Evaluating the Application and Limitations of Bio-Based Solvents within Organic Synthesis

Kirsty Leanne Wilson

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Evaluating the Application and Limitations of Bio-Based Solvents within Organic Synthesis

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By

Kirsty Leanne Wilson

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Publication List

1. *"Synthesis of 2-BMIDA 6,5-bicyclic heterocycles by Cu(I)/Pd(0)/Cu(II) Cascade Catalysis of 2-Iodoaniline/Phenol"*: C. P. Seath, K. L. Wilson, A. Campbell, J. M. Mowat and A. J. B. Watson, *Chem. Commun.*, 2016, **52**, 8703–8706.

2. *"Scope and Limitations of a DMF Bio-Alternative within Sonogashira Cross-Coupling and Cacchi-Type Annulation"*: K. L. Wilson, A. Kennedy, J. Murray, C. Jamieson and A. J. B. Watson, *Beilstein J. Org. Chem.*, 2016, **12**, 2005–2011.

3. *"Connecting the Dots: Method Development Using Sustainable Solvents"*: K. L. Wilson, J. Murray, H. F. Sneddon, K. M. P. Wheelhouse and A. J. B. Watson, *Chem*, 2017, **3**, 365–368.

4. *"Cyrene as a Bio-Based Solvent for the Suzuki–Miyaura Cross-Coupling"*: K. L. Wilson, J. Murray, C. Jamieson and A. J. B. Watson, *Synlett*, 2018, **29**, 650–654.

5. *"Cyrene as a Bio-Based Solvent for HATU Mediated Amide Coupling"*: K. L. Wilson, J. Murray, C. Jamieson and A. J. B. Watson, *Org. Biomol. Chem.*, 2018, **16**, 2851–2854.

6. *"Dimethyl Isosorbide (DMI) as a Bio-Derived Solvent for Pd-Catalysed Cross-Coupling Reactions"*: K. L. Wilson, J. Murray, H. Sneddon, C. Jamieson and A, J. B. Watson, *Synlett*, 2018, **29**, 2293–2297.

Abstract

The growing sustainability movement within the chemical industries endeavours to forge cleaner manufacturing processes which integrate the key principles of Green Chemistry. At the forefront of these initiatives are solvent replacement strategies, driven, in part, by increasingly stringent regulations surrounding the use of solvents of concern. A group of solvents which have fallen under particular scrutiny are polar aprotic solvents, such as DMF, NMP and DMAc. This solvent class is characterised by high polarity and superior solvating abilities, which has firmly established their use within synthetic organic and medicinal chemistry. However, they are also associated with reproductive toxicity and are regarded as teratogens. As such, their continued use within industry is becoming increasingly discouraged.

Direct replacement of polar aprotics using existing solvents often fails and, as such, novel alternatives are required. In this regard, the use of biomass feedstocks in the development of new solvents is an expanding area within Green Chemistry which aims to minimise the dependence on petroleum-based chemicals. Cyrene and dimethyl isosorbide (DMI) are two emerging solvents derived from cellulose. However, their application within organic chemistry is under explored and, as such, their use within industry is currently limited.

This research programme aims to investigate the use of these alternative solvents in synthetic transformations commonly utilised within the context of drug discovery in the pharmaceutical industries. Robust and general condition sets have been developed and thoroughly evaluated in the application of Cyrene as a medium for the Sonogashira and Suzuki–Miyaura cross-couplings, and amide bond formation. In addition, the methodology developed for the Sonogashira cross-coupling was extended to enable the efficient synthesis of pharmaceutically relevant heterocycles. Cyrene exhibited a pronounced base sensitivity, the effect and limitations of which were studied within organic reactions.

Additionally, the utilisation of DMI as an alternative solvent within prominent Pd-catalysed transformations was also evaluated. Accessible conditions for the Suzuki–Miyaura, Mizoroki–Heck and Sonogashira cross-coupling reactions were developed and the scope of the reactions investigated. Ultimately, it is hoped that exemplifying the use

of these solvents within organic synthesis and highlighting their limitations will influence their uptake by industrial practitioners.

Acknowledgements

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Abbreviations

Ac	Acetyl
API	Active Pharmaceutical Ingredient
AZ	AstraZeneca
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPin	Boronic acid, pinacolato ester
Cat.	Catalyst
CBz	Carboxybenzyl
CM	Cross-metathesis
COMU	1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholino)] uronium hexafluorophosphate
COSMO	Conductor-like screening model
CPME	Cyclopentyl Methyl Ether
DABCO	1,4-Diazobicyclo[2.2.2]octane
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DDT	Dichlorodiphenyltrichloroethane
DFT	Density Functional Theory
DIC	*N*,*N*'-Diisopropyl carbodiimide
DIPEA	*N*,*N*-diisopropylethylamine

DMAc	*N*,*N*-Dimethylacetamide
DMC	Dimethylcarbonate
DMF	*N*,*N*-Dimethylformamide
DMI	Dimethyl isosorbide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ECHA	European Chemicals Agency
Equiv.	Equivalent
ESIG	European Solvents Industry Group
Fmoc	Fluorenylmethyloxycarbonyl
GHB	γ-Hydroxybutyric acid
GSK	GlaxoSmithKline
GVL	γ-Valerolactone
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HSP	Hansen solubility parameters
KFTA	Potassium trifluoroacetate
KTP	Kamlet–Taft parameters
LCA	Life cycle analysis
LP	Liquid phase
2-MeTHF	2-Methyltetrahydrofuran

MeCN	Acetonitrile
MH	Mizoroki–Heck
MIDA	*N*-Methyliminodiacetic acid
MOF	Metal-organic-framework
NMP	*N*-Methylpyrrolidone
NMR	Nuclear Magnetic Resonance
OTBN	*o*-Tolylbenzonitrile
PyBOP	Benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate
RCM	Ring Closing Metathesis
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
rpm	Rotations per minute
SHE	safety, health and environmental
SM	Suzuki–Miyaura
SPhos	2-Dicyclohexylphosphino-2,6'-diisopropoxybiphenyl
SPPS	Solid Phase Peptide Synthesis
SVHC	Substance of Very High Concern
TBAF	Tetra-*n*-butylammonium fluoride
TBME	*tert*-butyl methyl ether
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl

TLC	Thin layer chromatography
Tol	Tolyl
T3P	Propylphosphonic anhydride solution
THF	Tetrahydrofuran
VOC	Volatile organic compound

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1 Introduction

Green Chemistry is, first and foremost, a method of preventing the impact that the chemical industries have upon the environment and human health.[1] Historically, environmental and health issues, such as those caused by DDT[2] and thalidomide, have been succeeded by public outcry, forcing a response from governments in the form of stricter laws and regulation. However, this reparative "knee-jerk" reaction lacks foresight, often only addressing the end-of-pipe products and waste streams. In contrast, the principles of Green Chemistry aim to reduce or eliminate the use and generation of hazardous substances at all stages of the manufacturing process.[1,3]

Paul Anastas and John Warner have been at the forefront of the drive towards safer and cleaner chemical synthesis by proposing the Twelve Principles of Green Chemistry (See below).[1,4] These are presented with the view that synthetic chemists have the potential to influence upstream procedures through conscious selection of feedstocks, and consistently examining and amending strategies so that they are "benign by design".[5]

1. **Prevention**. It is better to prevent waste than to treat or clean up waste after it is formed.
2. **Atom Economy**. Synthetic methods should be designed to maximise the incorporation of all materials used in the process to the final product.
3. **Less Hazardous Chemical Synthesis**. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. **Safer Solvents and Auxiliaries**. The use of auxiliary substances should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**. Energy requirements should be recognised for their environmental and economic impacts and should be minimised. Synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting wherever technically and economically possible.

8. **Reduce Derivatives**. Unnecessary derivatisation should be avoided whenever possible.
9. **Catalysis**. Catalytic reagents are superior to stoichiometric reagents.
10. **Design for Degradation**. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. **Real-time Analysis for Pollution Prevention**. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions, and fires.

Solvent use within manufacturing processes raises concerns due to the large volume in which they are employed.[6] They are highly valuable for their solvency properties and physical abilities to disperse heat and use in mass transfer events.[7] However, there are many factors which contribute to the desire to minimise or exclude their use, such as toxicity to humans and wildlife, and the impact on the local and global environment, including volatile organic compound (VOC) emission and their contribution to climate change.[8] In addition, treatment and disposal of waste streams and the energy required to achieve this must also be considered. Further discussion of these points can be found within the following sections.

1.1 Current Solvent Use

1.1.1 Solvent Types and their Origins

A solvent can be defined as a substance which is a liquid at the point of use, and is capable of dissolving, dispersing or extracting other materials. They are fundamental for maintaining modern living standards; with use in production, processing and cleaning integral to the manufacture of many everyday products.[9]

Solvents are broadly placed into two groups; inorganic (e.g. NH_3, H_2O) and organic, with organic solvents further separated into oxygenated (e.g. MeOH, acetone), hydrocarbon (e.g. pentane, benzene), and halogenated (e.g. $CHCl_3$, DCM) species. Due to the extensive applications of solvents and varied nature of both the end products and intermediaries, a range of solvents with diverse physical properties are required. These properties can be classified based on their polarity and chemical nature (Table 1).[9] Polar aprotics, such as *N*,*N*-dimethylformamide (DMF), are an important class of solvents as they have high dielectric constants (> 20) and, as such, are able to dissolve highly charged species or polar compounds. Furthermore, they are generally unreactive, and accordingly, make suitable mediums for many organic transformations.

Table 1 Solvent Classification[9]

Non-polar	Have a comparatively low dielectric constant. Are not able to form intermolecular bonds with solute e.g. hydrogen bonding.	e.g. pentane, petroleum ether
Polar	Have a dielectric constant > 15.	e.g. EtOH, DMSO
Protic	Have proton donor groups.	e.g. alcohols
Aprotic	Non hydrogen bond donor. Generally inert.	e.g. DMF, MeCN

Petrochemical building blocks, derived from crude oil and shale gas, are the major source of materials from which solvents are acquired. These include syngas, ethylene, benzene and aliphatic hydrocarbons. For example, the steam reforming of methane yields many important industrial feedstocks such as hydrogen and syngas, the latter being an essential

component in the manufacture of methanol which can be considered a platform molecule, with its derivatisation playing a key role in the synthesis of many solvents.[10]

In the production of DMF (Figure 1a), methanol is required to facilitate the synthesis of the two constituent intermediates.[11] Reduction of nitrogen *via* the Haber process to yield ammonia is subsequently followed by methylation, using methanol, to afford dimethylamine. This is concurrent with the carbonylation of methanol to methyl formate which then undergoes amidation with dimethylamine to yield DMF. In the case of tetrahydrofuran (THF, Figure 1b), methanol is oxidised to formaldehyde which subsequently engages with acetylene *via* ethynylation to furnish 2-butyne-1,4-diol. Reduction and dehydration then follow, yielding THF.

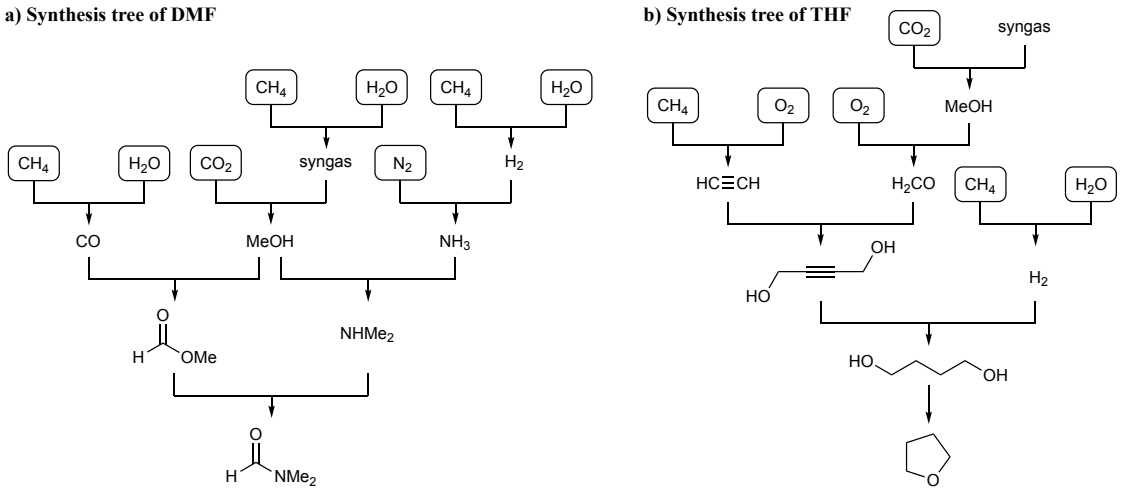


Figure 1 Synthesis trees of a) DMF and b) THF[11]

1.1.2 The Solvent Market

The prominence of solvent use in industrial processes is reflected in the global solvents market which was valued at $26.8 bn (£20.3 bn) in 2016 with a total volume of 28.3 million tonnes of solvent sold annually.[12] Furthermore, figures reported by the European Solvents Industry Group (ESIG) show that Europe's solvent manufacturers contribute an estimated €3 bn (£2.6 bn) to this economy, selling 5 million tonnes of solvent.[13]

Available data on solvent use by sector is often outdated, with the most recent statistics of solvent use in Western Europe having been published by ESIG in 1993 (Figure 2).[13]

However, it gives a reasonable indication of the market share and allows general trends to be established. The market was largely dominated by the manufacturers of paints and coatings, accounting for almost half of the industrial solvent use. Pharmaceutical and agrochemical industries are, collectively, the second largest consumers comprising 11% of the market.

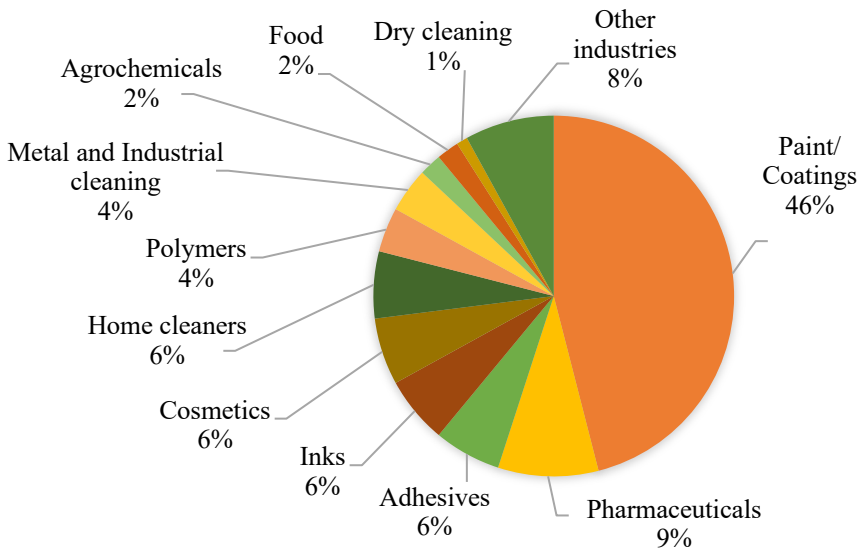


Figure 2 Solvent use by sector as published by ESIG (1993)[13]

These trends are reflected in more recent analysis of Swedish industrial solvent use by the Swedish Chemicals Agency (Figure 3).[14] Whilst the surveyed sectors differ, some comparisons may be drawn. For example, the paint industry is still a significant consumer of solvents. However, the market share has decreased with the introduction of water and oil-based paints and coatings. Furthermore, polymers/plastics, metal works and food production still maintain a similar usage.

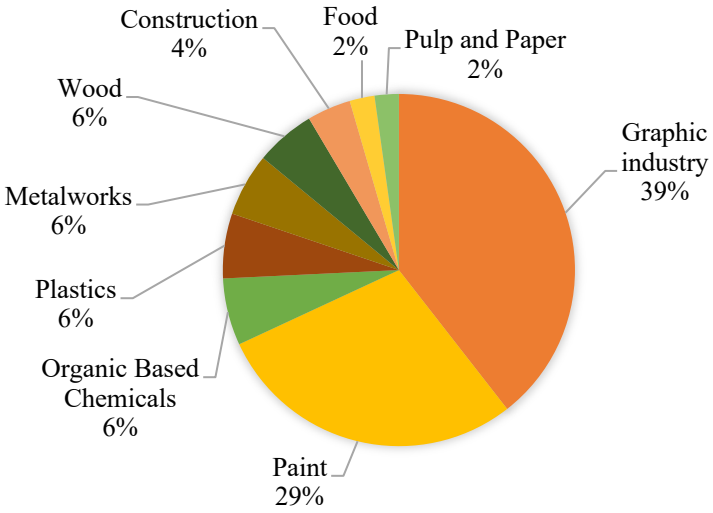


Figure 3 Swedish industrial solvent use (2010)[14]

1.1.3 Solvent Regulation and Solvents of Concern

Within Europe, solvent use is regulated by the European Chemicals Agency (ECHA) under a section of legislation called the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).[15,16] The importing or manufacture of significant amounts (greater than one tonne) of a chemical substance must be registered with ECHA, and the potential risks to human health or the environment evaluated. If the substance displays significant toxic properties or is found to have the potential to cause extensive damage to the environment, it may be subject to treatment as a Substance of Very High Concern (SVHC). With regards to human health, substances which are carcinogenic, mutagenic or toxic to the reproductive system are considered SVHCs. Bioaccumulation and persistence are properties which should be investigated when considering environmental risks.

Following extensive evaluation of risks and possible methods to minimise exposure, a SVHC may be nominated for the authorisation process, which aims to control and reduce the usage of a SVHC in favour of less dangerous alternatives. A "*Sunset date*" is identified and, from this point, the use or sale of a substance is prohibited unless a company/organisation has been granted exemption. Cases for exemption must outline the potential benefits and demonstrate, with evidence, how they offset the identified risks. Alternatively, restrictions may be placed upon a substance. These range from controlling

the concentration of a substance within products or the volume manufactured, to less extreme controls such as specific labelling and hazard identification (Classification and Labelling Procedure).

These increasingly stringent regulations are a major driving force towards sustainability within industry in relation to solvents and solvent substitution. Many are known to be toxic to human health and have therefore already been impacted by REACH. For example, benzene,[15] dichloromethane,[17] 1,4-dioxane,[18] and 1,2-dichloroethane are carcinogenic or suspected carcinogens, and as such are all SVHCs, with restrictions placed on the use of benzene and dichloromethane and additional authorisation needed for the use of 1,2-dichloroethane (DCE).[19]

A group of solvents which are of particular concern are polar aprotic solvents such as *N*-methylpyrrolidone (NMP), DMF, and *N*,*N*-dimethylacetamide (DMAc) which are widely used in small molecule synthesis and the manufacture of polymers.[20] These substances have been identified as SVHC due to their associated reprotoxicity and potential teratogenic properties.[16] In addition, DMF[21] and DMAc[22] have been included on the candidate list for authorisation and NMP has been subjected to the authorisation process, prompting the introduction of restrictions on its use and manufacture.[23]

The use of these solvents is generally interchangeable and there are very few alternatives available. For example, dimethyl sulfoxide (DMSO) is comparatively benign and offers similar solvating properties but is associated with its own risks, such as skin permeability and thermal instability, which limit its use on large scale production.[24] With no adequate alternatives currently available, it is imperative that new solvent systems are developed to aid in the successful transition from traditional polar aprotics.

1.2 Sustainable Solvents

1.2.1 The Bio-Based Economy

An early definition of sustainability states that *"sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs"*.[25] Society as a whole is currently dependent on fossil fuels, a

finite resource, which will not be as readily available for future generations. The bio-based economy aims to support the transition from this primary resource and the derived petrochemical materials to bio-based products and technologies, with an overall view to limit reliance on fossil fuels, reduce green-house gas emissions and diversify sources of energy and materials.[26] It is a production cycle utilising a diverse pool of renewable resources and considers the energy input, and waste streams of the production and consumption of these materials.[27]

The driving force behind the bio-based economy and sustainability is not solely based upon green issues but is motivated by many factors such as societal and economic issues.[28] Fossil fuels are a finite resource but are not currently in limited supply. However, the remaining reserves are becoming increasingly difficult to extract and, as such, extraction costs and potential hazards will increase. Additionally, many remaining supplies are located in areas of political instability. One aspect of the global bio-based economy is that it aims to breakdown the constraints of regional and centralised resources, promoting the use of local feedstocks and leading to development of rural areas.

Whilst the benefits of moving away from fossil fuels are apparent, it is important to consider the implications that this could have on the environment, economy and society.[26] Use of bio-based resources may increase the demand of land and encourage more intensive farming practices, leading to negative environmental effects such as deforestation, soil erosion and loss of biodiversity.[29] Additionally, this could also affect the production of food, causing inflation of prices and subsequently influencing endeavours to reduce poverty.

