and regulatory pressures to minimize the use of solvents that are designated as being high risk. Replacement for dipolar aprotic solvents,[20] such as problematic solvents DMF, NMP and DMAc, was recently highlighted as a priority within the pharmaceutical industry.[21] In turn, companies and academic researchers have put significant amounts of time, effort and expense into the development of more sustainable chemical processes that do not rely on high risk solvents.[22,23] A possible alternative to DMF and other polar aprotic solvents is Cyrene (**7**, dihydrolevoglucosenone, Fig. 2).[24] Cyrene is synthesised in a two-step process from waste cellulose.[25,26] Importantly, it has similar physical properties to other dipolar aprotic solvents, including DMF. The viability of Cyrene as a DMF replacement was recently demonstrated by Watson *et al.* in palladium mediated cross-coupling reactions.[27] In addition, Cyrene[28,29] was shown to be an effective solvent in S_N2 and S_NAr reactions[24] as well as for the synthesis of MOFs.[30] Interestingly, the use of Cyrene as a solvent for the addition of a nucleophile to a carbonyl has not been investigated despite the fact that these processes are known to be promoted by polar aprotic solvents.[31] Herein, we present the development and scope of the use of the bio-available solvent Cyrene (**7**) for the synthesis of ureas **6** from the reaction of isocyanates **4** with amines **5** (Fig. 2, eqn (2)). An emphasis was placed on minimizing the amount of waste produced during the work-up, isolation and purification of the product.

Results and discussion

To begin the investigation, the reaction of phenylisocyanate (**4a**) and pyrrolidine (**5a**) in Cyrene (**7**) was investigated (Scheme 1). Whilst the optimization of the reaction was straightforward, the isolation of the pure urea was more problematic. In order to minimize by-products, the reagents were added together at 0 °C and allowed to warm to rt for 1 h.

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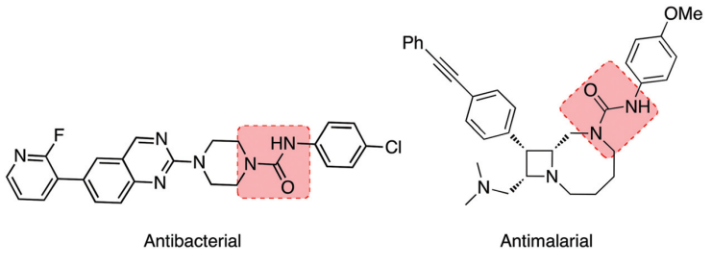


Fig. 1 Biologically active ureas.

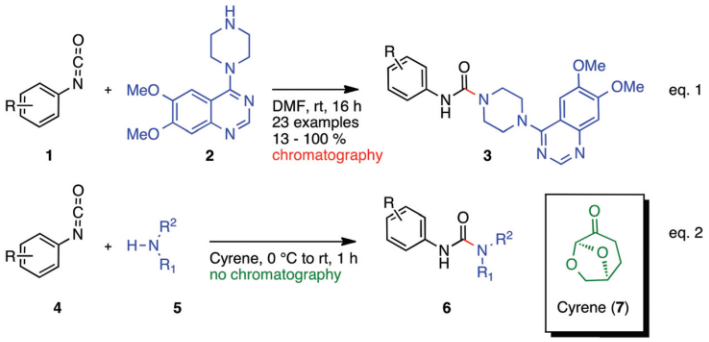
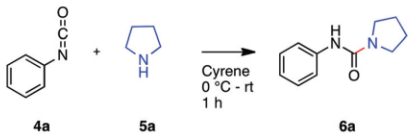


Fig. 2 Reaction of isocyanates and amines in DMF and Cyrene.



Scheme 1 Optimization of the synthesis of urea **6a** in Cyrene.

This protocol allowed for the development of a general procedure for both electron rich and electron deficient isocyanates (*vide infra*). Initially, the product was isolated by the addition of water and dichloromethane, liquid–liquid extraction, washing with water/brine, drying over magnesium sulphate and purified by column chromatography (hexanes/ethyl acetate). This extended procedure resulted in a high yield of the desired urea **6a**, 90%, but also led to a significant amount of waste in the form of organic solvents and contaminated aqueous waste. In addition, the Cyrene was found to co-elute with the product and additional column purification was sometimes required in order to get pure compounds. In order to minimize the use of organic solvents as well as the amount of waste produced in the isolation of the product, it was decided to examine alternative work-up procedures. The use of various acid/base work-up procedures all led to decomposition of both the urea and Cyrene. Finally, it was found that the addition of water to the Cyrene solution at the conclusion of the reaction resulted in precipitation of the desired urea. Filtration and washing with water gave analytically pure *N*-phenylpyrrolidine-1-carboxamide (**6a**) in a synthetically useful yield of 80% (*cf.* Scheme 2).

In order to access the efficiency of the two protocols, molar efficiency calculations were undertaken using the method of Watson *et al.*[32] in which:

$$\text{molar efficiency(Mol. E\%)} = [\text{moles product/moles starting material} + \text{additives} + \text{catalysts} + \text{solvents}] \times 100$$

The Mol. E% was calculated for each step of the process and the total molar efficiency ($\text{molE}_{\text{total}}$) is the multiplication of these values. Comparison of the molar efficiency of our original process, which was based on the industrial standard protocol, *versus* the optimized water washing method showed that use of the latter gave a 28-fold increase in molar efficiency (Fig. 3).[33] Similar water addition work-up procedures have been employed to help minimize the *E*-factors.[34] This simple procedure also removed all of the Cyrene from the product, which has been shown to be one of the key challenges of using this solvent.[27] Importantly, this method allowed for elimination of all non-bioderived solvents from the process with only Cyrene and water required.

With the optimized reaction and isolation procedure in hand the scope of the reaction of amines with phenyl isocyanates (**4a**) in Cyrene was examined (Scheme 2). A variety of secondary cyclic **5a–d** and acyclic amines **5e–n** were subjected

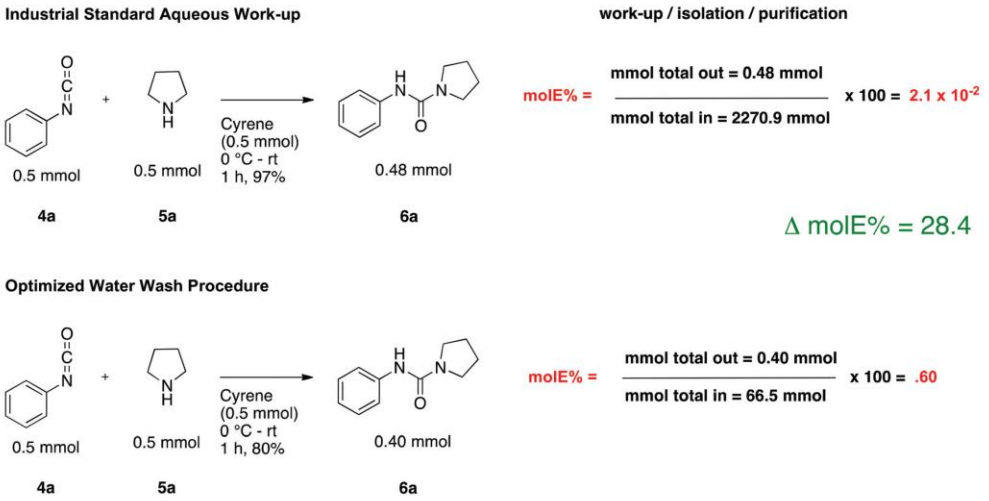
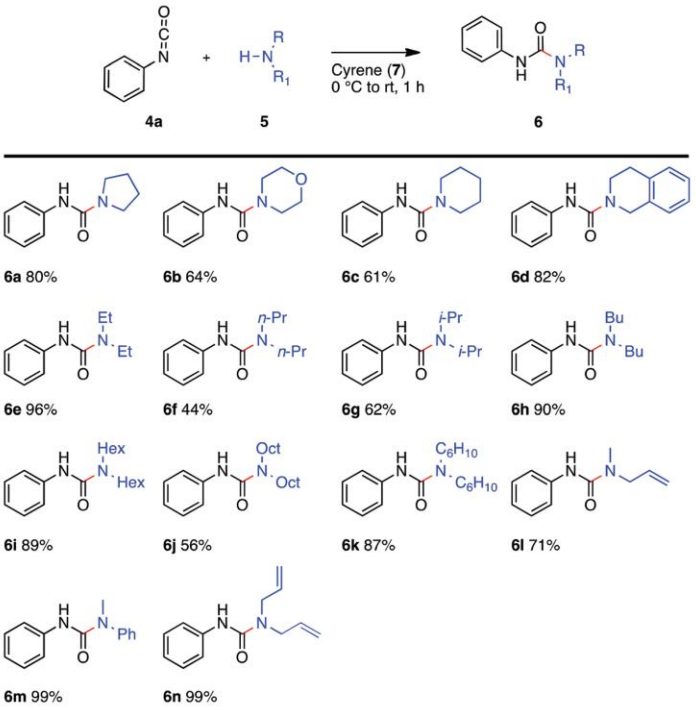


Fig. 3 Comparison of molar efficiency for the synthesis of ureas in Cyrene.