With a view to negate these implications, efforts have been focused upon the utilisation of biomass residues as feedstocks.[30] These are waste streams from food production and forestry such as straw, bagasse, bark and wood chippings, and therefore would not interfere with the production of food or increase demand on land use to an extreme extent. Before these lignocellulosic feedstocks can be converted into useful materials, the three constituent components, cellulose, hemicellulose and lignin, must first be separated (Figure 4). The cellulosic materials may then be converted into sugars either by biochemical (e.g. fermentation, enzymatic conversion), chemical (e.g. acid or base hydrolysis), or thermochemical (e.g. pyrolysis) processes which can then undergo further

transformation to produce alcohols or functionalised chemical building blocks.[31,32] In sugar platform biorefineries, the lignin extracted as a by-product is often subsequently used as fuel for production within the refining process. However, lignin is also an important source of oxygenated aromatic hydrocarbons and may additionally be transformed, *via* gasification, to syngas.[33,34]

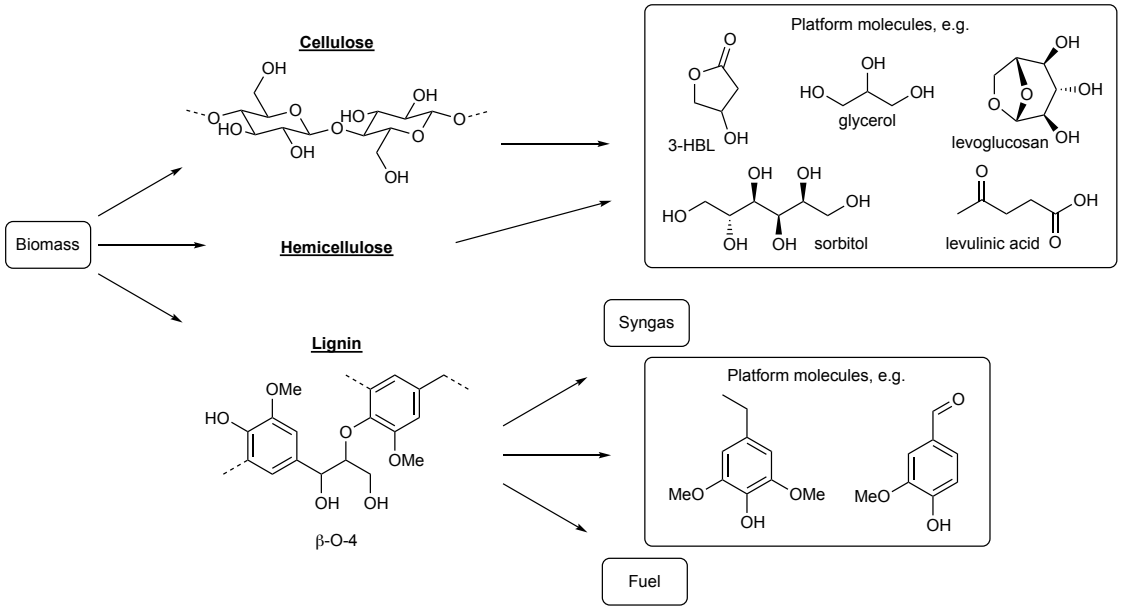


Figure 4 Constituents of biomass and their uses

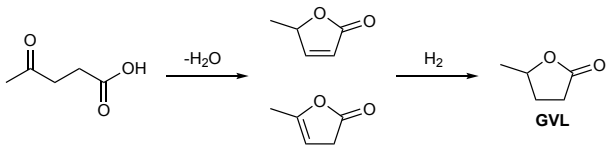
1.2.2 Bio-Based Alternative Solvents

Bio-based solvents are privileged products and highly sought after within the green chemistry community.[11,35,36] As previously discussed (Section 1.2.1, The Bio-Based Economy), many platform molecules can be accessed from lignocellulosic biomass. The chemical building blocks isolated from lignin are valuable resources for the synthesis of aromatic solvents such as benzene, toluene, xylene and naphthalene. However, for the purpose of the current study the following section will focus upon neoteric solvents derived from the cellulosic components of biomass.

1.2.2.1 γ-Valerolactone

γ-Valerolactone (GVL) can be synthesised from fructose or glucose, obtained from biomass. Following pyrolysis of the lignocellulosic material, levulinic acid is then dehydrated and catalytically reduced to produce GVL (Scheme 1).[37,38] With structural

similarities to the neurotransmitter γ-hydroxybutyric acid (GHB), GVL displays analgesic effects and induces muscle relaxation.[39] Notwithstanding these potential limitations, the physical and chemical properties which were first disclosed by Horváth *et al.* make it an attractive sustainable solvent.[40] GVL has a liquid range of -31 to 207 °C with a flash point of 96 °C and does not readily form peroxides which makes it safe for use on scale and for storage over long periods of time.[41]

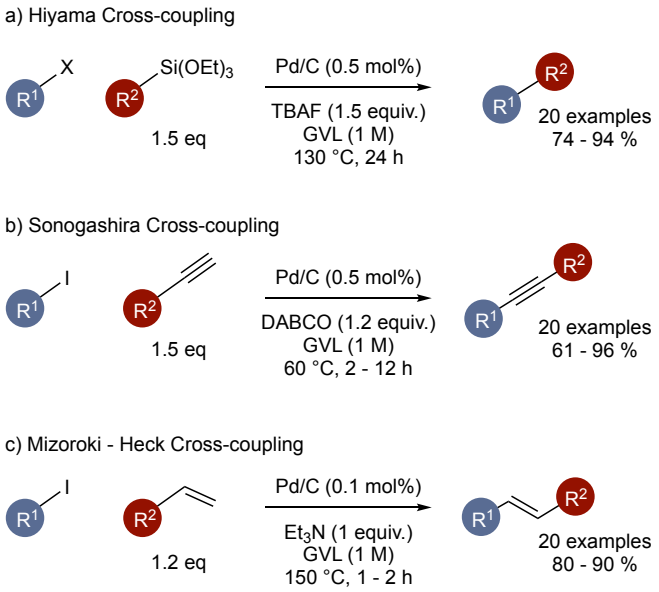


Scheme 1 General synthesis of GVL

GVL has been utilised in the pretreatment and processing of biomass[42,43] and can subsequently be used to facilitate the synthesis of GVL[44] and furfural.[45] Additionally, GVL has a similar dielectric constant to polar aprotic solvents and so could have potential applications in common organic transformations as an alternative to solvents of concern such as DMF and NMP.

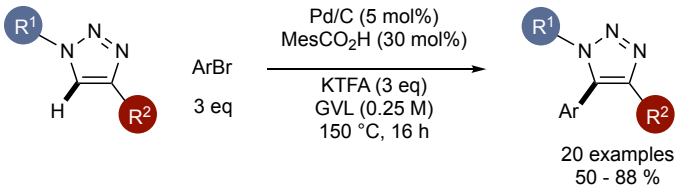
Vaccaro *et al*. have demonstrated the use of GVL in a range of palladium-catalysed bond forming reactions such as the Hiyama,[46] Sonogashira[47] and Mizoroki–Heck (MH) reactions (Scheme 2).[48] The processes developed utilise palladium on carbon (Pd/C), with the use of a heterogeneous catalyst being preferential within green chemistry as it facilitates facile recovery and reuse of the catalyst.

This group report higher catalytic activity when using traditional solvents within these transformations, with DMF and NMP both achieving high conversions in shorter reaction times due to the co-ordination effects of these solvents. This leads to higher levels of palladium leaching. By monitoring the concentration of palladium in the reaction mixtures and final products, they were able to determine that the use of GVL results in low levels of palladium leaching. Although this induces lower catalytic activity, which can be compensated by longer reaction times, the diminished metal contamination of products is desirable in the synthesis of active pharmaceutical ingredients.[49]



Scheme 2 Use of GVL in Pd-catalysed cross-coupling

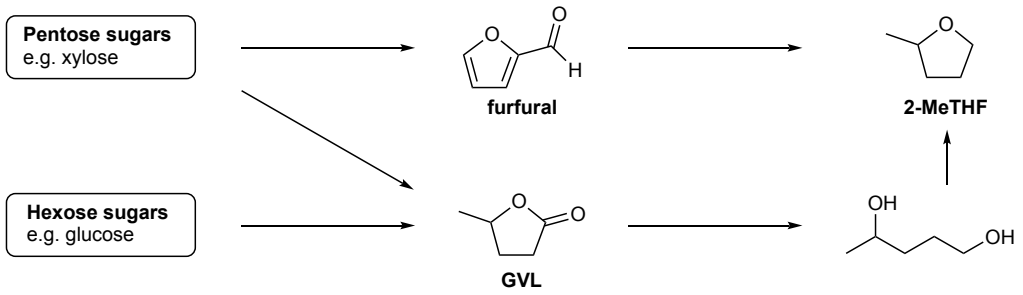
GVL has also proven to be a successful solvent in C-H activation chemistry such as the Catellani reaction[50] and the arylation of triazoles (Scheme 3).[51] Ackermann and Vaccaro *et al.* were able to demonstrate the synthesis of a broad range of fully functionalised tri-substituted triazoles utilising heterogeneous Pd/C, and were successfully able to recover and reuse the catalyst in subsequent processes with no erosion of yield. In addition to these transformations, steps have been made towards the utilisation of this alternative solvent in the hydroformylation of styrene[52] and the formylation of amines.[53]



Scheme 3 GVL as an alternative solvent in the C-H activation of 1,2,3-triazoles

1.2.2.2 2-Methyltetrahydrofuran

2-Methyltetrahydrofuran (2-MeTHF) is a bio-based solvent which has demonstrated extensive utility within organic synthesis as an alternative to THF.[54] 2-MeTHF can either be accessed by the catalytic hydrogenation of furfural,[55,56] a derivative of pentose sugars,[57] or from levulinic acid *via* GVL by the reduction to 1,4-pentandiol and subsequent dehydration (Scheme 4).[58,59,60] 2-MeTHF has been identified as non-mutagenic and non-genotoxic.[61] However, it does display a tendency towards the formation of peroxides, although the reported extent of this in comparison to THF is conflicted.[41,62]



Scheme 4 General synthetic routes towards 2-MeTHF

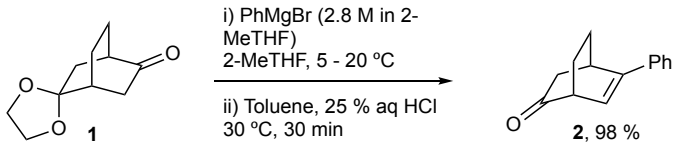
The green credentials of 2-MeTHF extend beyond its renewable nature. Its widespread use within industry can be attributed to its immiscibility with water (14 g/100 g at 20 °C) which allows simple aqueous extractions. This eases work-up procedures[63] and allows for the use of less water when compared with THF, with subsequent disposal of minimal aqueous waste achieved much more readily.[62] Additionally, 2-MeTHF may be recovered and dried by azeotropic distillation.

Both THF and 2-MeTHF are susceptible to degradation *via* acid hydrolysis.[54] In the case of 2-MeTHF, the predisposition towards the formation of a biphasic system is advantageous as it prevents mixing of the aqueous acidic and organic phases therefore preventing extensive degradation. This immiscibility has also been exploited in synthetic transformations such as alkylation of amine derivatives where 2-MeTHF is employed as an alternative to dichloromethane (DCM).[64]

The Lewis basic properties of THF and other ethereal solvents make them indispensable to organometallic chemistry as they increase effective aggregate concentration thus

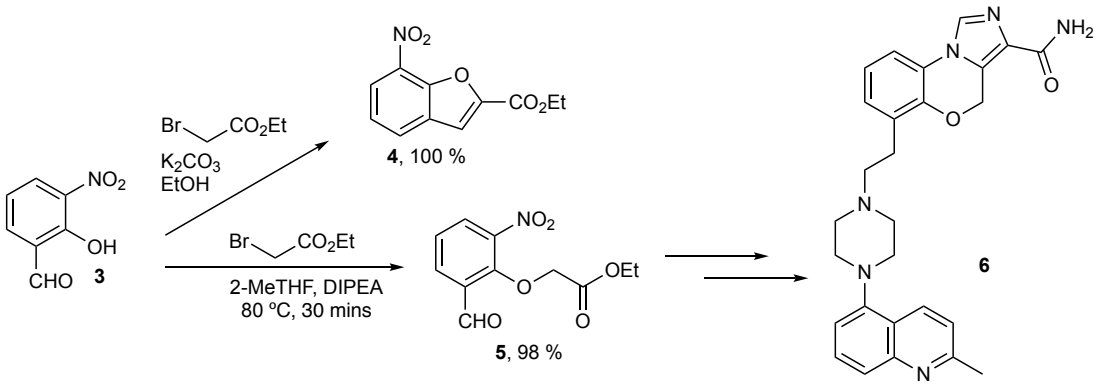
improving reactivity. 2-MeTHF displays comparable reactivity within lithiation chemistry, with high stability towards lithiating reagents reported compared to THF, allowing their use at higher temperatures.[65]

Similarly, 2-MeTHF can also be applied within Grignard reactions, performing efficiently whilst minimising the formation of Wurtz coupled products when employing benzyl Grignards.[66] In addition, Grignard reagents also demonstrate higher thermostability and solubility within solutions of 2-MeTHF leading to the commercial sale of such products.[67] The utility of such reagents has been demonstrated on kilogram scale in the synthesis of [2.2.2]oct-5-en-2-one, **2**.[68] Actelion Pharmaceuticals developed a six step process of **2** with a key step being the Grignard addition into the monoprotected diketone **1** to yield a mixture of tertiary alcohols followed by the acid-catalysed dehydration and deketalisation to yield **2** (Scheme 5).



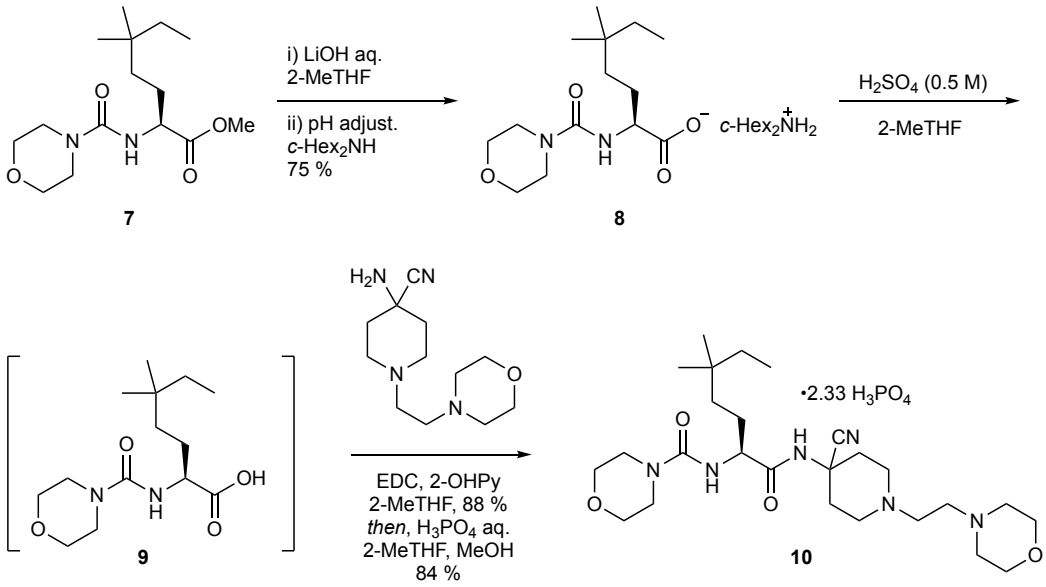
Scheme 5 Synthesis of [2.2.2]oct-5-en-2-one, **2**

2-MeTHF has become heavily utilised within industry with many process routes towards the synthesis of pharmaceuticals utilising the bio-based solvent. In the route development of candidate drug **6** for the treatment of depression and anxiety, researchers at GlaxoSmithKline (GSK) found that solvent selection played a key role in the *O*-acylation of phenol **3** (Scheme 6).[69] They identified that the use of ethereal solvents was integral in the suppression of an undesired cyclisation which facilitated the synthesis of functionalised benzofuran **4**. Both THF and 2-MeTHF were screened in the transformation with 2-MeTHF being selected due to a comparatively easier extraction process, streamlining the synthesis of intermediate product **5**.



Scheme 6 Solvent effects of the *O*-acylation of phenol **3**

Another pertinent example of the use of 2-MeTHF is in the large scale synthesis of Cathepsin S inhibitor **10**, developed at Boehringer–Ingelheim (Scheme 7).[70] Upon saponification of methyl ester **7**, drying of the ethereal solvent layer facilitated precipitation of the racemate which could be filtered off and, following salting, delivered **8** in high optical purity. The isolated salt was then subjected to acidification and the organics dried *via* azeotropic distillation before **9** was exposed to the amide coupling conditions.

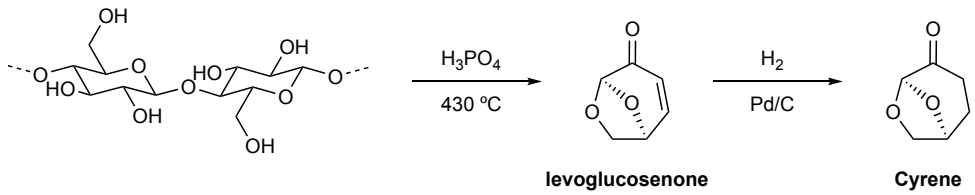


Scheme 7 Synthesis of Cathepsin S inhibitor **10**

1.2.2.3 Cyrene

Developed by Circa, dihydrolevoglucosenone (Cyrene™)[71] is a bio-based solvent which can be accessed from waste streams of cellulose utilising their novel Furacell™ technology.[72,73] The process is feedstock agnostic, able to tolerate multiple sources of lignocellulosic material (e.g. straw, bagasse), and has been designed to be energy neutral and sustainable. Cellulose is selectively converted to the platform molecule levoglucosenone in an acid catalysed pyrolysis, producing carbaceous char as the only waste product which can be used as fuel for the Furacell process (Scheme 8). Alternatively, the char may also be used as fertiliser as the use of a phosphoric acid catalyst produces a phosphorus rich material.

Following dehydration, levoglucosenone is then isolated *via* fractional distillation and hydrogenated to yield Cyrene.[73–75] Efforts are being made towards developing more sustainable hydrogenation conditions.[76] Optimisation has facilitated the development of solvent-free conditions, increasing the hydrogen pressure to combat slower reaction rates caused by low hydrogen solubility and poor catalyst diffusion.[74] Whilst the feedstocks and the products for this process satisfy Green Chemistry principles (i.e. renewable, benign and degradable), the requirement of high temperatures and pressures could be considered drawbacks. In addition, the use of non petroleum-based sources of hydrogen and alternative catalysts would need to be addressed.



Scheme 8 Synthesis of Cyrene *via* Furacell technology

Cyrene was first identified as a potential solvent by Clark *et al.* in 2014. Assessment of the physical properties of Cyrene was conducted using multiple calculations and evaluation of parameters (Table 2).[77] DFT/COSMO[78] was used to determine the σ-surface, depicting the charge density distribution of Cyrene which showed distinct dipoles in the molecule. The Kamlet–Taft parameters (KTP) were also obtained, which measure the hydrogen bond donating (α), and hydrogen bond accepting (β) abilities in addition to

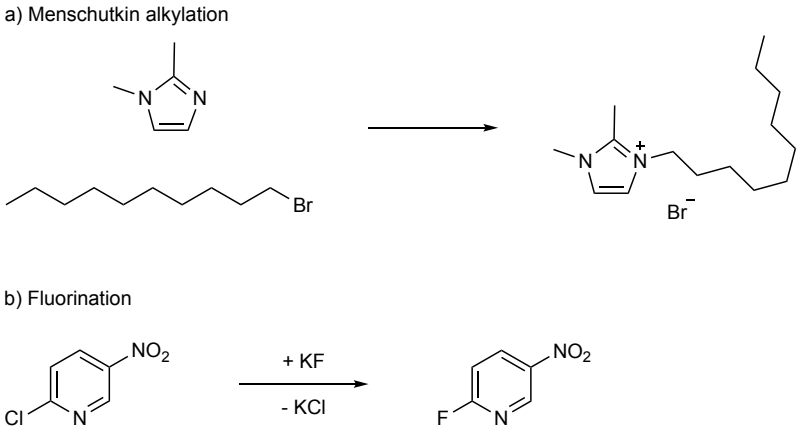
the dipolarity (π^*) of a solvent.[79] These figures indicate that Cyrene is aprotic with a dipolarity similar to those of traditional polar aprotic solvents. Additionally, the group calculated the Hansen solubility parameters (HSP) which predict how likely a solute will dissolve in a solvent based on three individual parameters; energy from dispersion forces (δ_D), energy from polar intermolecular forces (δ_P), and energy from intermolecular hydrogen bonding (δ_H).[80] The three values can be used as coordinates to place the solvent in the Hansen space. The closer two solvents are in this three-dimensional space, the more closely related they are, and therefore, are more likely to share the same solubilising properties.