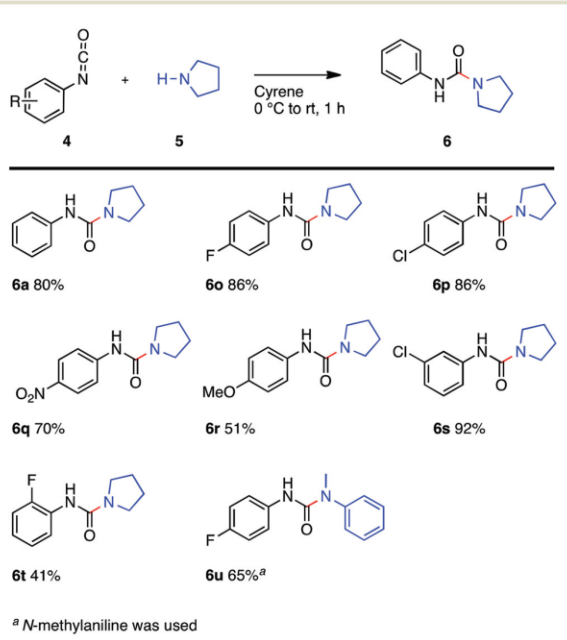
Scheme 2 Synthesis of ureas **6** from phenyl isocyanate **4a** and amines **5** in Cyrene **7**.

to the reaction conditions.[35] It was found that in addition to pyrrolidine (**5a**), cyclic amines piperidine (**5b**), morpholine (**5c**) and 1,2,3,4-tetrahydroisoquinoline (**5d**) gave the desired ureas, **6a–d** in good yield. *N*,*N*-Dialkyl amines **5e–j** with chain length between 2–8 carbons afforded ureas **6e–j** in good yields. In addition, *N*,*N*-dicyclohexylamine (**5k**) gave urea **6k** in 87% yield. Next, unsymmetrical secondary amines were subjected to the reaction conditions. Both *N*-methyl-*N*-allyl-amine (**5l**) and *N*-methylaniline (**5m**) gave the desired ureas, **6l** and **6m**, in good yields when subjected to the standard

conditions. Finally, bis-*N*-allylamine (**5n**) afforded 1,1-diallyl-3-phenylurea (**6n**) in excellent yield when reacted with phenyl isocyanate (**4a**).

Next, the effects of a substituent on the aryl isocyanates were investigated. Thus, a series of substituted aryl isocyanates **4** were reacted with pyrrolidine (**5a**) to give ureas **6o–u** (Scheme 3). Using the optimized conditions for phenyl isocyanate (**4a**) afforded the desired ureas **6o–u** in moderate to good yield. Having an electron-withdrawing group at the 4-position, such as in 4-fluoro-, 4-chloro- and 4-nitrophenyl isocyanates (**4b–d**), led to increased yields relative to the more electron rich 4-methoxyphenyl isocyanate. The use of 2-fluorophenyl isocyanate gave the desired urea **6t** in a lower yield than the 4-fluorophenyl isocyanate isomer. This result suggests that the steric hindrance imposed by having an *ortho* substituent on the aromatic ring leads to a decrease in yield. Finally, 4-fluorophenyl isocyanate was reacted with *N*-methylaniline under the standard conditions to give 1-methyl-1,3-diphenylurea (**6u**) in good yield.

In situ ^{19}F NMR was used to compare the rate of the formation of ureas from isocyanates and amines in Cyrene *versus* the industrial standard solvents DMF and CH_2Cl_2. The room temperature reaction of 4-fluorophenyl isocyanate (**4b**) and pyrrolidine (**5a**) to give urea **6o** in the three solvents of interest was monitored by NMR spectroscopy. All of the reactions were found to be complete in less than 5 minutes when run at 1 M concentration. The relatively fast rates of these reactions is due to the activating 4-fluoro moiety on the phenyl isocyanate. Importantly, this analysis provided further support for the viability of Cyrene to replace the industrial standard solvents DMF and CH_2Cl_2 in this process.



[a] *N*-methylaniline was used

Scheme 3 Effect of substituent on isocyanate reactivity.

Conclusions

In summary, a green, mild and efficient approach towards the synthesis of ureas from aryl isocyanates and secondary amines in the bio-alternative solvent Cyrene was developed. Both the scope of the amine nucleophile and the effect of substitution on the aryl isocyanate were investigated. This method provides an important alternative to the current industrial use of DMF and halogenated solvents for this process. Importantly, it eliminates the need for the use of both these toxic solvents as well as any non-bioderived organic solvent. Of even more importance is the fact that simply treating the reaction mixture with water solved one of the key problems associated with the use of Cyrene as a solvent, its removal from the product.

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4.3.4 Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene™

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Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene™†

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Cyrene™ as a bio-alternative dipolar aprotic solvent: a waste minimizing and molar efficient protocol for the synthesis of amides from acid chlorides and primary amines in the bio-available solvent Cyrene™ is disclosed. This protocol removed the use of toxic solvents, such as dimethylformamide and dichloromethane. A simple aqueous work-up procedure for the removal of the high boiling solvent Cyrene™ resulted in up to a 55-fold increase in molar efficiency (Mol E.%) *versus* standard operating procedures. In order to rapidly compare the molar efficiency of this process against other methodologies an Excel based Mol. E% calculator was developed that automates many of the calculations. An investigation into the hydration of Cyrene™ found that it readily hydrates to form a geminal diol in the presence of water and that this process is exothermic.

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Introduction

Amides are an important class of compound that have been exploited in a number of fields, such as the pharmaceutical, agrochemical and material sciences. Amides have had a profound impact on the pharmaceutical industry as highlighted by the large number of drugs that contain an amide moiety as well as the significant percentage of reactions performed by medicinal chemists to form amide linkages.[1] Most of the top-15 best selling drugs in 2017 contained an amide,[2] with amide drugs traditionally being some of the highest grossing of all time (Fig. 1).[3] Furthermore, amides themselves are increasingly exploited as catalysts, ligands, reagents, solvents and substrates for a multitude of synthetic transformations.[4]

Due to their importance, novel methods for the synthesis of amides are constantly being developed.[5] One of the most efficient and highly utilized methods for the synthesis of amides is the reaction of acid chlorides and amines. For example a series of acid chlorides were reacted with anilines to give amides, which were screened as positive allosteric modulators of metabotropic glutamate receptor 4 with CNS exposure in rats (Scheme 1, eqn (1)).[6] In this typical example, a variety of amides were synthesized in good yields using the solvent dimethylformamide (DMF), but extensive work-up and purification protocols were required, including aqueous washing and column chromatography. Amides can be synthesized in a variety of different reaction media, though the majority of reactions have been performed in DMF, *N*-methyl-2-pyrrolidone (NMP), dichloromethane (CH_2Cl_2) or tetrahydrofuran (THF).[7] There has been increased regulatory constraints placed on toxic, petroleum-based solvents that are the mainstay of industrial synthesis. The development of safer solvents is one of the

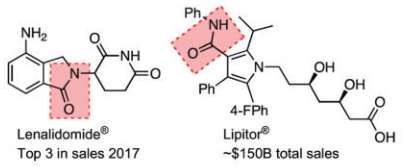
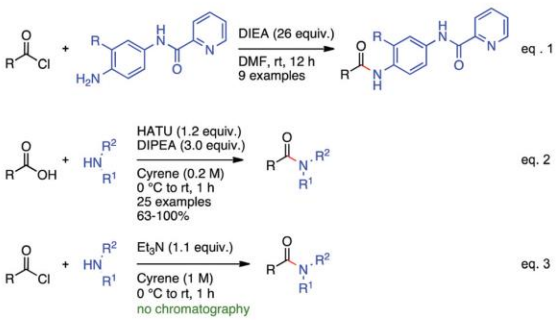


Fig. 1 Important amide pharmaceuticals.



Scheme 1 Synthesis of amides in DMF and Cyrene™ (**1**).

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core tenets of the twelve principles of Green Chemistry.[8] One reason behind the inclusion of solvents in this key list is that between 75–80% of waste associated with the synthesis of pharmaceuticals comes from solvents.[9] In order to combat the cost of solvents, in terms of time, expense and to the environment, a variety of solvent selection guides were put forward.[10] One key class of solvent that currently does not have a direct replacement are dipolar aprotic, such as *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP).[11] Both of these compounds were recently added to the REACH restricted substances list, which severely limits their ability to be used as industrial solvents.[12] Thus, academic researcher and industry have put significant efforts into developing sustainable chemical processes that do not rely on high risk solvents.[13,14]

A possible alternative dipolar aprotic solvent[15] is the bio-available compound Cyrene™ (**1**), dihydrolevoglucosenone, which can be synthesized in two-step processes from waste cellulose.[16] Cyrene™ (**1**) has similar properties to other dipolar aprotic solvents, such as DMF, and it has been put forward as a bio-based alternative for this class of solvent (Fig. 2). Since being proposed by Clark and co-workers in 2014 as a potential bioavailable solvent, Cyrene™ (**1**) has been utilized in a number of applications.[17] For example, Cyrene™ (**1**) was shown to be useful in the processing of graphene[18] as well as in MOF[19] synthesis, membrane synthesis[20] and resin swelling applications.[21] Traditional organic reactions, such as S_N2, S_NAr[14] and acyl substitution processes[22] have also been accomplished in Cyrene™ (**1**). In addition, palladium-catalyzed cross coupling reactions, such as the Sonogashira, Cacchi type annulations[23] and Suzuki–Miyaura reactions[24] were conducted using Cyrene™ (**1**) as a solvent. Interestingly, a number of processes were not compatible with Cyrene™ (**1**) as a solvent, including bio-catalysis applications[25] and situations where it could act as an electrophile.[26] During the course of our study, Watson and co-workers reported the use of Cyrene™ (**1**) as a solvent in the HATU mediated synthesis of amides from carboxylic acid and amines in the presence of excess base (Scheme 1, eqn (2)).[27] Herein, we report the use of the bio-available solvent Cyrene™ (**1**) for the synthesis of amides from the reaction of amines and acid chlorides (Scheme 1, eqn (3)). Molar efficiency calculations, conducted on a semi-automated Excel based calculator, were used to guide the development of a work-up, isolation and purification protocol that minimized the amount of waste that was produced. In addition, a study into the hydration of Cyrene™ (**1**) showed the facile nature of its conversions to a geminal diol as well as the exothermic nature of this process.