Table 2 Physical properties of Cyrene and selected polar aprotic solvents

	Cyrene	**NMP**	**DMF**	**DMAc**	**DMSO**
α	0.00	0.00	0.00	0.00	0.00
β	0.61	0.75	0.71	0.73	0.74
π^*	0.93	0.90	0.88	0.85	1.00
δ_D/MPa$^{0.5}$	18.8	18.0	17.4	16.8	18.4
δ_p/MPa$^{0.5}$	10.6	12.3	13.7	11.5	16.4
δ_H/MPa$^{0.5}$	6.9	7.2	11.3	10.2	10.2
BP/ °C	203	202	153	165	189
ρ /g mL^{-1}	1.25	1.03	0.94	0.94	1.10

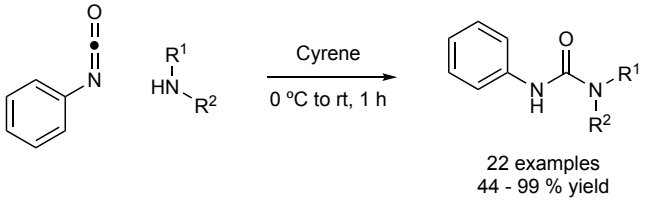
Based on these three parameters (DFT/COSMO, KTP, and HSP), it was determined that Cyrene is most closely related to NMP. To evaluate the solvent performance, Cyrene was employed in two substitution reactions; the Menschutkin alkylation[81] and fluorination of a heterocycle (Scheme 9). The Menschutkin alkylation proceeds *via* an S_N2 mechanism, with its rate found to depend heavily on the solvent type with protic solvents being

detrimental to the reaction.[82] As such, polar aprotic solvents are commonly employed. When the rates of the reaction in Cyrene were compared to those using conventional solvents, it was found that Cyrene performed comparatively, only being outperformed by solvents containing sulfur (e.g. DMSO). In the S_NAr reaction of 2-chloro-4-nitropyridine, it was found that Cyrene was able to facilitate the transformation, matching the performance of NMP.



Scheme 9 Initial evaluation of Cyrene in substitution reactions

Following these initial applications as a solvent in organic synthesis, Camp *et al*. reported the use of Cyrene in the synthesis of ureas (Scheme 10).[83] The reaction of isocyanates with amines is considered to be the most atom efficient method of producing ureas, adhering to green chemistry principles.[1] However, the use of DMF and chlorinated solvents in this process is prevalent[83] and leads to the use of excess solvents and the production of vast amounts of aqueous waste during purification. The procedure developed by Camp utilises precipitation as the method of isolation, negating the need for work-up solvents and minimising the volume of aqueous waste. Additionally, no further purification is needed, delivering methodology with increased molar efficiency when compared to the corresponding reaction carried out in DMF.



Scheme 10 Synthesis of ureas using Cyrene as reaction solvent

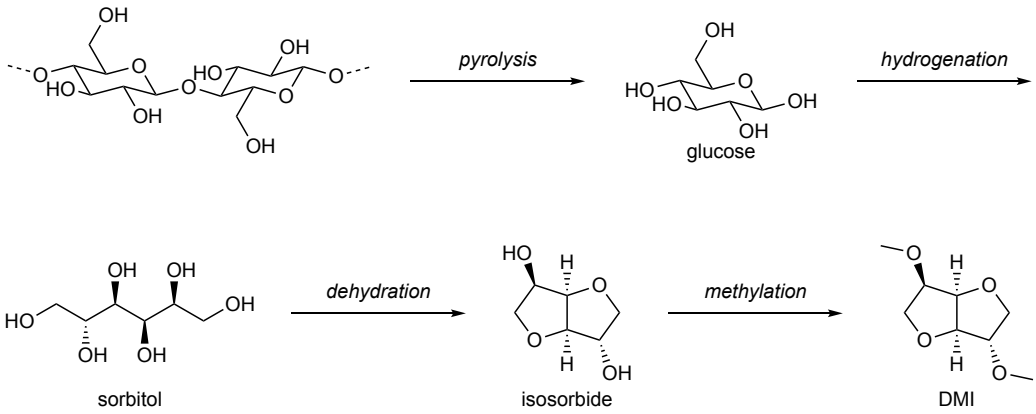
In addition to these organic transformations highlighted, which utilise Cyrene as an alternative reaction medium, it has also been applied in the synthesis of materials. Shuttleworth *et al*. demonstrate how the application of Cyrene can be advantageous in the synthesis of graphene, a nanocomposite with many potential applications.[84,85] The bulk processing of graphene is commonly carried out by liquid exfoliation, where graphite is dispersed in a solvent and briefly sonicated followed by centrifugation.[86] The solvent plays a key role in this process, affecting dispersion and concentration of the graphene obtained.[87] Traditional solvents (e.g. NMP and DMF) often deliver low yields of single layer graphene which can be overcome with increased sonication times. However, this often leads to deterioration in particle quality.

Initial studies to establish dispersion concentration of graphene gave exceptional results, with the concentration of dispersed graphene in Cyrene found to be 0.24 mg/mL (*c.f.* NMP 0.018 mg/mL). Improvement on this initial concentration to 0.70 mg/mL could be made by increasing the sonication time. The graphene flakes produced were thinner and larger than those made using NMP and additionally displayed fewer defects. These improved characteristics were proposed to be due to the higher viscosity of Cyrene which has a positive effect on stabilising and preserving the integrity of graphene flakes when using ultrasound processing.[84]

Cyrene has also been utilised in the synthesis of metal-organic-frameworks (MOFs), porous materials consisting of metal nodes joined *via* organic linkers.[88] Katz *et al*. were able to demonstrate the use of Cyrene in the synthesis of a range of MOFs with larger particle sizes observed compared to those synthesised in DMF.[89]

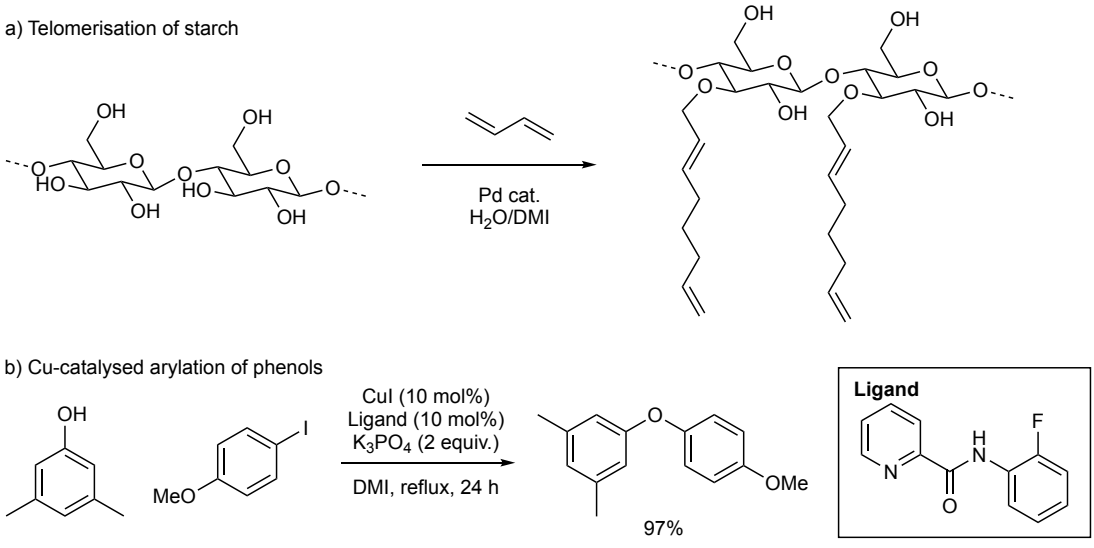
1.2.2.4 Dimethyl Isosorbide

Dimethyl isosorbide (DMI) is a sugar-derived solvent with established application in the formulation of cosmetics and pharmaceuticals.[90–94] The general synthesis involves pyrolysis of cellulose to glucose followed by hydrogenation to sorbitol (Scheme 11).[95] Dehydration of this platform molecule yields isosorbide which is then methylated to give DMI.[96–98] A method to directly access isosorbide from cellulose has also been developed.[99]



Scheme 11 General synthesis of DMI from cellulose

Despite the solubilising properties and polarity of DMI, its use as a solvent is yet to be investigated fully. Exploratory research has been carried out into the role of DMI as a co-solvent in the modification of starch *via* a process called telomerisation (Scheme 12a)[100] and also in epoxidation reactions.[101] Additionally, DMI was included in an extensive screen of green solvents for the Cu-catalysed arylation of phenols (Scheme 12b).[102] However, DMI was not selected for investigation of the substrate scope of this process.



Scheme 12 a) Telomerisation of starch. b) Cu-catalysed arylation of a phenol derivative

1.3 Solvent Use within the Pharmaceutical Industry

Collectively, the pharmaceutical and agrochemical industries are the second largest consumer of solvents in Europe (Figure 2).[13] Typically, in medicinal chemistry, solvent constitutes greater than 50% of mass input of the total materials used in the synthesis of active pharmaceutical ingredients (APIs),[103] with GSK estimating their solvent use in a manufacturing process as 80–90%.[104]

The vast range of chemical reactions and variety of materials used within the design and synthesis of small molecules requires the use of a diverse set of solvents.[105–109] GSK report that alcohols and aromatics constituted 50% of their solvent usage, with polar aprotics making up a further 6%.[110] A subsequent study to determine the trends of solvent usage within the literature, surveyed 388 papers published between 1997 and 2012 within *Organic Process Research and Development* (OPRD).[111] The data showed that DCM was the most commonly used solvent of concern, followed by acetonitrile (MeCN) which, with the remaining polar aprotics, account for greater than 50% of usage.

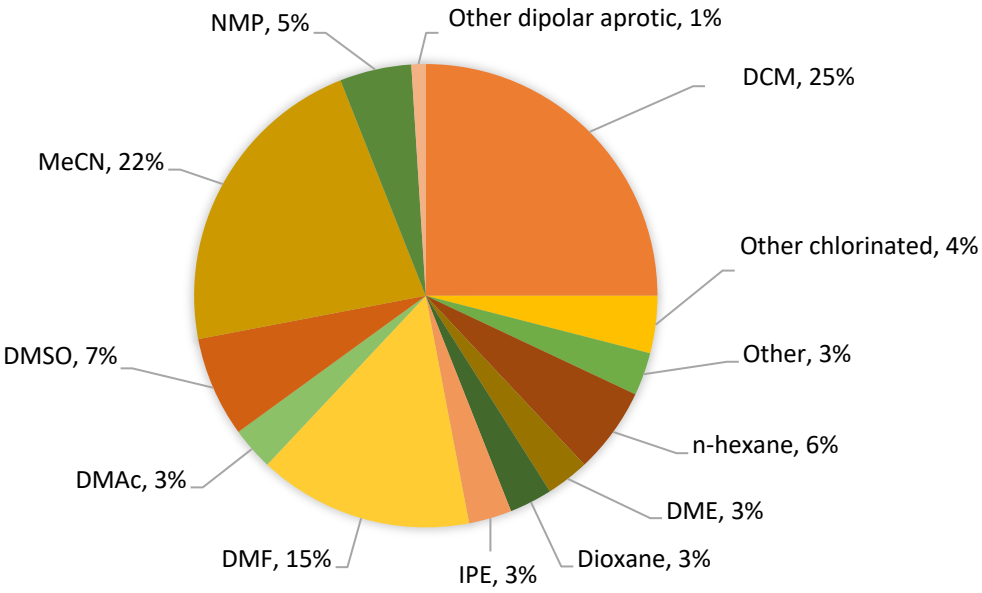


Figure 5 Survey of usage of solvents of concern

Dipolar aprotic solvents are indispensable to the pharmaceutical industry due to their polarity which, for example, aids in stabilising intermediates of S_NAr and S_N2 reactions, thus increasing the reaction rate.[112] Their solubilising properties also make them

important solvents for reactions involving highly polar compounds and the synthesis of peptides. An in-depth survey of the use of polar aprotics by Wells *et al.* showed that MeCN was most commonly used, followed by DMF.[111] Whilst the use of these two solvents was consistent across the years surveyed, the frequency of NMP use has increased. Evaluation of the combined values for the applications of DMF, DMAc, NMP and DMSO showed that nucleophilic substitution reactions (SN RXN) accounted for 47% of use and further 37% for other, solubility related issues (Figure 6).

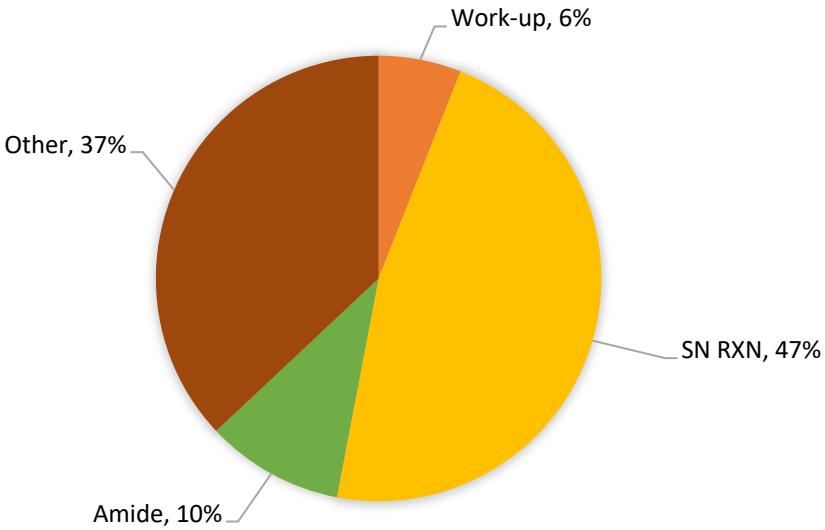


Figure 6 Combined use of DMF, NMP, DMAc and DMSO

1.4 Approaches Towards Solvent Substitution

Due to the significant volumes of solvents used for drug development, from discovery phase to process and manufacturing scales, solvent use has fallen under strict scrutiny within the pharmaceutical industry.[104,113–115] Main themes within this area are the reduction of solvents used during purification of intermediates and cleaning of reactors, and a higher occurrence of solvent recycling to reduce emissions caused by incineration. The replacement of harmful solvents to those which are more benign is also a key focus, particularly with regards to polar aprotic solvents such as DMF and NMP. Increased awareness of solvent replacement strategies and their implementation at the early stages of route design, in addition to the development of neoteric solvents which meet the needs

of chemical reactivity and health and safety, are highlighted as important approaches towards these goals.[116–118]

1.4.1 Solvent Selection and Direct Replacement

General solvent selection guides are designed to encourage practitioners to make incremental steps towards the design of more sustainable processes, by being able to assess their reaction manifolds and identify potentially problematic solvents. The reports detail which solvents pharmaceutical companies find favourable or unfavourable based on the evaluation of safety, health and environmental (SHE) considerations, with some guides also factoring operational costs and life cycle analysis (Table 3).

Table 3 Factors considered in the development of solvent selection guides

Year	Organisation	Factors considered
1999	GSK	Waste, environmental impact, health, safety[119]
2005	GSK	Waste, environmental impact, health, safety, LCA[120]
2008	Pfizer	Environmental/regulatory considerations, worker safety[121]
2011	GSK	Waste, environmental impact, health, safety, LCA, flammability/explosion, reactivity/stability, legislation flag, physical properties[122]
2013	Sanofi	Environmental hazard bands, health, safety, physical properties, water miscibility, source, industrial/legal constraints, ICH limits, biodegradability, persistence, cost[123]
2016	CHEM21	Health, H-index, ICH limits, safety (incl. process safety), physical properties[124]
2016	GSK	Waste, environmental impact, health, safety, LCA, flammability/explosion, reactivity/stability, legislation flag, physical properties[125]

The approaches to the development of the guides are broadly similar and, as expected, perspective evolves with the publication of new information and metrics allowing more detailed analysis of the sustainability credentials of a given solvent. The first publication of a solvent selection guide was in 1999 by GSK who ranked the solvents in four areas; waste, environmental impact, health, and safety.[119] Each score for these factors was based on the assessment of different criteria such as incineration (waste), recyclability (waste), acute and chronic health effects (health) and exposure limits (safety). Subsequent publications in 2005 and 2011 included a full life cycle analysis (LCA), which assesses the sustainability of a solvent from cradle-to-gate, and also expanded the number of solvents in the study.[120,122] Further embellishment by GSK was published in 2016 which added a further 44 solvents to the study and employed new methods of assessment.[125]

Pfizer's approach to solvent selection is directed more towards medicinal chemists, classifying the solvents into preferred, usable and undesirable and offering advice on suitable substitutions when available.[121] Sanofi also offer a similar, colour based ranking in addition to ID cards for each solvent which summarises the properties of the individual solvent and presents advice where substitution is advised.[123]

In an effort to collate the data published independently by each company, CHEM21 – a working group consisting of members of the European pharmaceutical industries and universities – also published an in-depth solvent guide.[124] The extensive study covers many aspects including process safety (e.g. flammability, flash point), ICH limits, physical properties, environmental impact (e.g. aquatic toxicity, bioaccumulation, VOC generation), and health criteria. In addition to more traditional solvents, this study also evaluates less common and neoteric solvents. However, a complete data set is not yet available for some new solvents which have thus been ranked as problematic.

An approach by AstraZeneca (AZ) aims to address the approach of solvent shortlisting based solely on SHE aspects and not accounting for the purpose and functionality of a solvent.[126] It has long been established that solvent properties have a great influence over the kinetics and success of a reaction and, as such, AZ have developed an interactive tool which presents the user with a selection of solvents based on molecular properties and behaviours (e.g. polarity, solvent-solute interactions etc.). Banned and restricted solvents

such as benzene and HMPA are included as reference points. The user is then able to filter these solvents based on physical properties, and SHE aspects.

1.4.2 Targeted Solvent Replacement Strategies

Despite ready availability of guidance materials and the clear advantages of adopting green chemistry practices within drug discovery, uptake is slower than in process chemistry and manufacturing. This is due to key differences within the roles of these departments. Medicinal chemistry is reliant on the high-throughput preparation of a structurally diverse library, whereas process and manufacturing lead focused optimisation of the synthesis of a specific target molecule to reduce cost and waste – principles which align with those of green chemistry. As such, where solvent selection is considered, medicinal chemists will often employ conventional solvents which are most commonly encountered within the literature. Targeted solvent substitution initiatives provide an in-depth study into solvent alternatives for a specific function. This is beneficial for medicinal chemists as little or no optimisation would be necessary, allowing rapid access to sustainable and divergent syntheses.

1.4.2.1 Chromatography

The largest component of the waste stream from medicinal chemistry is the spent solvent from chromatographic purification. Generally, synthetic chemists rely on two binary solvent systems; ethyl acetate (EtOAc)/alkanes, and MeOH/DCM, the latter solvent system causing safety concerns due to the carcinogenic properties of DCM.[127] Efforts have been made towards addressing the sustainability issues associated with chromatography in the form of targeted solvent selection guides, which provide direct alternatives for the MeOH/DCM system.

The first approach was published by researchers at Amgen, who evaluated 26 drug-like compounds to produce an accessible guide.[128] Using heptane as their bulk medium, they identified a 3:1 EtOAc:EtOH solvent mix could be employed as the modifying solvent to achieve good separation of compounds. Tailing and streaking of non-neutral compounds

could be stemmed using a suitable additive. Comparison of the 3:1 EtOAc:EtOH/heptane system with MeOH/DCM at varying concentrations is presented on an easy-to-follow scale.

Another study from our own laboratories focused on directly substituting DCM as the bulk media in a binary solvent system with the expectation that this would encourage a broader adoption by medicinal chemists.[129] The library of selected compounds included 74 fragment-like compounds and a further 21 drug-related structures, encompassing a broad range of functionality and properties. CPME, TBME, 2-MeTHF, dimethylcarbonate (DMC), and EtOAc (with *i*-PrOH) were all screened as alternative bulk media and their performance as an eluent system evaluated by comparing the range of R_f values. CPME was found to give a wider range of R_f values with more even distribution, indicating that MeOH/CPME systems would provide suitable separations.