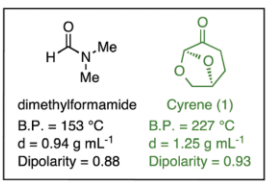


Fig. 2 Comparison of the physical properties of DMF and Cyrene™ (**1**).

Experimental section

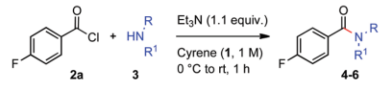
General procedure

To a stirred solution of an acid chloride (0.5 mmol, 1.0 equiv.) in Cyrene™ (**1**, 0.5 mL, 1 M) at 0 °C were added triethylamine (0.55 mmol, 1.1 equiv.) and a primary amine (0.5 mmol, 1.0 equiv.). The resultant mixture was allowed to warm to rt over 1 h. Water (5 mL) was added and the mixture was stirred until the product precipitated. The precipitate was filtered and washed with water to give the pure amide. For the preparation of NMR samples, the solid was dissolved in ethyl acetate, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure.

Results and discussion

To begin the study into the use of Cyrene™ (**1**) as a solvent for the synthesis of amides the reaction of 4-fluorobenzoyl chloride (**2a**) and a variety of amines **3** was investigated (Table 1). Thus, the reaction of the acid chloride **2a** with pyrrolidine (**3a**), aniline (**3b**) and benzylamine (**3c**) in the presence of triethylamine afforded the desired amides **4–6** in good yields. Whilst the optimization of the reaction was straightforward, the isolation of the pure amides required further investigation. Three different work-up procedures were investigated and their molar efficiency values[28,29] were calculated using a semi-automated Excel based calculator (*vide infra*).[30] An aqueous work-up followed by column chromatography afforded (4-fluorophenyl)(pyrrolidine-1-yl)methanone **4a** in excellent isolated yield (Table 1, entry 1). In contrast to our work on the synthesis of pyrrolidine-derived ureas,[18] amide **4a** did not precipitate upon the addition of ten equivalents of water. The crude reaction mixture was also loaded directly onto a silica gel column for purification, which gave the desired amide **4a** in good yield. The removal of the aqueous work-up step resulted in a 1.4-fold increase in molar efficiency (Table 1, entry 1 *vs.* 2). Switching to the use of primary amines, aniline (**3b**) and benzylamine (**3c**), allow for the direct precipitation of the product amides **5a** and **6a**, respectively, which did not require any additional isolation or purification. Safety note: Addition of water to neat Cyrene™ (**1**) is an exothermic process (*vide infra*). By removing the requirement for both an aqueous work-up and column

Table 1 Optimization of the synthesis of amides **4–6** in Cyrene™ (**1**) using molar efficiency calculations

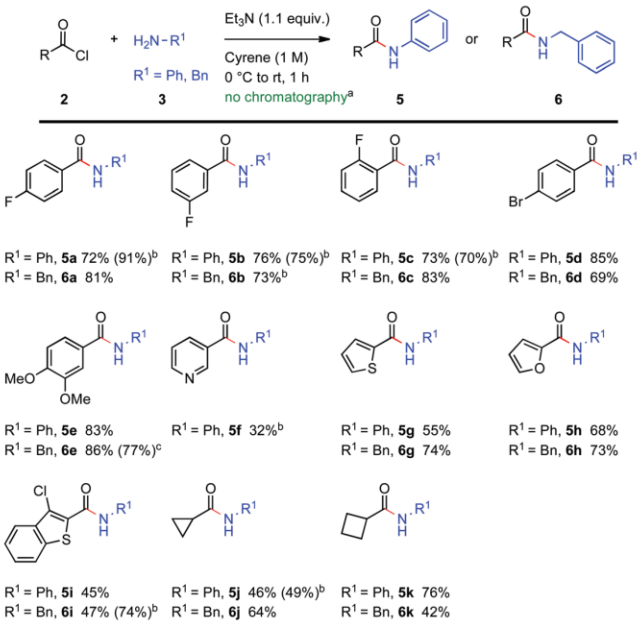


Entry	Amine	Work-up	Yield (%)	Relative Mol. E%
1	Pyrrolidine	Aqueous; then column	91 **4a**	1
2	Pyrrolidine	Column	75 **4a**	1.4
3	Aniline	Precipitate	72 **5a**	24
4	Benzylamine	Precipitate	81 **6a**	28

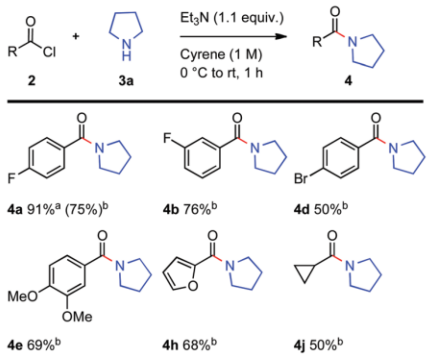
chromatography, up to a 28-fold increase in molar efficiency was achieved (Table 1, entry 1 *vs.* 4). Thus, one of the key challenges in the use of high boiling dipolar aprotic solvents, their separation from the product, was overcome by using this improved isolation procedure. Importantly, only bio-derived solvents, water and Cyrene™ (**1**), were required for the synthesis of amides from acid chlorides and primary amines.

With the optimized reaction and isolations procedure in hand, the reaction of aniline (**3b**) and benzylamine (**3c**) with acid chlorides **2** was investigated (Scheme 2). Fluoro- and brominated benzoyl chlorides gave the desired amides **5a–d**/**6a–d** in good yield. For example, the reaction of 2-fluorobenzoyl chloride with either aniline or benzylamine, gave amides **5c**/**6c** in greater than 70% isolated yield. Interestingly, in some cases an increased yield was obtained by stirring the aqueous mixture for 24 h, but this was not always the case, *cf.* amide **5a** *vs.* **5c**. Electron-rich acid chloride, 3,4-dimethoxybenzoyl chloride afforded amides **5e**/**6e** in high yield. The synthesis of amide **6e** could be run on a 5.0 mmol scale without a significant decrease in yield. It is possible that the electron rich nature of the system slows down the addition of water to the acid chloride leading to higher yields. Reactions between heterocyclic benzoyl chlorides, such as pyridine, thiophene, furan and benzothiophene with aniline (**3b**) gave amides **5f–5i** in moderate yields. Slightly higher yields for acid chloride-containing heterocycles were observed when benzylamine (**3c**) was used as the nucleophile to form amides **6g–6i**. Finally, aliphatic acid chlorides reacted with aniline (**3b**) or benzylamine (**3c**) to give amides **5j,k**/**6j,k** in moderate yields. The reaction of acid chlorides that contained long alkyl chains did not give product amides that precipitated upon the addition of 10 equivalents of water. Based on *in situ* ^{19}F NMR experiments (*vide infra*), amide formation is nearly quantitative, with the rest of the starting material being converted to the carboxylic acid. The majority of the water necessary for the hydrolysis of the acid chloride is introduced into the system *via* the use of reagent grade Cyrene™ that has not been dried. The fluctuation in isolated yields is most likely a reflection of the solubility of the products in a 10 : 1 mixture of water to Cyrene™ (**1**). Alternative work-up procedures including sonication, varying the amount of water added and the addition of salts did not have a beneficial effect on the isolated yield of the products.

Next, the addition of a secondary amine to a variety of acid chlorides was investigated. Pyrrolidine (**3a**) was reacted with electron-deficient, electron-rich, heterocyclic and alkyl acid chlorides under the standard conditions used for the primary amines (Scheme 3). As stated previously, the resultant amides did not precipitate from the solution upon the addition of water, but rather oiled out to form a non-separable emulsion. In order to increase molar efficiency, a direct chromatography method was employed to isolate and purify the amides. This is despite the fact that a traditional work-up/purification protocol resulted in an increased isolated yield of the tertiary amide. For comparison, an aqueous work-up followed by column chromatography for amide **4a** gave a 91% yield, whilst direct chromatography (*i.e.* loading the crude reaction directly onto the silica gel) of the solution afforded amide **4a** in 75% yield. Electron rich and heterocyclic acid chlorides afforded the desired amides **4e** and **4h**, respectively, in slightly higher yields than their halogenated counterparts, **4a**, **4b** and **4d**.



Scheme 2 Synthesis of amides from acid chlorides and primary amines in Cyrene (**1**). [a]Aqueous work-up. [b]24 h stir in water. [c]5.0 mmol scale.



Scheme 3 Synthesis of amides **4** from acid chlorides and primary amines in Cyrene™ (**1**). [a]Aqueous work-up. [b]Solution directly purified by column chromatography.

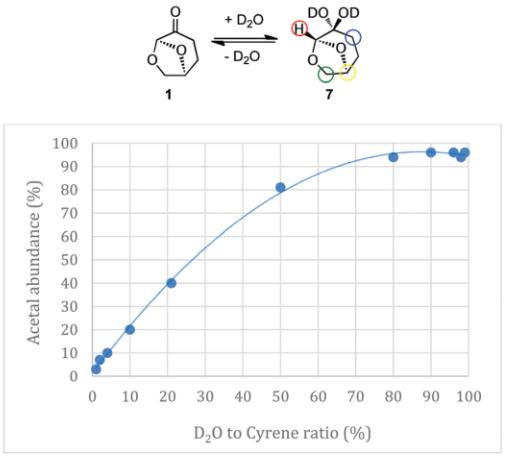


Fig. 3 Hydration of Cyrene™ (**1**) to form geminal diol **7** as the amount of D_2O is changed. Solid lines between points are visual aids.