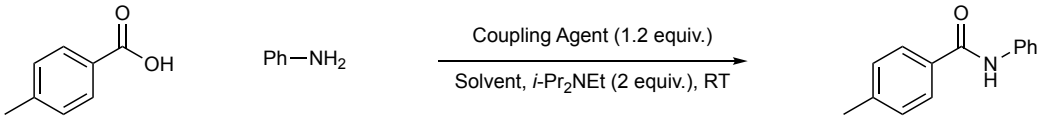
1.4.2.2 Synthetic Transformations

A further contribution from our own laboratories consisted of a comprehensive study of amide bond formation which evaluated a number of commonly employed coupling reagents using alternative solvents in addition to benchmark solvents such as DMF and DCM (Figure 7).[130] The investigation monitored four representative coupling reactions, establishing rate of conversion for each transformation and finding that, across the range of reactions, EtOAc and DMC (with COMU as the coupling reagent) performed comparably to DMF and DCM. A similar approach was undertaken in the evaluation of reductive amination.[131] The group surveyed 12 representative reactions with examples from each class of amine, in addition to alkyl and aryl aldehydes, using three reducing agents and 10 solvents. It was found that $NaBH(OAc)_3$ was more amenable to solvent exchange, with conventional solvents such as DCM, DCE and DMF being readily replaced by EtOAc.

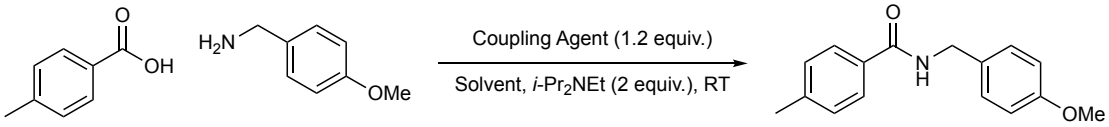
Amide Coupling Reagents	Solvents	
COMU	*tert*-Burty methyl ether (TBME)	*N,N*-Dimethylformamide
DIC/HOBt	Cyclopentyl methyl ether (CPME)	Ethyl acetate (EtOAc)
HATU	Dichloromethane (DCM)	*iso*-Propyl alcohol (*i*-PrOH)
PyBOP	Dimethylcarbonate (DMC)	2-Methyl tetrahydrofuran (2-MeTHF)
T3P		

Representative Reactions

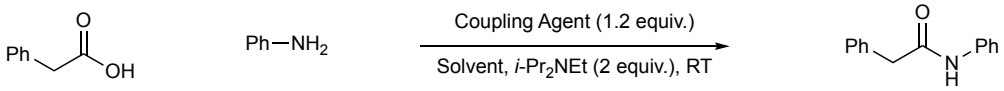
Reaction 1: Aryl Acid - Aryl amine



Reaction 2: Aryl Acid - Alkyl amine



Reaction 3: Alkyl Acid - Aryl amine



Reaction 4: Alkyl Acid - Alkyl amine

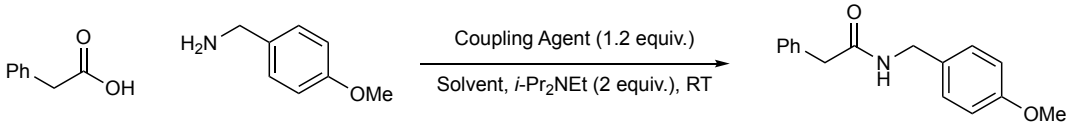


Figure 7 Coupling reagents, solvents and representative reactions employed in the 2013 study of amide bond formation by Watson *et al.*

Additionally, solvent use within olefin metathesis has also been examined.[132] Olefin metathesis is an important tool for the installation of double bonds, and frequently relies on the use of solvents of concern such as DCM and toluene. The study aims to provide guidance on catalyst and solvent selection within both ring closing metathesis (RCM) and cross-metathesis (CM). Carbonates, EtOAc and DMC proved to be viable alternatives in RCM, demonstrating high conversion and selectivity. Low conversions were recorded for the CM transformation. However, these were in agreement with the corresponding conversions in benchmark solvents toluene and DCM.

1.4.2.3 Solid Phase Synthesis

Solid Phase Peptide Synthesis (SPPS) has also been subjected to extensive investigation, with the groups of Albericio and de la Torre leading these studies.[133–135] SPPS is typified by its use of excess solvents, with large volumes being used for multiple washings, deprotection and coupling steps (Figure 8). Furthermore, the solvents conventionally used in this process - NMP, DMF, DCM - are solvents of concern. The first publication established the solubility of common coupling reagents and amino acid derivatives in 2-MeTHF and CPME and additionally addressed the solvents ability to swell resin in comparison to traditional solvents.[133] Following these investigations the group were able to screen coupling conditions in both, liquid and solid phase synthesis, finding that 2-MeTHF and CPME could be successfully employed in DIC-mediated coupling methods.

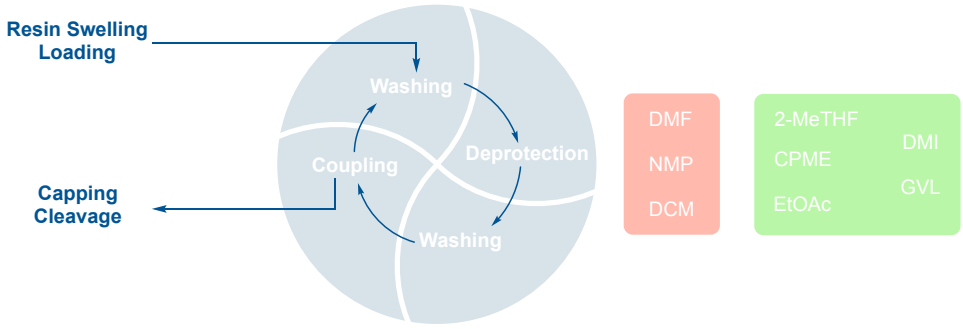


Figure 8 General summary of SPPS, conventional solvents (red) and alternative solvents (green)

Further to this, the groups addressed the washing and deprotection steps of the procedure, surveying different solvents (*i*-PrOH, EtOAc, 2-MeTHF).[135] It was found that these steps could be carried out using 2-MeTHF, with additional EtOAc washes, although elevated temperatures were required for the coupling and deprotection steps to ensure more efficient synthesis. As the removal of the Fmoc protecting group proved to be challenging, a thorough study of this deprotection step was conducted.[135] A wide ranging solvent screen, including many neoteric solvents such as GVL and DMI, was carried out. Resin swelling properties and solubility testing of a full range of Fmoc-protected amino acids was first established, followed by the evaluation of the deprotection step. They were able to demonstrate that GVL performed comparably with DMF, and additionally was

superior to 2-MeTHF, in the swelling of both tested resins and in the removal of the Fmoc group.

An extensive study within the area of solid phase synthesis has also been carried out by researchers at the University of York.[136] However, focus was placed upon the investigation of the swelling properties of 25 green solvents in comparison to the established solvents. Nine resins were screened, with many of the alternative solvents outperforming benchmark solvents such as NMP, DMF and DCM. For example, 2-MeTHF and DMI proved to be good general solvents for the swelling of many commercial resins such as Merrifield and ParaMax resins. The use of 2-MeTHF was then demonstrated within the solid-supported Ugi reaction, and compared with the analogous MeOH-based reaction, with 2-MeTHF delivering the amide product in higher yields.

2 Project Background and Aims

As stated above, the replacement of polar aprotic solvents is a recurring theme within the pharmaceutical and fine chemical industries due to the health issues they pose and the enforcement of increasingly stringent regulations (Section 1.1.3 Solvent Regulation and Solvents of Concern). Direct substitution of this class of solvent has proven difficult due to the unique physical and solubilisation properties they possess. Subsequently, the development of neoteric solvents to fulfil the roles of these problematic solvents has become an important area of research.

Many initiatives involved in the search for alternative solvents also aim to address key sustainability issues, utilising renewable sources and developing products which are inherently benign to both human health and the environment (Section 1.2.2 Bio-Based Alternative Solvents). Sustainable solvents are often limited by production scale and cost which are both factors influenced by commercialisation and increased uptake.

As previously discussed, it is often difficult to encourage the uptake of unconventional solvents within medicinal chemistry (Section 1.4.2 Targeted Solvent Replacement Strategies). This is due to the divergent nature of the syntheses performed, and time constraints which precludes solvent optimisation.[109] Reaction specific exploration utilising new solvents, such as the studies conducted in GVL, is beneficial in demonstrating the capabilities of the reaction media and often provides insight into the handling and reactivity of such solvents.

The bio-based solvents Cyrene and DMI both exhibit solvation properties similar to those of DMF and NMP (Figure 9). Additionally, these solvents display low toxicity, are non-mutagenic and have fewer associated environmental issues. As yet, Cyrene and DMI have found limited application in synthetic organic chemistry, prompting the investigation which is the subject of the current study. With a view to encourage the use of these solvents within the pharmaceutical industry, particularly in the discovery phase of drug development, we sought to evaluate their capacity in transformations which would traditionally require the use of polar aprotic media and were relevant to medicinal chemists.

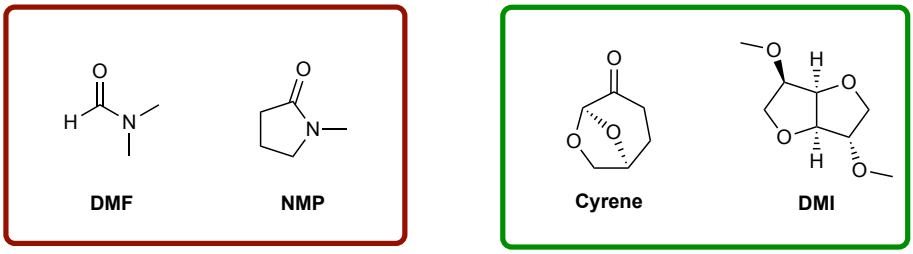


Figure 9 Cyrene and DMI as possible alternatives for DMF and NMP

The transformations were selected based upon published data sets from industry and surveys of reaction classes within the literature (Table 4).[105–107,109] Amide bond formation *via* acylation was consistently identified as a high frequency reaction. This is unsurprising due to the ubiquitous nature of the amide functionality within drug compounds. Indeed, from the data set presented by Roughley and Jordan, 55% of compounds contained the functionality.[107] This is consistent with figures published using the AZ IBEX database by Brown and Boström.[106]

C–C bond formation was also highlighted as a common transformation, with Pd catalysed cross-coupling reactions featuring heavily in the analyses. The modular approach of cross-coupling is suited for high throughput chemistry allowing for efficient, divergent syntheses. Of these reactions, the Suzuki–Miyaura (SM) cross-coupling reaction is most frequently utilised, providing access to important biaryl fragments which were found to occur in 39% of test compounds (Roughley and Jordan).[107] Another notable C–C bond forming reaction reported is the Sonogashira reaction. Although the products of this transformation do not generally feature within drug compounds, internal alkynes provide principal intermediates for further synthetic transformation.[137]

Table 4 Summary of analyses of common reaction classes

Year	Method	Notable Observations
2006	Analysis of 128 drug candidate synthesis from AZ, GSK and Pfizer. 1039 transformations.[109]	Amide bond formation: 8% total reactions C–C bond formation: 11% total (2.5% total Pd catalysed)
2010	Analysis of 4800 array reactions within GSK. Limited discussion of reaction class.[105]	Pd catalysed coupling: 22% total reactions
2011	Analysis of 139 publications from AZ, GSK and Pfizer. 7315 reactions. 3566 test compounds. Reaction class and distribution of functionality analysed.[107]	Amide bond formation: 16% total reactions C–C bond formation: 12% • 40% SM (5% total) • 18% Sonogashira (2% total)
2016	Analysis of 125 *J. Med. Chem.* publications from 2014. Multiple occurrences of a reaction were not counted (n = 125).[106]	Amide bond formation occurred in 50% SPPS occurred in 7% SM occurred in 22% Amide bond formation and SM were most common production steps

These commonly employed procedures rely heavily on polar aprotic solvents to ensure reaction success and broad applicability within medicinal chemistry. As such, demonstrating the utility of Cyrene and DMI within these benchmark transformations would be anticipated to encourage the introduction of these novel solvents within the pharmaceutical industry and provide incremental steps towards the development of more sustainable processes in the research and development phase of drug discovery. The conditions must be accessible to medicinal chemists and suitable for divergent synthesis. Accordingly, commercial reagents and catalysts, and standard laboratory equipment will be used.

3 Results and Discussion

3.1 Cyrene as a Bio-Based Solvent in Organic Synthesis

The development of Cyrene has been discussed extensively in Section 1.2.2.3. Derived from waste streams of cellulose, Cyrene has been shown to be a viable alternative to polar aprotic solvents. In addition, the promising LCA aligns with green chemistry principles and sustainability initiatives of industry.[138]

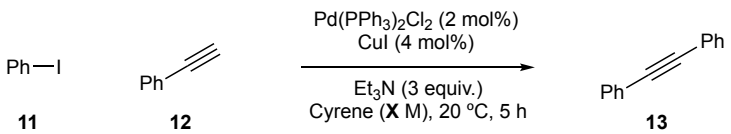
To investigate the application and limitations of Cyrene use within synthetic and medicinal chemistry three widely exemplified reactions – Sonogashira and SM cross-couplings, and amide bond formation – were selected for evaluation.

3.1.1 Investigation of Cyrene as an Alternative Solvent in the Sonogashira Cross-Coupling and Cacchi-Type Annulation Reactions

The Sonogashira reaction is an indispensable method of forming *sp*–*sp*^{2} bonds, and is used frequently within the pharmaceutical industry.[137,139] Although the products of this reaction are not commonly encountered within drug compounds, they are important intermediates for further synthesis, undergoing facile addition reactions to furnish prominent functional groups and heterocycles.[137]

To interrogate the utility of Cyrene within the context of Sonogashira cross-coupling we established a benchmark reaction using iodobenzene (**11**) and phenyl acetylene (**12**). A literature derived catalyst system was used ($Pd(PPh_3)_2Cl_2$/CuI), and the isolated yield of diphenylacetylene (**13**) obtained. Pleasingly, excellent yields were obtained at the onset of the study (Table 5, Entry 1) allowing the reaction to be run at higher concentrations (Entry 3), therefore reducing mass input.

Table 5 Effect of concentration on reaction yield

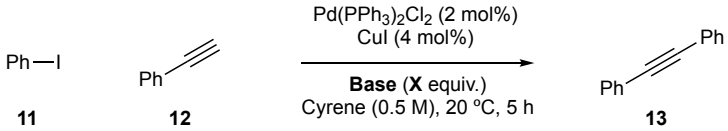


11 **12** **13**

Entry	Concentration (M)	Isolated Yield (%)
1	0.3	98
2	0.1	94
3	0.5	> 99

To further limit waste, we investigated the compatibility of different bases within this transformation (Table 6). The Sonogashira reaction requires the formation of a copper acetylide species *via* coordination of copper to, and deprotonation of, the acetylene moiety.[140] Pyridine failed to facilitate this transformation due to insufficient pK_a, and alternative organic bases offered no significant advantages over Et_3N, with which we were successfully able to limit the amount used with no erosion of yield observed (Entry 5). However, during this process, a potential limitation of Cyrene was identified. In the presence of inorganic bases such as K_3PO_4 and Cs_2CO_3 (Entries 1 and 2), we observed the formation of a solid precipitate from the reaction mixture. A full investigation of this anomaly is discussed in Section 3.1.2 (Investigation of Base Sensitivity).

Table 6 Effect of base on reaction yield



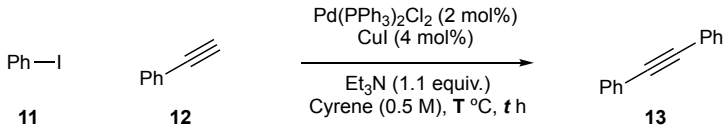
Entry	Base	Equivalents	Isolated Yield (%)
1	K_3PO_4	3	-
2	Cs_2CO_3	3	-
3	DIPEA	3	85
4	Pyridine	3	0
5	Et_3N	1.1	98

6	Et_3N	1.5	94
7	Et_3N	2	92

[a]Solidification of reaction mixture

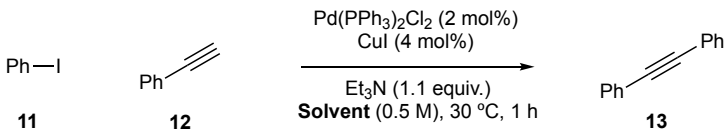
Following this, a short temperature and time study (Table 7) was carried out identifying that this transformation could be completed in one hour at a slightly elevated temperature of 30 °C (Entry 5). Furthermore, we were able to establish that the Cyrene-based system was superior when compared to using DMF or THF as the solvent system (Table 8).

Table 7 Effect of temperature and time on reaction yield



Entry	Temp. (°C)	Time (h)	Isolated Yield (%)
1	20	1	86
2	20	3	94
3	20	5	98
4	25	1	91
5	30	1	96

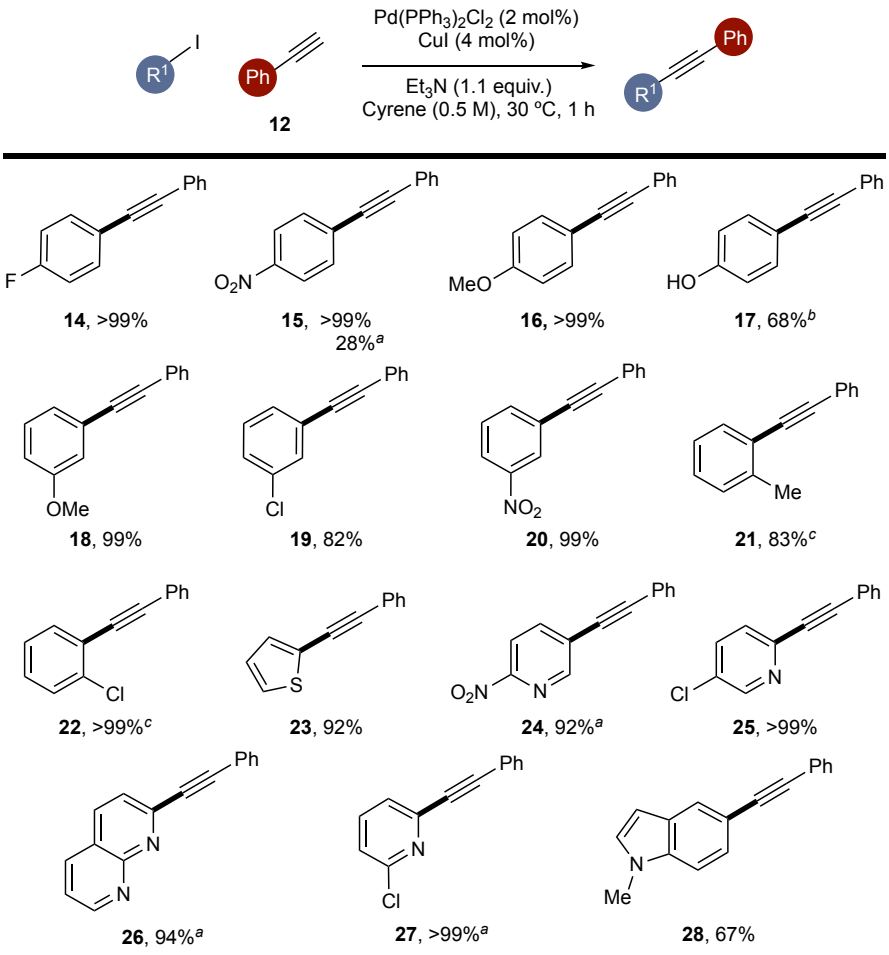
Table 8 Comparison of traditional solvents and Cyrene



Entry	Solvent	Isolated Yield (%)
1	Cyrene	96

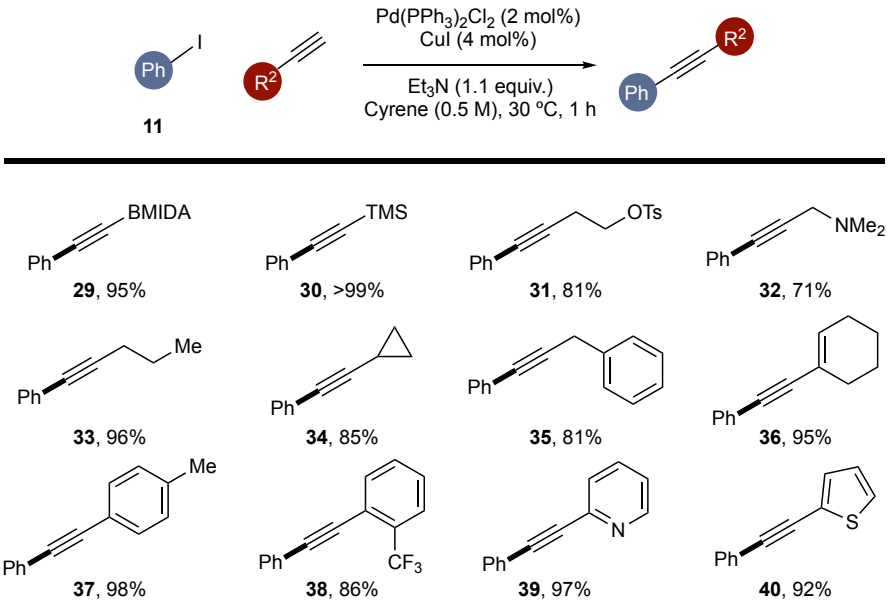
2	THF	81
3	DMF	87

With these optimised conditions in hand, we then sought to explore the scope of the reaction. Pleasingly, when applied to the coupling of a variety of aryl halides with phenylacetylene, the conditions developed utilising Cyrene displayed high generality (Scheme 13). A broad range of functionality could be accommodated on the aryl iodide ring including examples of both electron-withdrawing (e.g. **14**, **15**) and electron donating (e.g. **16**) groups, in addition to a variety of heteroaryl iodides (e.g. **23**, **25**), furnishing the corresponding coupled products in high yields. Additionally, electron-deficient heteroaromatic bromides were well tolerated (**24**, **26**, **27**). Notably, aryl rings bearing an *o*-substituent (**21**, **22**) required a longer reaction time.



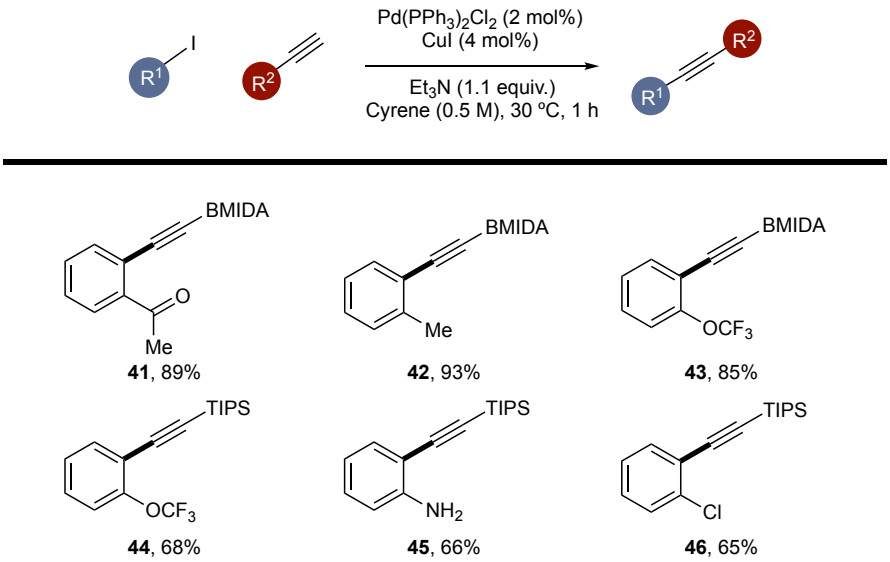
Scheme 13 Scope of the coupling of aryl halides with **12**. [a]Aryl bromide used. [b]2 equiv. Et_3N. [c]24 h reaction time

Furthermore, the conditions could facilitate the coupling of a wide range of terminal alkynes (Scheme 14). As expected, a range of functional groups were well tolerated with aliphatic (e.g. **33**, **34**) and aromatic substituents (e.g. **38**, **39**) undergoing coupling with high yields obtained. The substituents ranged in steric bulk and electronic properties. In addition, alkynes substituted with heteroatoms could also be coupled, such as ethynyl boronic acid, MIDA ester and ethynyltrimethylsilane, to furnish **29** and **30**, respectively, which are both important synthetic handles and can be manipulated in further reactions.



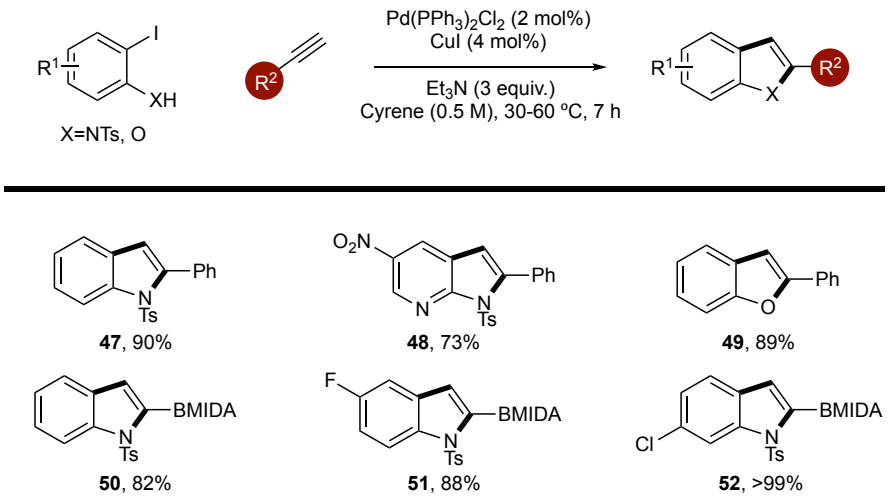
Scheme 14 Scope of the coupling of acetylenes with **11**

Although the coupling of *ortho*-substituted aryl halides with phenylacetylene had previously required extended reaction times, we found that this was not necessary when using other alkyne/*o*-substituted iodoarene combinations (Scheme 15) and we were subsequently able to synthesise a range of substrates bearing sterically encumbered functionality.



Scheme 15 Coupling of heteroatom-substituted alkynes with *o*-substituted aryl iodides

Subsequent to these studies, we sought to investigate the extension of this methodology in a one pot Sonogashira/annulation to access functionalised indole (e.g. **47**, **50**), azaindole (**48**) and benzofuran (**49**) cores. Indoles are important pharmacophores, present in many drug compounds and ranging in applications including analgesic, anti-inflammatory, antihistamine and anticancer treatments.[141] Indeed, the survey carried out by Roughley and Jordan revealed that the indole scaffold was present in 13% of compounds evaluated.[107] Likewise, benzofurans are a versatile scaffold utilised within drug discovery.[142] Through strategic selection of coupling partners, specifically *o*-amino or *o*-hydroxyl aryliodides, we could carry out the Sonogashira coupling followed by a 5-*endo*-dig cyclisation upon increasing the reaction temperature from 30 °C to 60 °C (Scheme 16). This streamlined procedure also accommodates the incorporation of a BMIDA group (**50**, **51**, **52**), furnishing pharmaceutically relevant scaffolds, suitable for divergent syntheses, with a functional handle in the 2-position which allows further derivatisation to be achieved.[143]



Scheme 16 Scope of one pot Sonogashira/Cacchi-type annulation

This study indicates that Cyrene is a promising alternative solvent for use in the Sonogashira reaction when used in conjunction with the compatible base Et_3N. Generality of the conditions were demonstrated, and the methodology could be used in the synthesis of pharmaceutically relevant moieties including indoles and azaindoles.

3.1.2 Investigation of Base Sensitivity

As discussed above, when carrying out the base screen for optimisation of the Sonogashira reaction (Section 3.1.1), a precipitate was observed, causing complete solidification of the reaction mixture and hindering the determination of yield (Table 6, Entries 1 and 2). Two products were isolated from the precipitate whose structures indicated that Cyrene participated in a homo-aldol condensation to give **53** which then underwent elimination to produce aldol adduct **54**. This structure was further confirmed by X-ray crystallography (Figure 10).

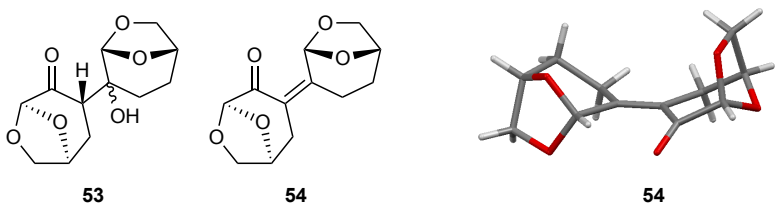


Figure 10 Aldol condensation and elimination products **53** and **54** and single X-ray structure of **54**

The formation of the dimer was not apparent when using Cyrene in the presence of alternative organic bases. Additionally, at the time, sensitivity towards bases was not noted by the manufacturers of Cyrene. As such, we surveyed a range of bases at various temperature to qualitatively evaluate the limitations of Cyrene under such conditions (Table 9). By carrying out ^{1}H NMR and TLC analysis, we were able to observe the formation of the aldol condensation products (e.g. Cs_2CO_3, Figure 11).

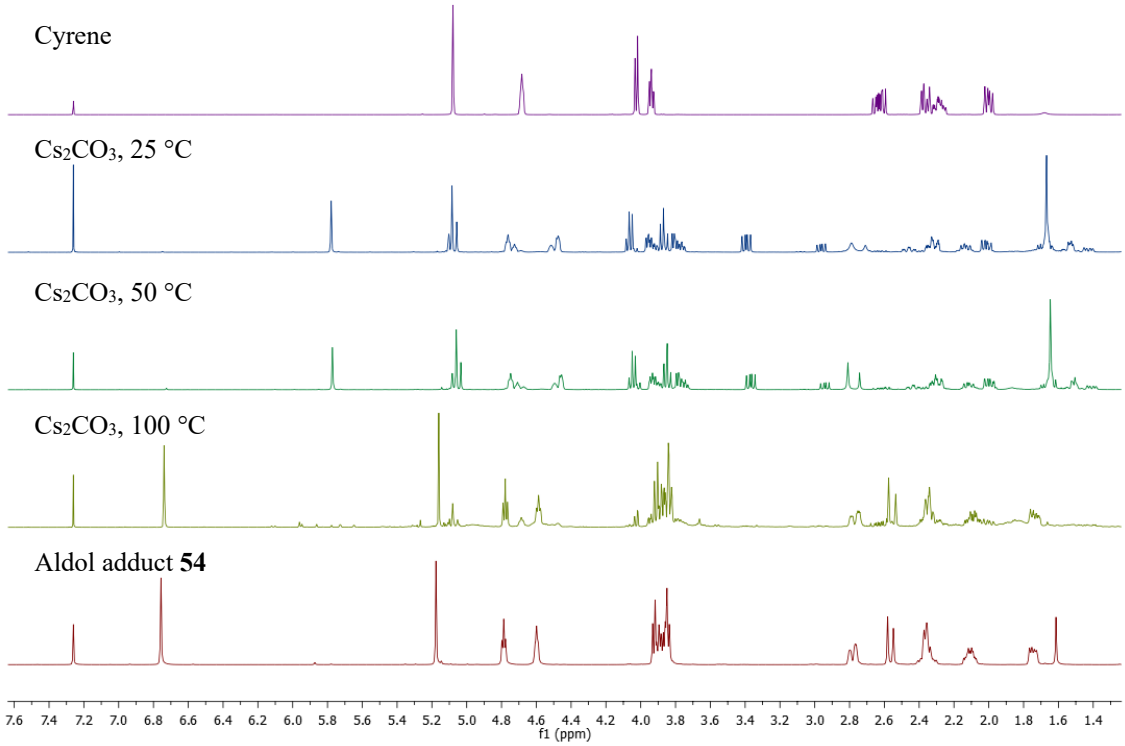


Figure 11 ^{1}H NMR spectra for reactions of Cs_2CO_3 at various temperatures

The study established that Cyrene exhibited a clear sensitivity towards bases, forming the aldol adduct in the presence of all those tested with the exception of DIPEA and Et_3N (Entries 4 and 6, respectively) at temperatures above 25 °C. Additionally, KOAc (Entry 1) was the only inorganic base to not effect dimerization at room temperature. The extent of the reaction and influence on the state of the mixture varied from gelation to complete solidification. However, we were able to identify that bases such as Et_3N and DIPEA under mild reaction temperatures were compatible with Cyrene.

Table 9 Qualitative evaluation of the base sensitivity exhibited by Cyrene

Entry	Base	pK_a	Temp (°C)	Reaction (Y/N)[a]
1	KOAc	4.8	25	N
			50	Y
			100	Y
2	Pyridine	5.2	25	N
			50	Y
			100	Y
3	K_2CO_3	10.3	25	Y
			50	Y
			100	Y
4	DIPEA	10.8	25	N
			50	N
			100	Y
5	Cs_2CO_3	10.3	25	Y
			50	Y
			100	Y
6	Et_3N	10.6	25	N
			50	N
			100	Y
7	K_3PO_4	12.7	25	Y

			50	Y
			100	Y
8	DBU	12	25	Y
			50	Y
			100	Y
9	KOH	14.2	25	Y
			50	Y
			100	Y
10	^{t}BuOK	17.0	25	Y
			50	Y
			100	Y
11	NaH	37	25	Y
			50	Y
			100	Y

[a]Analysis by TLC and ^{1}H NMR

As discussed, it is believed that the formation of dimer **54** proceeds *via* an aldol condensation followed by elimination of water to form the alkene. From analysis of the data in Table 9, it is evident that the driving force of this process is not based solely upon pK_a of the base. For example, K_2CO_3, Cs_2CO_3, Et_3N and DIPEA all have similar pK_as, however, their reactivity with regards to dimer formation differs. Inorganic bases, such as K_2CO_3, Cs_2CO_3 and K_3PO_4, are hygroscopic and, therefore, proficient desiccants, readily forming the corresponding hydrates.[144] It is thought that this property facilitates the sequestering of water and therefore drives the forward elimination reaction. With

bases of higher pK_a or at higher temperature the kinetic and thermodynamic effects of these factors is sufficient to prevent the retro-aldol reaction.

Overall, this study has highlighted a key limitation of Cyrene and has established parameters for the base compatibility of this alternative solvent. Bases are ubiquitous throughout synthetic organic chemistry and as such, the base sensitivity is an issue which must be considered when using this solvent.

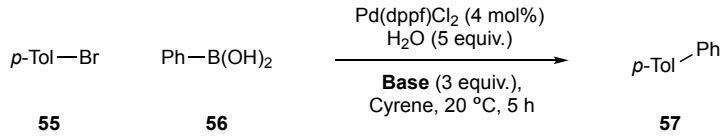
3.1.3 Investigation of Cyrene as an Alternative Solvent in the Suzuki–Miyaura Cross-Coupling

The SM cross-coupling is the most prolifically used Pd-catalysed reaction within the pharmaceutical industry.[106,107,145,146] Its prominence is largely due to the robust nature of the methodology and the ready availability of the stable chemical building blocks and catalysts. In addition, the biaryl products provide useful vectors for the exploration of chemical space. This is evident in the increased presence of these motifs within the development of drug compounds.[107]

The use of inorganic bases such as K_3PO_4, K_2CO_3 and Cs_2CO_3 is commonplace within this procedure as they readily facilitate the generation of hydroxide, which is essential for the turn-over of both possible catalytic pathways.[147,148] Given the base sensitivity exhibited by Cyrene, the formation of adduct **54** would be unavoidable and, as such, it would be necessary to develop conditions which would negate the effects of the aldol adduct precipitate.

Initial investigations began with a screen of bases (Table 10). As expected, inorganic bases produced large amounts of aldol adduct **54** causing the solidification of reaction mixtures using K_3PO_4 and K_2CO_3 (Entries 1 and 2) and gelation using Cs_2CO_3 (Entry 3). Et_3N (Entry 4), milder inorganic bases (Entries 6, 7, and 8) failed to give high yield and in addition, utilising a fluoride source (KF, Entry 5) also resulted in poor isolated yield. We selected to continue the investigations using Cs_2CO_3 as high product formation was observed. However, the production of dimer caused large inconsistencies in the yields obtained and the levels of precipitation varied.

Table 10 Effect of base on reaction yield



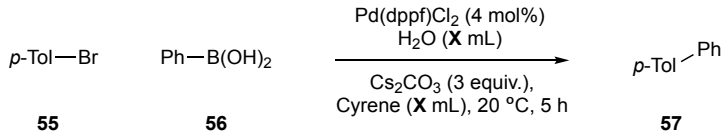
55 **56** **57**

Entry	Base	Isolated Yield μ ± σ (%)[a]
1	K_3PO_4	-[b]
2	K_2CO_3	-[b]
3	Cs_2CO_3	82 ± 16
4	Et_3N	13 ± 3
5	KF	7
6	KOAc	1
7	Na_3PO_4	1
8	Na_2CO_3	1

[a] Yield given as the mean and standard deviation of four reactions [b]Solidification of reaction mixture

The effect of water at a fixed (Table 11), and variable (Table 12) overall concentration was then carried out. From these studies, it was possible to establish that the water/Cyrene ratio and dilution played an important role in the process. High dilution with organic solvent was detrimental to the reaction (Table 11, Entries 1-6), with yield only improving when the concentration of Cyrene neared 0.25M. Additionally, it was established that large volumes of water could be accommodated in this procedure and, whilst this did not improve consistency of the isolated yield, it improved homogeneity of the reaction mixture (Table 12). As such, these co-solvent levels of water (Entry 10) were employed in further optimisation reactions.

Table 11 Fixed concentration (0.125 M) study of the effect of water on reaction yield

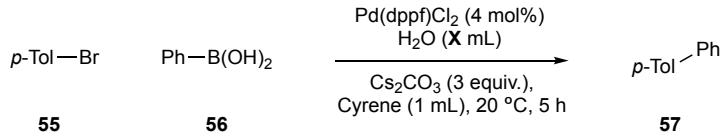


55 **56** **57**

Entry	H_2O volume (mL)	Cyrene volume (mL)	Isolated yield μ ± σ (%)[a]
1	0	2	-[b]
2	0.02	1.98	-[b]
3	0.05	1.95	-[b]
4	0.09	1.91	5 ± 0
5	0.23	1.77	6 ± 1
6	0.45	1.55	12 ± 2
7	0.9	1.1	34 ± 1
8	1	1	61 ± 35
9	1.35	0.65	58 ± 1
10	1.8	0.2	31 ± 0

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture

Table 12 Variable concentration study on the effect of water on reaction yield



55 **56** **57**

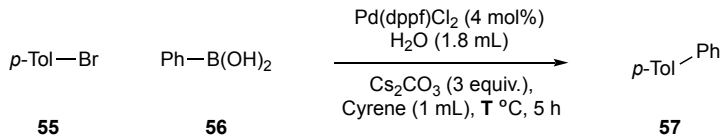
Entry	H_2O volume (mL)	Total volume (mL)	Concentration (M)	Isolated yield μ ± σ (%)[a]
1	0	1.00	0.250	-[b]

2	0.02	1.02	0.245	82 ± 16
3	0.05	1.05	0.238	21 ± 4
4	0.09	1.09	0.229	41 ± 26
5	0.23	1.23	0.203	37 ± 21
6	0.45	1.45	0.172	41 ± 27
7	0.9	1.90	0.132	57 ± 30
8	1	2.00	0.125	66 ± 28
9	1.35	2.35	0.106	72 ± 15
10	1.8	2.80	0.089	81 ± 15

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture

The effect of temperature was next investigated (Table 13). When using water as an additive (5 equiv.), we observed complete solidification of the reaction mixture at elevated temperatures (Entry 1). However, at co-solvent levels, we found the reaction mixture was more amenable, facilitating the transformation in high isolated yields and allowing for increased temperatures, which improved consistency of the data obtained (Entry 4).

Table 13 Effect of temperature on reaction yield

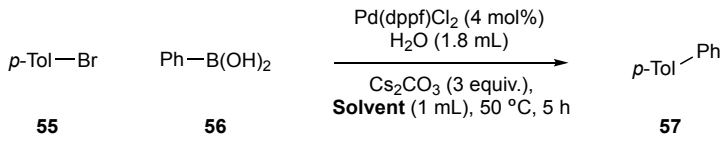


Entry	Temperature (°C)	Isolated yield (%)[a]
1	30	-[b,c]
2	20	81 ± 15
3	30	80 ± 12
4	50	94 ± 5

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture. [c] Cyrene (1 mL), H_2O (5 equiv.)

The performance of Cyrene against more conventional solvents used in the SM reaction was also evaluated (Table 14). Under equivalent reaction conditions we found that Cyrene delivered comparable yields to those obtained using THF, DMF and 1,4-dioxane (Entries 2, 3 and 4). Additionally, it was established that the absence of an organic solvent was detrimental to the reaction (Entry 5) due to reduced solubility of reaction components.