Finally, the reaction of pyrrolidine (**3a**) with cyclopropanecarbonyl chloride afforded the desired amide **4j** in moderate yield. Based on the substrate scope study it was found that amides derived from primary aliphatic or benzylic amines can be precipitated directly from Cyrene™ (**1**) whereas the products from the reaction of secondary amines required purification by column chromatography.

The rate of the formation of amides from acid chlorides and amines in Cyrene™ (**1**) *versus* the industrial standard solvents DMF, NMP and acetonitrile were examined using *in situ* ^{19}F NMR with hexafluorobenzene as an internal standard. Monitoring the reaction of 3-fluorobenzoyl chloride and aniline (**3b**) in the presence of triethylamine at room temperature showed complete conversion to amide **5b** in less than 5 minutes for the four solvents that were investigated.

Investigation into the hydration of cyrene™ (1)

A study into the hydration of Cyrene™ (**1**) was undertaken in order to better understand why it could be separated from the product amide *via* the addition of water. Whilst the hydrate of Cyrene **7** [31] as well as related 6,8-dioxabicyclo[3.2.1]octanone ring systems in which there is a substituent at the β-position are reported,[32,33] at the start of our study there is was no NMR data available for the hydrate or information on the effect of water concentration on the equilibrium. Very recently, De bruyn *et al.* reported on the hydration of Cyrene™ (**1**) and the ability of the solutions to solvate simple organic compounds.[34] In contrast to this work, mixtures of varying concentrations of D_2O and Cyrene™ (**1**) were subjected to NMR analysis to provide insights into the equilibrium process (Fig. 3). Safety note: Addition of water to neat Cyrene™ (**1**) is an exothermic process. It was found that the addition of 2.5 mL of water to 2.5 mL of Cyrene™ (**1**) resulted in an increase in temperature of over 14 °C (*cf.* Fig. S12†).[26] Initially, it was found that in the presence of 10 equivalents of D_2O, 96% of Cyrene™ (**1**) was hydrated to geminal diol **7**. No ring opening of the cyclic acetal of Cyrene™ (**1**) was observed in this study. Importantly, the structure of geminal diol **7** was confirmed by 2D NMR experiments with nOe observed in the HMBC spectra between the proton adjacent to the cyclic acetal (circled in red) and the carbons next to the ethers as well as alpha to the geminal diol, highlighted in green, yellow and blue, respectively. Furthermore, as the percent of D_2O increased from 1% to 99% the equilibrium shifted from ketone **1** to geminal diol **7**. At a ratio of 1 : 1 of D_2O to Cyrene™ (**1**), over 80% of the ketone was hydrated. These results are in stark contrast to a simple ketone, such as acetone, which exists predominately as the carbonyl in aqueous solution.[35] The facile hydration of Cyrene™ (**1**) and the subsequent change in its solvating ability helps to explain why amides **5** and **6** precipitated upon the addition of water. Interestingly, when 1 M solutions of a 1 : 1 mixture of Cyrene™ (**1**) to D_2O in DMSO-d^6, MeCN-d^3 or acetone-d^6 over the same concentration range were analyzed by ^1H NMR, only the non-hydrated keto form of Cyrene™ (**1**) was observed. These results suggest that in the presence of an excess of organic solvent that the keto form is highly favored and that Cyrene™ (**1**) will behave like a dipolar aprotic solvent. Control over the hydration of Cyrene™ (**1**) should allow for its facile recycling and lead to novel applications.

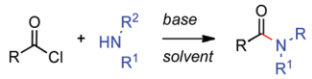
Molar efficiency calculator and calculations

In order to compare the efficiency of our method to existing protocols, molar efficiency calculations were undertaken using the method of Watson and co-workers[24,25] in which:

$$\text{Molar efficiency (Mol. E\%)} = \left[\frac{\text{moles product}}{\text{moles starting material} + \text{additives} + \text{catalysts} + \text{solvents}}\right] \times 100$$

Molar efficiency calculations are a useful way to calculate reaction efficiency in discovery medicinal chemistry as they enable comparisons of the multitude of transformations that