Table 14 Comparison of traditional solvents and Cyrene

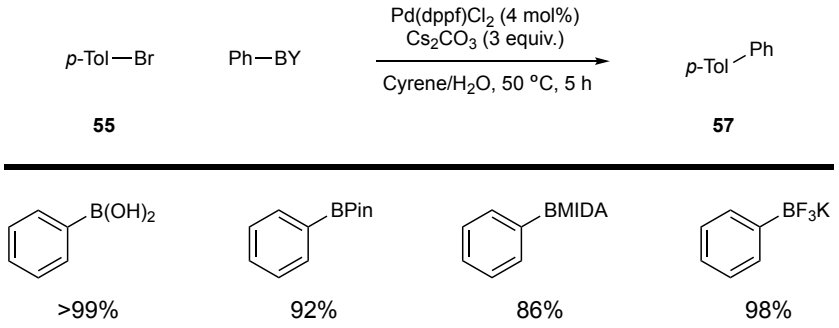


55 **56** **57**

Entry	Solvent	Isolated yield (%)
1	Cyrene	94 ± 5[a]
2	THF	92
3	DMF	98
4	1,4-Dioxane	>99
5	H_2O	31

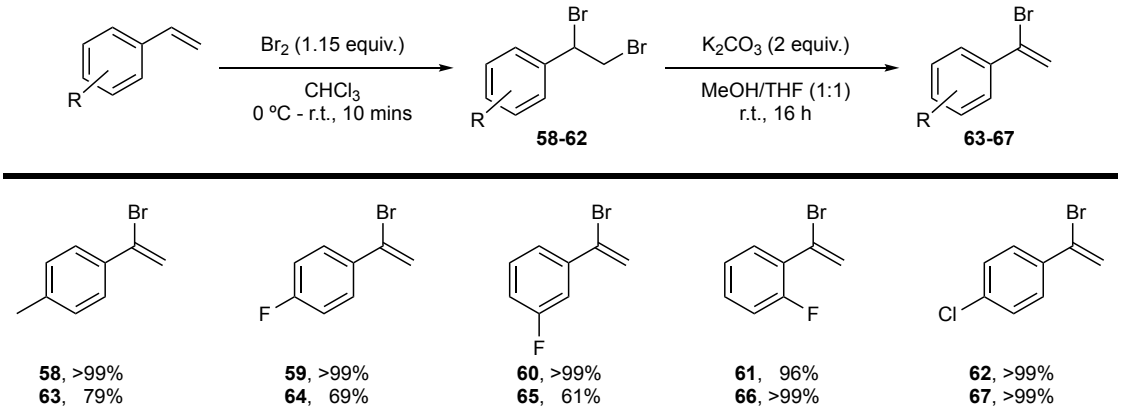
[a] Yield given as the mean and standard deviation of four reactions

The optimised conditions were then applied to investigating the tolerance of routinely utilised organoboron species within the SM coupling (Scheme 17). Cyrene was effective in the coupling of 4-bromotoluene with phenyl boronic acid and phenyl boronic acid pinacol ester (BPin). In addition, protected boron species requiring a hydrolysis event (i.e. BMIDA and BF_3K), could also be accommodated.



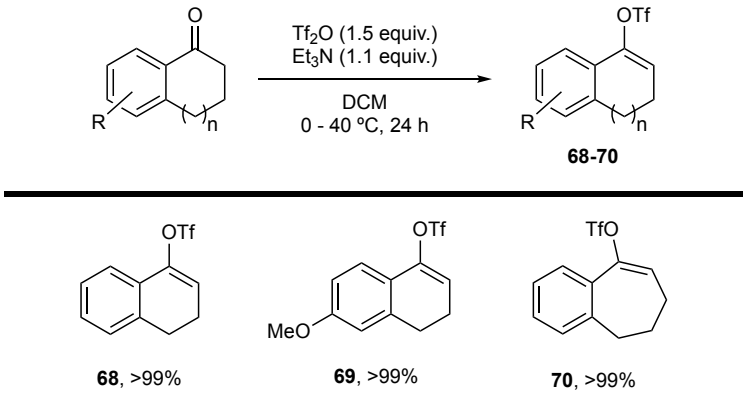
Scheme 17 Scope of the organoboron coupling partner

Prior to a comprehensive study of the scope of the reaction, the synthesis of intermediates was undertaken. Vinyl bromides (**63-67**) were synthesised from their styrene counterparts in a two-step transformation (Scheme 18). The addition of bromine across the alkene moiety could be facilitated to furnish the corresponding dibromides (**58-62**) in excellent yields. This was then followed by a base catalysed elimination to yield the desired vinyl bromides in respectable yields.

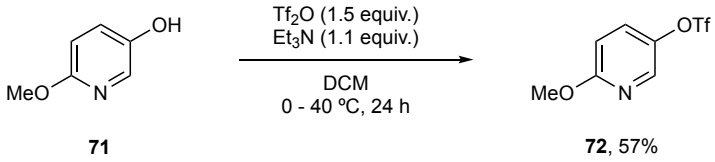


Scheme 18 Synthesis of vinyl bromide intermediates

A range of vinyl trifluoromethane sulfonates were also synthesised from the analogous ketone species (Scheme 19). Using Et_3N, and trifluoromethanesulfonic anhydride to trap the enolate intermediate, the corresponding triflates (**68-70**) could be formed in high yields. Similarly, triflate **72** could be synthesised from alcohol **71** (Scheme 20).



Scheme 19 Synthesis of vinyl trifluoromethane sulfonates from corresponding ketones



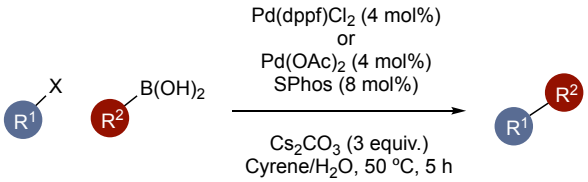
Scheme 20 Synthesis of intermediate **72**

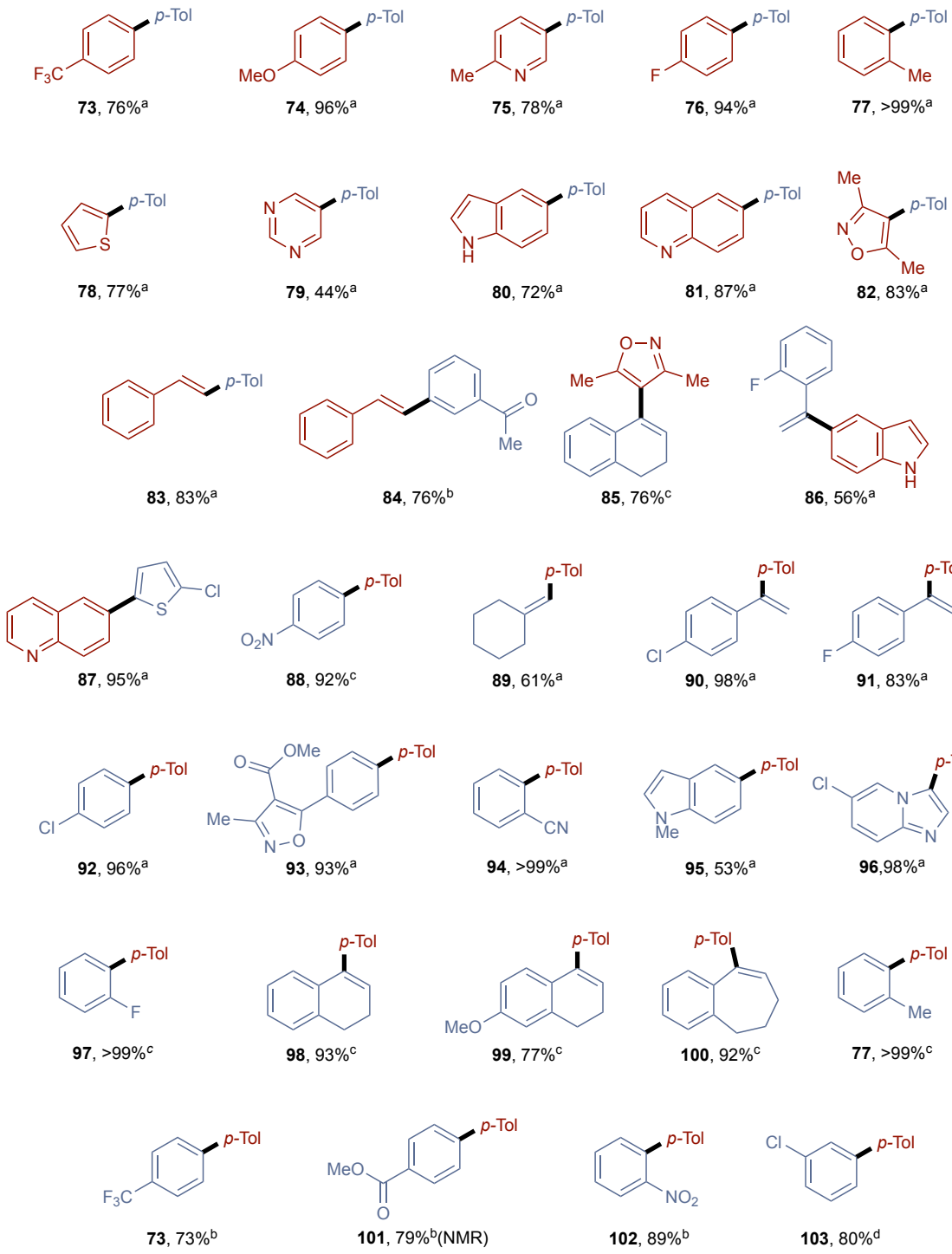
Continuing with the main study, the coupling of boronic acids with a variety of nucleophiles (Scheme 21) was first investigated. Halides and pseudo-halides (X = OTf, e.g. precursors to **88**, **100**) were both broadly accommodated, with chlorides undergoing coupling with a modified catalyst system (**84**, **102**). As expected of the SM reaction, an extensive array of functionality, ranging in steric and electronic contributions, were tolerated on both coupling components. For example, the coupling of the sterically hindered 3,5-dimethylisoxazoleboronic acid proceeded smoothly to deliver **82** and **85**. Aryl (e.g. precursors to **73**, **77**, **92**, **103**) and vinyl species (e.g. precursors to **84**, **90**, **98**) afforded high yields when exposed to the reaction conditions and, additionally, heteroaromatic substrates could be coupled efficiently, for example to deliver **78**, **81**.

Furthermore, pharmacologically relevant indole scaffolds and drug-like fragments such as **80**, **86**, **95** and **96** could be efficiently accessed.

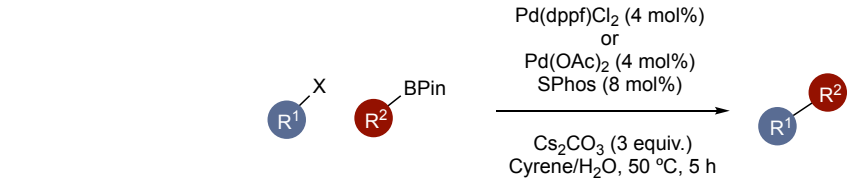
Similarly, BPin esters demonstrated excellent reactivity, affording high yields across a wide range of small-molecules (Scheme 22). As observed in the coupling of boronic acids, a broad tolerance of functionality was recorded. The coupling of vinyl BPins proceeded successfully to furnish products with enhanced three-dimensional properties (e.g. **111**, **115**). Furthermore, the coupling of vinyl BPin species with vinyl bromides and triflates could be accomplished to furnish synthetically useful dienes **116** and **119**. Additionally, aromatic and heteroaromatic BPins could be coupled efficiently to deliver the target molecules in high yields (e.g. **107** and **108**, respectively). Similarly, a range of electrophiles could be reacted including vinyl (e.g. **118** and **120**), aromatic (e.g. **105** and **114**), and heteroaromatic (e.g. **106** and **113**). In addition, the coupling of sterically hindered electrophiles, such as 5-chloro-2-bromo-3-methylbenzothiophene, furnished the desired product **112** in respectable yields.

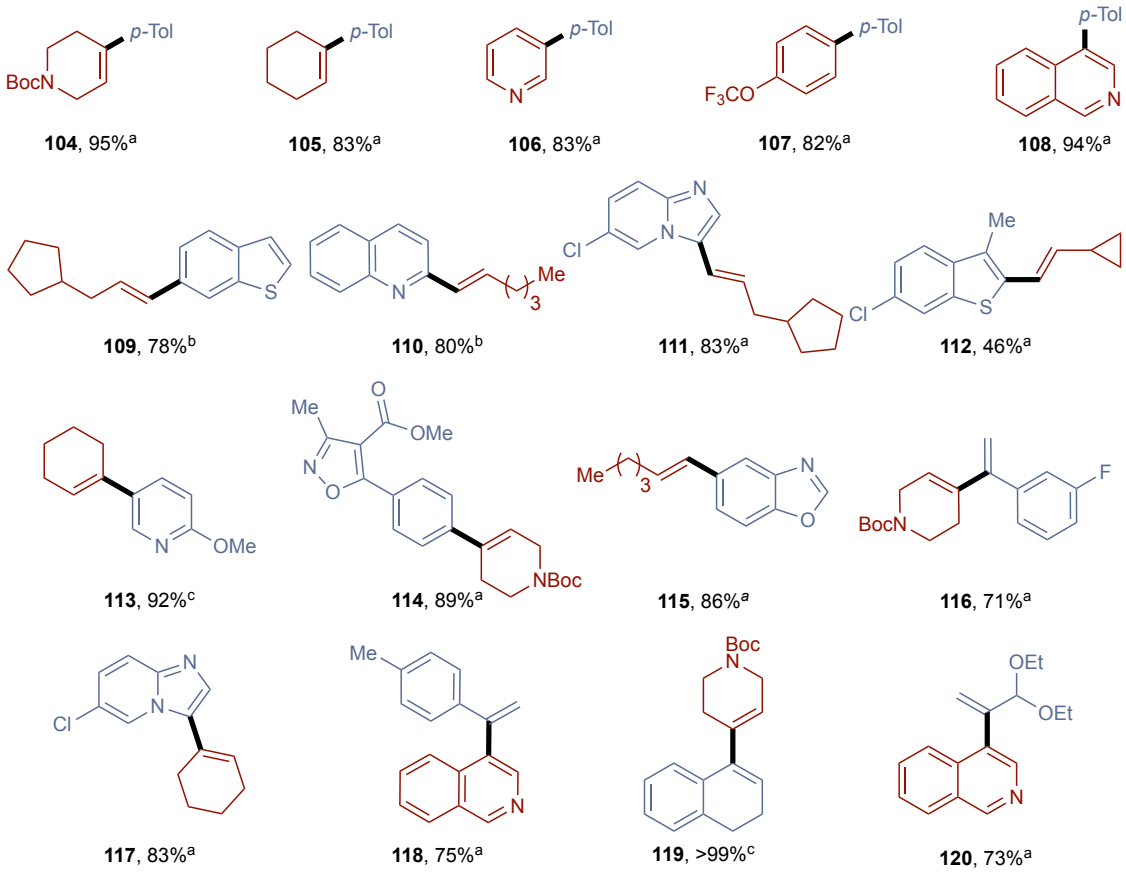
Some boronic acids and esters, including 2-heterocyclic boronic acids, are inherently unstable, therefore limiting their use and efficiency within the SM cross-coupling.[149] However, the analogous protected moieties are powerful coupling partners as they undergo slow-release in situ hydrolysis, restricting the concentration of the unstable boronic acid and suppressing decomposition.[149] Pleasingly, it was found that protected boron species such as BMIDA, as used in the synthesis of **121** and **122**, and BF_3K, as used in the synthesis of **123**, coupled efficiently with respectable yields obtained (Scheme 23).



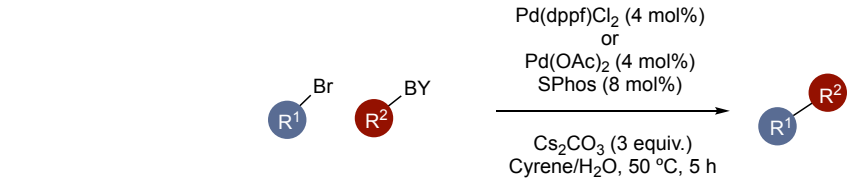


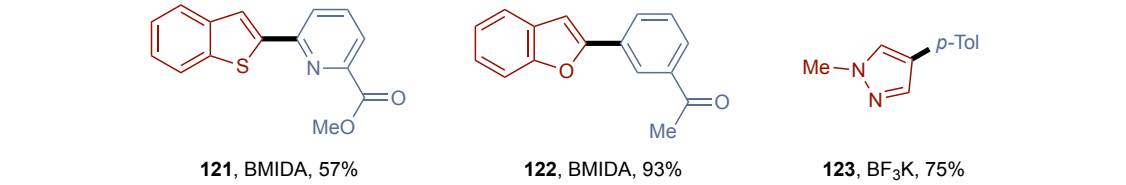
Scheme 21 Scope of the SM coupling with various boronic acids. [a]X = Br. [b]X = Cl. [c]X = OTf. [d]X = I





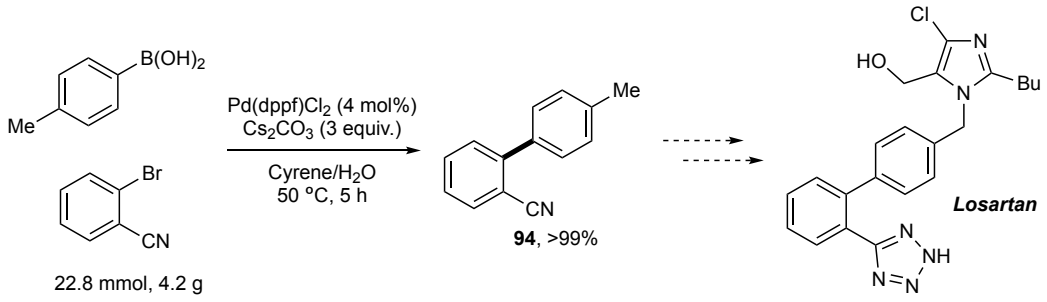
Scheme 22 Scope of the SM coupling with various BPin esters. [a]X = Br. [b]X = Cl. [c]X = OTf





Scheme 23 Scope of SM coupling with protected boron species

Subsequent to the exhaustive survey of reaction scope, the use of these Cyrene-based SM cross-coupling conditions were evaluated on a preparative scale (Scheme 24) in the synthesis of *o*-tolylbenzonitrile (OTBN), a valuable intermediate in the synthesis of drugs used clinically for the treatment of hypertension (sartans, e.g. losartan).[150] On a larger scale, the production of Cyrene dimer **54** could give rise to issues during purification. Additionally, the high boiling point of Cyrene precludes removal *via* distillation. On a small scale, these issues are both easily resolved by chromatographic purification, which becomes less feasible on a larger scale. As such, it was necessary to develop an extraction procedure which could be employed to facilitate the removal of the aldol by-products. This was achieved by extracting **94** in a medium polarity solvent mixture (40% EtOAc in petroleum ether), allowing **54** to be removed *via* filtration. Excess Cyrene could then be removed by aqueous washing and the coupled product isolated in high yields.



Scheme 24 Gram-scale synthesis of OTBN, **94**

In summary, Cyrene has been demonstrated as an alternative solvent in the SM cross-coupling. The reactivity and generality of these conditions are comparable to conventional systems utilising traditional solvents and, as exemplified in the gram-scale synthesis of **94**, dimer formation is manageable from the perspective of purification. However, the practicality of this procedure, in addition to the implications on the cost of recovery and waste disposal of the by-products, will likely limit the application of Cyrene within this transformation. Nonetheless, a broad range of small molecules, including many novel drug-like fragments, have been synthesised *via* the SM coupling using Cyrene-based conditions.

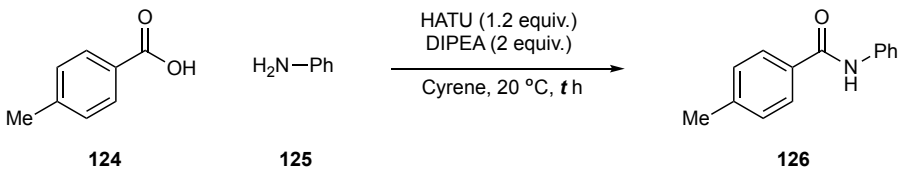
3.1.4 Investigation of Cyrene as an Alternative Solvent in Amide Bond Formation

As indicated in Section 2 (Project Background and Aims), amide bond formation is consistently identified as the most utilised reaction within medicinal chemistry. Indeed, the amide bond is ubiquitous within both the natural world and pharmaceutical industry, featuring in both proteins and drug compounds.[106,107]

This transformation is formally a condensation between a carboxylic acid and amine, but conventionally makes use of coupling agents to activate the acid towards nucleophilic attack. Common coupling reagents include *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholino)] uronium hexafluorophosphate (COMU), and carbodiimides such as diisopropyl carbodiimide (DIC). Synthesis *via* these methods tend to be more efficient, requiring lower temperatures and displaying a broader scope of reactivity.[151] However, due to low solubility of these agents and reacting components, amide bond formation often relies on the use of solvents of concern. Watson *et al*. report a survey of amidations using SciFinder which revealed that 83% of reactions found employed either DCM (36%) or DMF (47%).[130]

Due to the frequency that this reaction is performed within industry and the large volumes of solvent required for this transformation, particularly in SPPS, it is important that alternatives are investigated. To this end, we began the assessment of Cyrene in HATU-mediated amide bond formation in a model reaction involving the coupling of *p*-toluic acid (**124**) and aniline (**125**). Initial investigations into reaction time established that complete conversion could be achieved within one hour (Table 15). However, repeat reactions failed to deliver consistency.