Table 2 Comparison of Mol. E% of amide forming reactions



Entry	Acid chloride 1	Amine 2	Solvent	Work-up[a]	Mol. E%	Relative Mol. E%	PMI (kg kg^{-1})
1	4-Fluorobenzyl chloride	Pyrrolidine	Cyrene	A	0.0053	2.0	6119
2	4-Fluorobenzyl chloride	Pyrrolidine	Cyrene	B	0.0070	2.7	6109
3	4-Fluorobenzyl chloride	Aniline	Cyrene	C	0.123	47	75
4	4-Fluorobenzyl chloride	Benzylamine	Cyrene	C	0.143	55	63
5[37]	Chloroformate	2-Phenylethylamine	DMF	A	0.0111	4.3	3582
6[38]	4-Fluoro-3-(trifluoromethyl) benzoyl chloride	1-Benzyl-2,3-dihydro-1*H*-pyrrolo [2,3-*b*]quinolin-4-ylamine	DMF	A	0.0026	1	7807
7[39]	4-Fluorobenzyl chloride	*N*-(2-Aminophenyl)-acetamide	CH_2Cl_2	A	0.0073	2.8	10 630
8[40]	4-Fluorobenzyl chloride	2-Bromoaniline	CH_2Cl_2	A	0.0115	4.4	3154
9[41]	3-Fluorobenzyl chloride	5,7-Dichloroquinolin-8-amine	THF	A & D	0.0026	1	1777

[a] Work-up conditions: (A) aqueous work-up followed by column chromatography (B) column chromatography (C) precipitation (D) recrystallization.

are used at this phase of research. Also, this green metric allows for the cross-comparison of the subtleties within a particular reaction and it is this ability to rapidly quantify difference that has been used in this research. In order to quickly access the molar efficiency of the reported method and compare it to existing literature a semi-automated Excel based Mol. E% calculator was developed.[26] The calculator automates many of the efficiency calculations and converts solvents from mL to mmol. In order to evaluate all of the relevant papers a number of assumptions needed to be made about standard work-up procedures for which no detailed information is generally provided. The following standards were used:

1. Chromatography: 100 g SiO_2 per 1.0 mmol (up to 10 mmol): 50 g SiO_2 per 1.0 mmol (up to 10 mmol) using an automated purification system,

2. Chromatography: 1.0 L solvent for first 1.0 mmol and then 500 mL solvent for each mmol thereafter (up to 10 mmol): 0.5 L solvent and then 250 mL solvent for each mmol thereafter (up to 10 mmol) when using an automated purification system,

3. Silica gel plug: 10.0 g silica gel (up to 10 mmol),

4. Recrystallization: 5.0 mL per 1.0 mmol (up to 10 mmol),

5. Drying agent: ($MgSO_4$ or Na_2SO_4) 2.0 g per 1 mmol (up to 10 mmol).

With the calculator in hand, the Mol. E% of the optimized protocol for the synthesis of amides was compared with standard reaction methods in the problematic solvents DMF and CH_2Cl_2 as well as the commonly used solvent THF (Table 2 and ESI†). As stated previously, it was found that changing from an aqueous work-up/chromatography to a precipitate protocol in our study resulted in up to a 28-fold increase in Mol. E% (Table 2, entries 1–4). Similar amidation reactions in DMF were found to be significantly less efficient, with the precipitate protocol showing up to a 55-fold improvement (Table 2, entries 2, 3 *vs.* 5, 6). Methods that used the halogenated solvent CH_2Cl_2 were found to be approximately 14-fold less efficient (Table 2, entries 2, 3 *vs.* 7, 8). Finally, a similar amidation method employing THF as the solvent was found to be one of the least efficient protocols of those investigated (Table 2, entry 9). Thus, the newly developed Excel based calculator allowed for the rapid calculation of the Mol. E% values for various solvent systems and demonstrated that the precipitation method is up to 55-fold better than standard industrial processes. In addition, the process mass intensity (PMI),[36] which is defined as the ratio of the total mass of materials to the mass of the isolated products, of each of the nine protocols was calculated. Satisfyingly, the same trend was observed with the precipitation methods showing a significant improvement on existing protocols (Table 2, entries 3 and 4 *vs.* 5–9).

Conclusion

In conclusion, a molar efficient protocol for the synthesis of amides from acid chlorides and amines has been developed. The substrate scope of this green and mild method has been investigated with respect to acid chlorides and primary amines. This method provides an important alternative approach to the current industrial use of halogenated solvents and dimethylformamide. Importantly, the work-up procedure eliminates the need for the use of any non-bioderived organic solvents from the process. The simple addition of water allows for complete removal of the Cyrene™ (**1**) without the need for extensive isolation and purification protocols, which are required using existing technologies. In order to rapidly compare this method with those previously reported an Excel based Mol. E% calculator was developed. Mol. E% calculations showed that the Cyrene™ (**1**) precipitation method is significantly more efficient than the previously reported protocols using more toxic solvents, such as DMF and dichloromethane. This protocol allows for the rapid synthesis of amides under mild, more sustainable conditions.

Associated content

Experimental procedures, $^{1}H/^{13}C\{^{1}H\}/^{19}F$ NMR data for all compounds, molar efficiency calculations and Excel based Mol. E% calculator.

Conflicts of interest

The authors declare no competing financial interest.

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