Table 15 Effect of time on reaction conversion



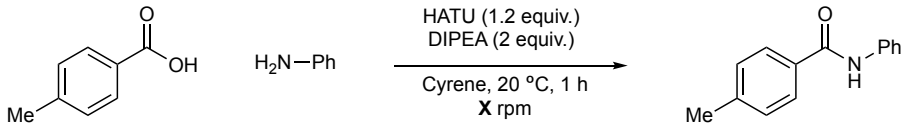
124 **125** **126**

Entry	Time (h)	Conversion μ ± σ (%)
1	1	84 ± 21
2	2	83 ± 27
3	4	81 ± 0
4	8	98 ± 2
5	16	91 ± 13
6	24	87 ± 13
7	48	86 ± 7

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Further evaluation revealed the inconsistencies arose due to variable stirring rate (Table 16). By controlling this factor, we were able to establish that faster stirring rates facilitated high conversion to **126** (Entry 4). Although the reaction mixture was homogeneous, we propose that the variability could be caused by the viscosity of Cyrene leading to inefficient mixing. By increasing the stoichiometry of DIPEA, we observed a decreased dependency on the stirring rate (Table 17 and Table 18). Thus, we were able to perform further reactions without monitoring this factor.

Table 16 Effect of stirring rate on reaction conversion



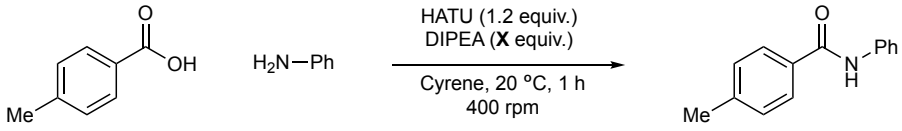
124 **125** **126**

Entry	Stirring Rate (rpm)	Conversion μ ± σ (%)[a]
1	100	51 ± 10
2	200	73 ± 3

3	400	71 ± 3
4	800	96 ± 7
5	1200	91 ± 11

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Table 17 Effect of DIPEA stoichiometry on reaction conversion

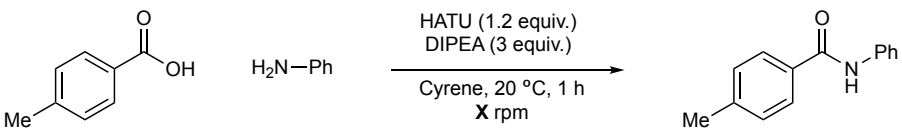


124 **125** **126**

Entry	Base (equiv.)	Conversion μ ± σ (%)[a]
1	1	83 ± 4
2	2	96 ± 7
3	3	92 ± 2
4	5	90 ± 6
5	10	96 ± 4
6	20	76 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Table 18 Effect of stirring rate on reaction conversion when using 3 equiv. base



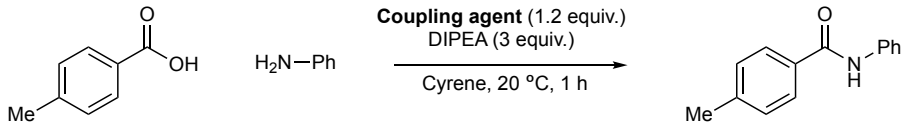
124 **125** **126**

Entry	Stirring Rate (rpm)	Conversion μ ± σ (%)[a]
1	200	92 ± 5
2	400	92 ± 2
3	800	>99 ± 0

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Following the reaction optimisation using HATU, we screened other common coupling agents (Table 19) and bases (Table 20). Under these conditions, further improvement was not observed, with HATU emerging as the optimum choice of coupling reagent, in combination with DIPEA as the base.

Table 19 Evaluation of coupling reagents using Cyrene media

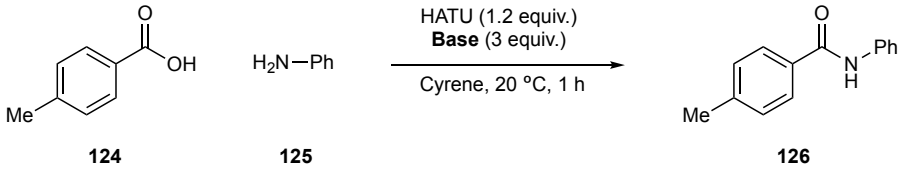


124 **125** **126**

Entry	Coupling Reagent	Conversion μ ± σ (%)[a]
1	HATU	92 ± 2
2	COMU	14 ± 2
3	DIC/HOBt	9 ± 7
4	PyBOP	29 ± 1
5	T3P	4 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Table 20 Evaluation of alternative bases using Cyrene media



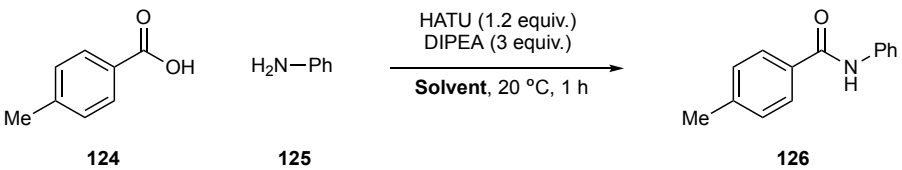
124 **125** **126**

Entry	Base	Conversion μ ± σ (%)[a]
1	DIPEA	92 ± 2
2	Et_3N	67 ± 4
3	NMM	43 ± 3
4	Lutidine	35 ± 1

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

Finally, the performance of Cyrene within this transformation was evaluated against the conventional solvent DMF, and additionally solvents which have been advocated as sustainable alternatives (Table 21). Under these conditions, Cyrene as the reaction medium delivered equally high conversion as those achieved under analogous conditions using DMF. In addition, superior conversions were obtained when compared with proposed green alternatives such as CPME, EtOAc, *i*-PrOH, and 2-MeTHF.

Table 21 Evaluation of conventional and alternate solvents within HATU-mediated amide bond formation

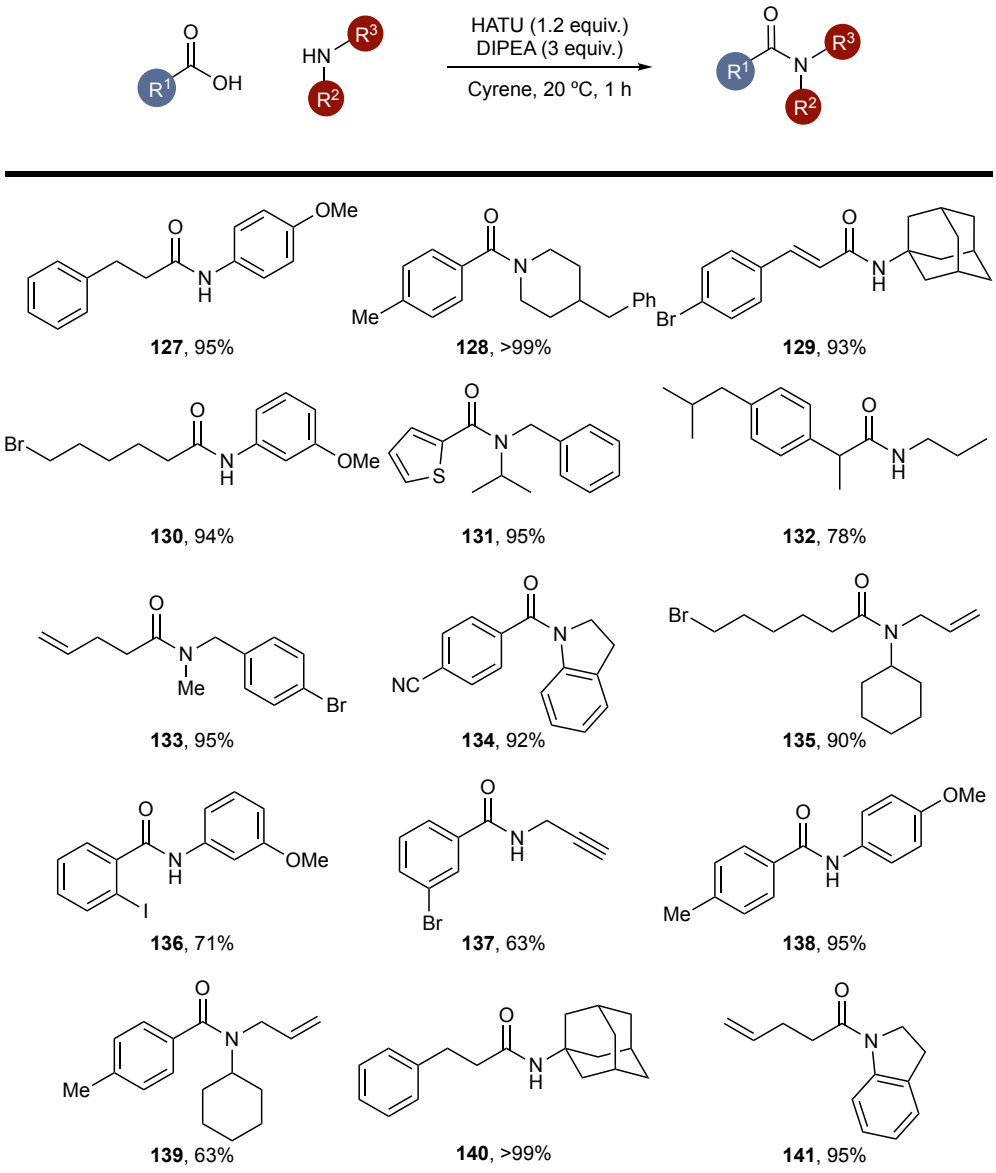


124 **125** **126**

Entry	Solvent	Conversion μ ± σ (%)[a]
1	DMF	94 ± 1
2	Cyrene	92 ± 2
3	CPME	18 ± 2
4	EtOAc	72 ± 6
5	*i*-PrOH	29 ± 4
6	2-MeTHF	28 ± 5

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency over three reactions.

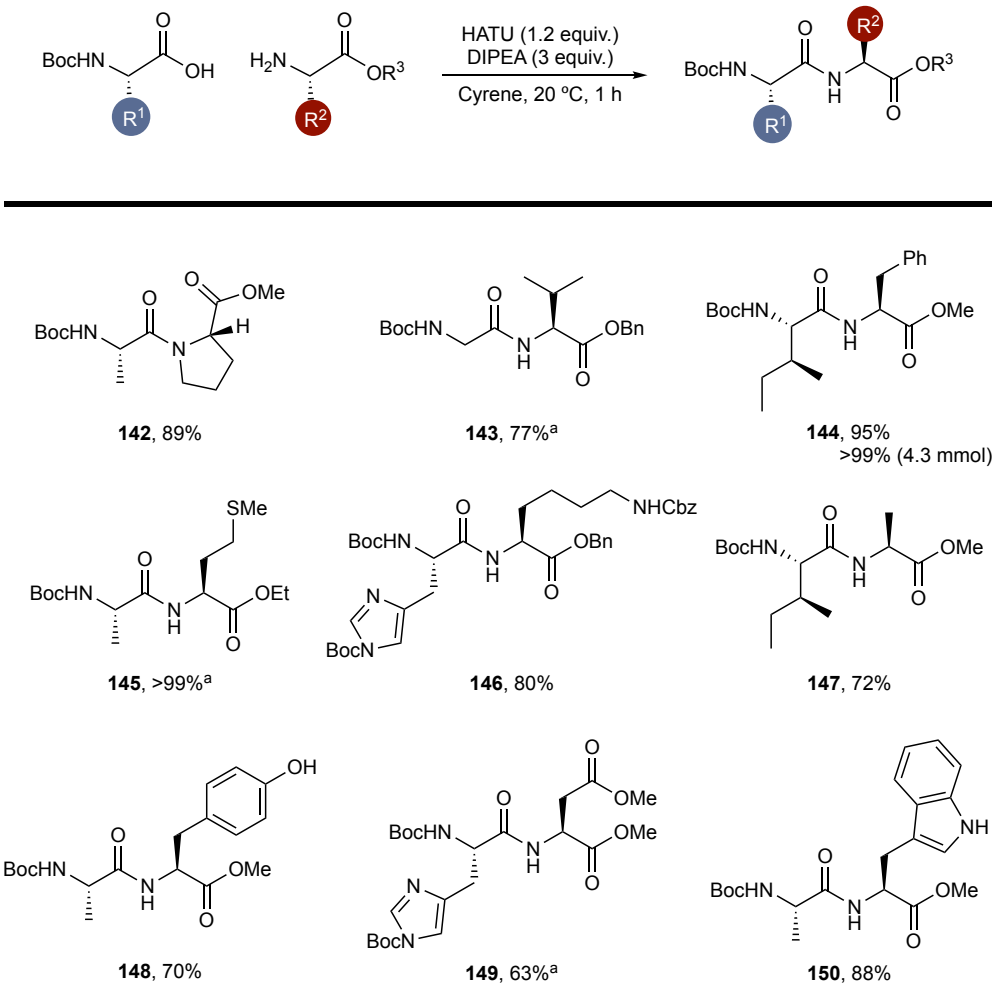
Using the optimised condition set, the efficacy of Cyrene in the coupling of a range of carboxylic acids and amines (Scheme 25) was subsequently examined. Coupling was broadly successful, with alkyl (**127**, **130**, **132**) and aryl (**134**, **136**, **137**) carboxylic acid moieties, with varied substitution patterns, tolerated well within the transformation. Additionally, a range of amines were accommodated including primary (**129**, **138**), and secondary cyclic (**128**, **141**) and acyclic (**131**, **139**) species.



Scheme 25 Scope of Cyrene-based, HATU-mediated amide coupling

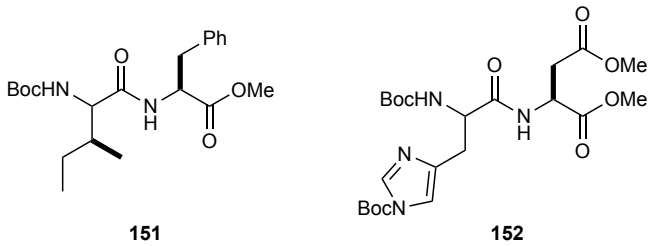
The conditions were next applied to peptide synthesis in the coupling of protected amino acids (Scheme 26). A broad range of functionality was tolerated, with high isolated yields obtained in most examples. In addition to amino acids bearing alkyl (**143**, **147**) and aryl (**144**, **148**) residues, we also found that those containing heteroatomic (**145**, **146**) and heteroaromatic (**149**, **150**) were also coupled efficiently. However, in some cases, unreacted coupling partners were isolated, as such we found it necessary to increase the

stoichiometry of HATU to improve yields (**143**, **145**, **149**). These conditions were also amenable to gram-scale synthesis, facilitating the formation of **144** in high yields on a 4 mmol scale. Furthermore, Cyrene could be removed following aqueous washing, delivering the product in high analytical purity without requiring chromatographic purification.



Scheme 26 Scope of Cyrene-based, HATU-mediated coupling of amino acids. [a]2.5 equiv. HATU

Importantly, no racemisation was observed. Enantiopurity could be determined by ^{1}H NMR as the spectra of the two diastereomers are visibly dissimilar. The diastereotopic mixtures **151** and **152** (Scheme 27) were synthesised and their NMR traces compared to those of the enatiopure compounds (See Experimental for full details).



Scheme 27 Diastereomeric mixtures **151** and **152** synthesised for racemisation study

For example, visible peak splitting can be observed in the ^{1}H NMR spectrum of **151** indicating the presence of diastereomers (Figure 12). In contrast, the sprectrum of the enantiopure **144** does not show any splitting (Figure 13).

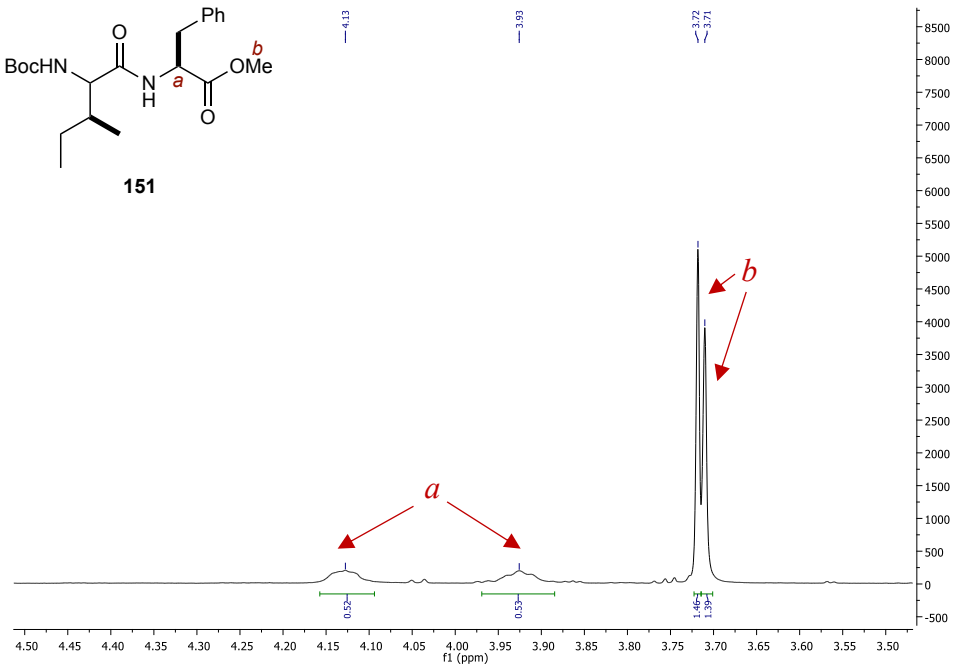


Figure 12 ^{1}H NMR of the Diastereotopic mixture **151**

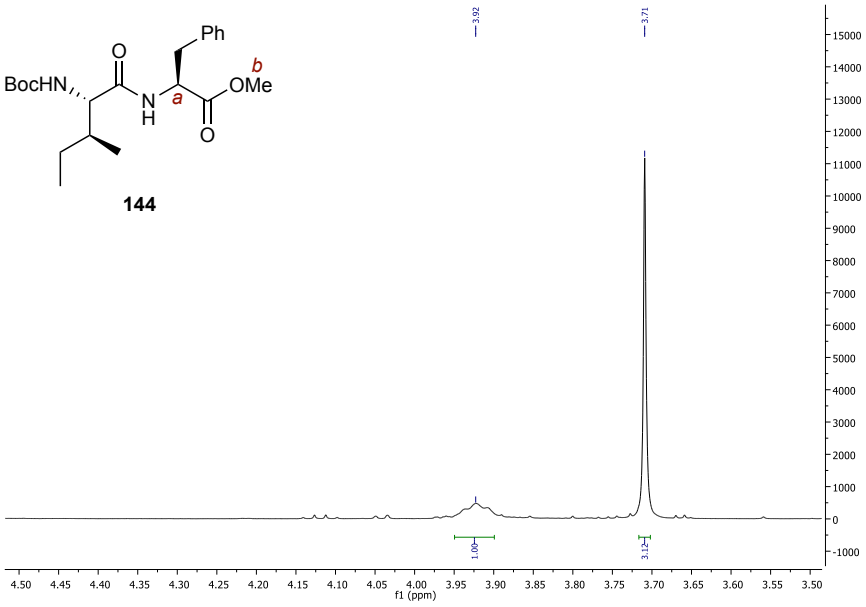


Figure 13 ^{1}H NMR of the enantiopure compound **144**

3.1.5 Investigation of Cyrene as an Alternative Solvent in Solid Phase Peptide Synthesis

Following the success of amide coupling in the batch synthesis of peptides, we sought to assess the capacity of Cyrene within SPPS. As discussed in Section 1.4.2.3 (Solid Phase Synthesis), solvent is a major component of waste in the synthesis of peptides *via* this method as it is used for multiple washing and coupling steps (Figure 14). With the increasing presence of peptides as drug candidates, more sustainable procedures are needed.[152,153]

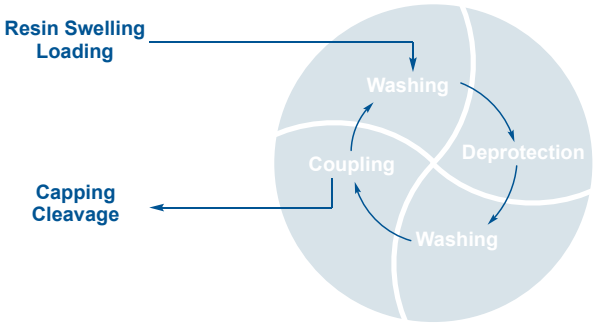
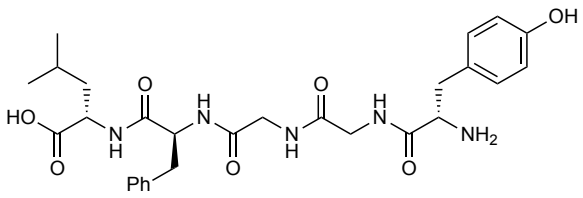


Figure 14 General procedure for SPPS

To investigate the proficiency of Cyrene we attempted the synthesis of Leu-Enkephalin (Figure 15, **153**), a pharmacologically useful polypeptide which possesses powerful analgesic properties.[154]



153

Figure 15 Structure of Leu-Enkephalin

Initial loading (with leucine) and swelling of the resin was carried out according to an established procedure using DCM.[155] Subsequent washing, deprotection and coupling steps were carried out in Cyrene. However, on preparation of a stock solution of piperidine in Cyrene (20% v/v) for deprotection of the Fmoc protecting group, we observed a colour change from colourless to deep yellow. This was attributed to the formation of Cyrene dimer **54**. As such, we opted to use EtOAc as the bulk media in further deprotection steps, and washing steps were performed using EtOAc, followed by Cyrene prior to coupling using Cyrene.

Despite multiple attempts, coupling did not proceed, and leucine was identified as the only product. The loading test carried out (Section 6.9), indicated EtOAc gave comparable loading values to DMF. This demonstrates that EtOAc could successfully be employed as the bulk medium in Fmoc deprotection and, as such, was not the cause of unsuccessful coupling. A potential issue could be the resin used and inefficient swelling in Cyrene throughout the coupling procedure. Alternatively, small levels of residual piperidine could effect dimerisation causing blockages within the resin matrix. In addition, the use of a Merrifield bubbler connected to a nitrogen line, caused the reaction mixture to bubble over due to the viscosity of Cyrene.

Due to these problematic factors and potential issues, it was deemed that Cyrene was not a viable alternative solvent for SPPS *via* this method. As such, investigations were not continued.

3.1.6 Summary of Findings from the Studies of Cyrene as an Alternative Solvent

Conditions have been developed which exemplify Cyrene as an alternative bio-based medium, for the Sonogashira reaction, SM cross-coupling and amide bond formation. Cyrene performs comparably to the traditional solvents used in each of these reactions and the conditions demonstrated excellent reactivity and broad generality of functional tolerance in each reaction. However, the observation of base sensitivity and susceptibility to dimerise limits its use within synthetic transformations unless the conditions are strictly controlled. These studies illustrate the importance of evaluating new solvents and understanding their limitations. It also highlights the need for a variety of solvent alternatives that stable under a range of conditions.

3.2 Dimethyl isosorbide

As discussed in Section 1.2.2.4 (Dimethyl Isosorbide), DMI is a sugar-based solvent with no currently identified pernicious properties towards human health and the environment. Its excellent solubilising properties make it a promising alternative for polar aprotic solvents in organic synthesis. As such, three prominent Pd-catalysed bond forming reactions – Sonogashira, SM and MH cross-couplings – have been selected to investigate the capacity of DMI within synthetic organic and medicinal chemistry.

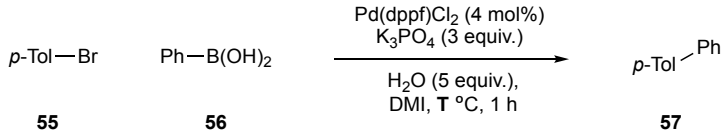
3.2.1 Investigation of DMI as an Alternative Solvent in the Suzuki–Miyaura Cross-Coupling

As previously highlighted in Section 2, the SM cross-coupling is a valuable tool to medicinal chemists and more sustainable methods to facilitate the transformation are highly desirable.[106,107] From the current study Cyrene has been identified as a potential alternative within the context of this transformation (Section 3.1.3). However, its base sensitivity and propensity for dimerisation (Section 3.1.2), could discourage the use of Cyrene within the SM reaction. Therefore, evaluation of further examples of green solvents would be highly beneficial.

DMI does not display any sensitivity towards bases and, as such, it was possible to employ conditions established within our laboratories[156–158] to the benchmark coupling

of bromotoluene (**55**) and phenylboronic acid (**56**). Interrogation of reaction temperature (Table 22) showed that high conversions of **57** could be achieved at 40 °C in one hour (Entry 3). In addition, investigation of catalyst loading showed that this could be reduced to 1 mol% before significant erosion of conversion was observed (Table 23, Entry 3).

Table 22 Effect of temperature on reaction conversion

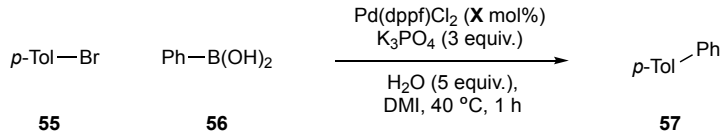


55 **56** **57**

Entry	Temperature (°C)	Conversion (%)[a]
1	20	62
2	30	72
3	40	93
4	60	>99

[a] ^{1}H NMR % conversion calculated as an average of two reactions

Table 23 Effect of catalyst loading on reaction conversion

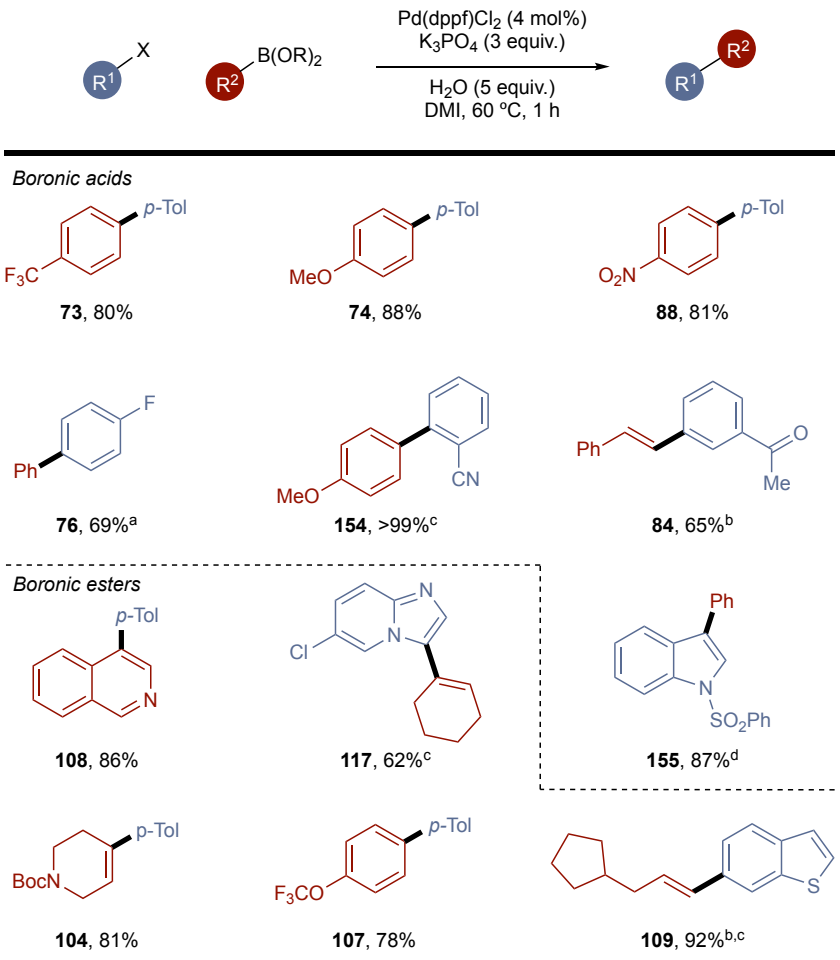


55 **56** **57**

Entry	Catalyst loading (mol%)	Conversion (%)[a]
1	4	93
2	2	92
3	1	92
4	0.5	80

[a] ^{1}H NMR % conversion calculated as an average of two reactions

Using these conditions, a small range of substrates could be prepared at 60 °C (Scheme 28, **154**, **117**, **109**). However, to ensure the generality of the procedure, it was necessary to increase the catalyst loading to 4 mol%. This higher catalyst loading enabled the synthesis of a wide range of substrates, with broad tolerance of both reacting components observed. Both aryl (e.g. precursors of **73**, **108**), and vinyl (e.g. precursors of **84**, **104**) boronic acids and BPins were susceptible to coupling with high yields obtained. In addition, as is standard within the SM cross-coupling, electrophile variation was well tolerated, and a range of halides and pseudo-halides could be accommodated (**74**, **76**, **109**).



Scheme 28 Scope of DMI-based SM cross-coupling. [a]X = OTf, [b]X = Cl, Pd(OAc)2 (4 mol%), SPhos (8 mol%), [c]Pd cat. (2 mol%, 0.005 mmol), [d]1.2 equiv. phenylboronic acid.

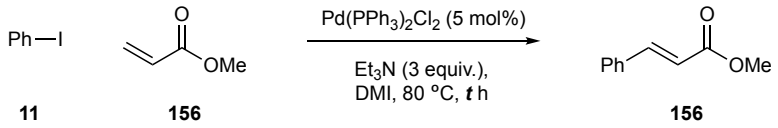
The results obtained therefore support the use of DMI as a sustainable solvent in the SM reaction. In addition to this, DMI represents an advantage over Cyrene due to the superior chemical stability and compatibility with bases.

3.2.2 Investigation of DMI as an Alternative Solvent in the Mizoroki–Heck Cross-Coupling

The MH cross-coupling is a useful tool for the formation of sp^2-sp^2 bonds. An attractive feature of this methodology is its versatility in synthesising both branched and unbranched alkenes, within inter- and intramolecular reactions, using activated, unfunctionalised alkenes as coupling components.[159] As such, it has found extensive application in total synthesis,[146] including the development of drug compounds such as Taxol.[160] However, as is common within Pd-catalysed cross coupling reactions, the MH reaction frequently employs solvents of concern. Therefore, it is of value to identify alternatives. Given the successful demonstration the DMI could be used in the SM process, this was selected for study in the corresponding MH reaction.

Initial screenings were carried out using iodobenzene (**11**) and methyl acrylate (**156**), using a $Pd(PPh_3)_2Cl_2$ catalyst system, as the standard reaction. This manifold demonstrated excellent reactivity, facilitating complete conversion to **157** in only one hour (Table 24, Entry1). However, reduced temperatures were detrimental to the reaction (Table 25).

Table 24 Effect of time on reaction conversion



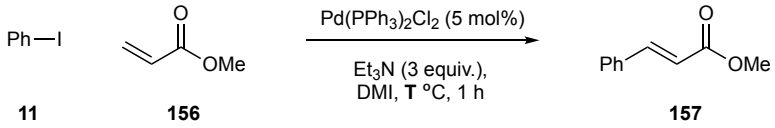
11 **156** **156**

Entry	Time (h)	Conversion (%)[a]
1	1	>99
2	2	98

3	4	98
4	8	>99

[a] ^{1}H NMR % conversion calculated as an average of two reactions

Table 25 Effect of temperature on reaction conversion



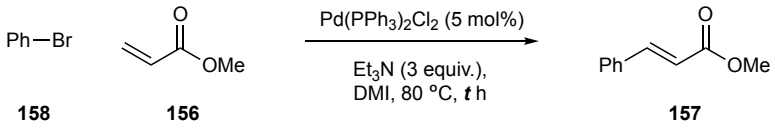
11 **156** **157**

Entry	Temperature (°C)	Conversion (%)[a]
1	23	0
2	30	<1
3	40	<1
4	60	12
5	80	>99

[a] ^{1}H NMR % conversion calculated as an average of two reactions

Following optimisation of the iodobenzene system, focus was turned to the analogous bromide system using bromobenzene (**158**). Using the optimised conditions as a starting point, we found that the reaction did not proceed (Table 26, Entry 1). However, increased reactivity was observed over extended reaction times (Entry 6). Subsequently, following a short temperature study (Table 27), it was identified that more elevated temperatures facilitated the transformation, in high conversions, to **157**.

Table 26 Effect of time on reaction conversion

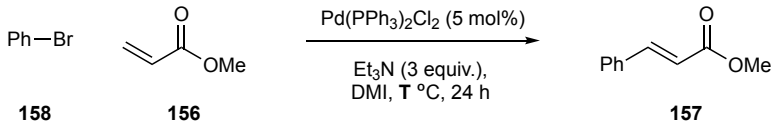


158 **156** **157**

Entry	Time (h)	Conversion (%)[a]
1	1	<1
2	2	7
3	4	11
4	8	16
5	16	67
6	24	81

[a] ^{1}H NMR % conversion calculated as an average of two reactions

Table 27 Effect of temperature on reaction conversion



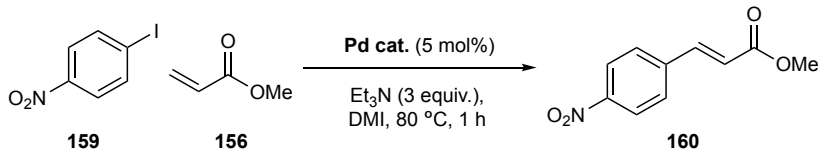
158 **156** **157**

Entry	Temperature (°C)	Conversion (%)[a]
1	80	81
2	100	89
3	115	98

[a] ^{1}H NMR % conversion calculated as an average of two reactions

These optimised conditions, utilising the $Pd(PPh_3)_2Cl_2$ catalyst system, were then used to interrogate the scope of the reaction. Upon investigating the use of electron poor substrates, more specifically 4-iodonitrobenzene (**159**), the reaction was found to be unsuccessful (Table 28, Entry 1). A brief screen of catalysts was carried out, in which the $Pd(dppf)Cl_2$ complex demonstrated high reactivity (Entry 3) and could facilitate the coupling in high isolated yield of **160**.

Table 28 Effect of catalyst variation on reaction conversion using electron poor systems

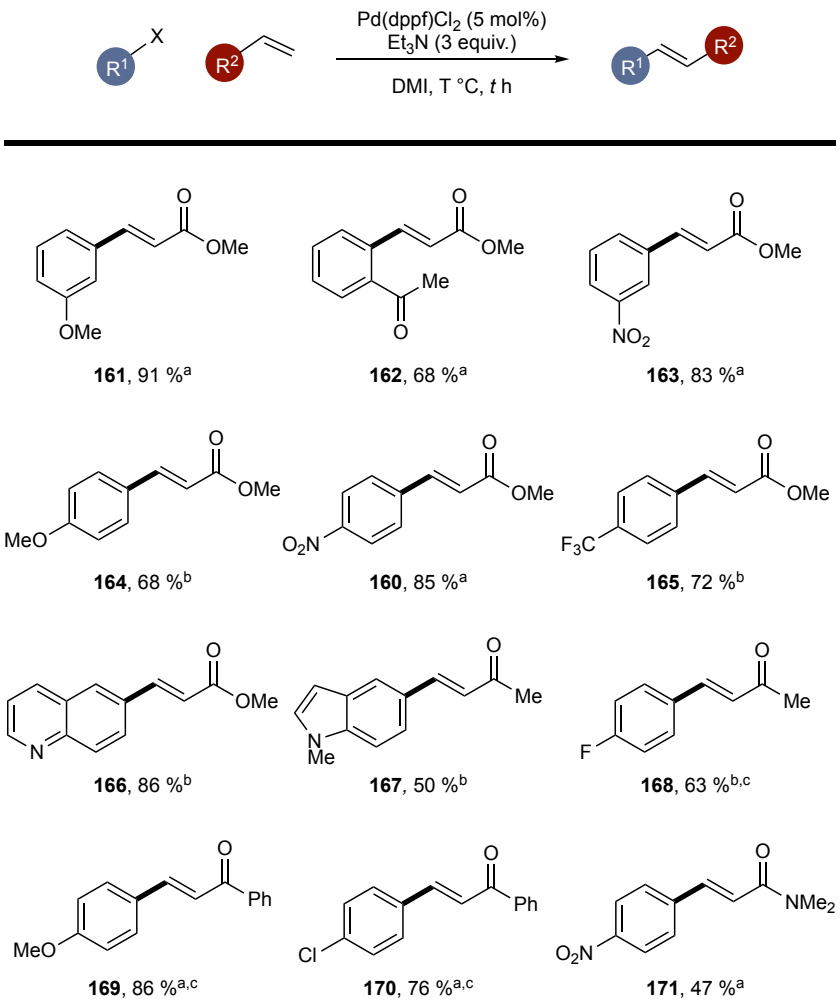


159 **156** **160**

Entry	Catalyst	Isolated Yield (%)
1	$Pd(PPh_3)_2Cl_2$	0
2	$Pd(PPh_3)_4$	0
3	$Pd(dppf)Cl_2$	85

[a] NMR % conversion calculated as an average of n=2

In addition, when applied to further substrates, this catalyst system demonstrated high levels of generality (Scheme 29). A broad range of aryl halides could be coupled including aryl iodides and bromides with varying substitution patterns and electronic properties. Furthermore, heteroaryl halides could also be accommodated to furnish products **166** and **167**. Some divergence of the alkene coupling partner was also tolerated, although yields were found to vary. This data further established confidence in using DMI as a sustainable replacement solvent in palladium mediated cross-couplings. Based on this, attention then turned to examining the use of DMI in the Sonogashira reaction.



Scheme 29 Scope of DMI-based MH cross-coupling. [a]X = I, 1 h, 80 °C, [b]X = Br, 24 h, 115°C, [c]K_3PO_4 used as base.

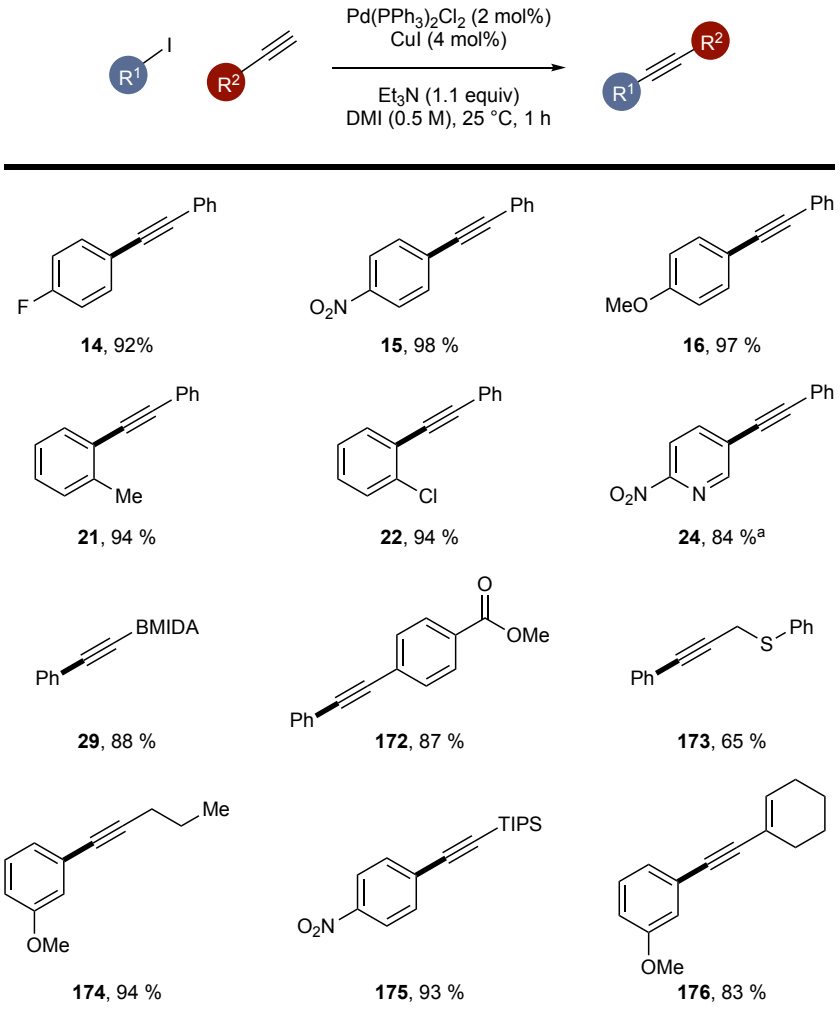
3.2.3 Investigation of DMI as an Alternative Solvent in the Sonogashira Cross-Coupling

As extensively discussed in Sections 2 and 3.1.1, the Sonogashira coupling is a valuable reaction within medicinal chemistry,[106,107] as the products formed are useful intermediates for further synthetic manipulations.[137]

Using conditions previously optimised for the studies involving Cyrene (Section 3.1.1), it was established that the coupling of 4-fluoroiodobenzene and phenylacetylene proceeded smoothly, delivering **14** in high isolated yield. Accordingly, these conditions

were applied to a focused substrate scope (Scheme 30). Broad tolerance was again observed with a wide range of functionality accommodated on both coupling partners.

Interestingly, the issues observed when using Cyrene within the coupling of sterically encumbered *o*-substituted aryl halides (Scheme 13, **21**, **22**) were not apparent. As such, when using the DMI-based system, coupling of these substrates could be conducted in one hour with the products isolated in high yields.



Scheme 30 Scope of DMI-based Sonogashira cross-coupling. [a]5-Bromo-2-nitropyridine as coupling partner.

Overall, this last study has indicated the broad applicability of DMI to cross-coupling chemistry. Additionally, this solvent system does not suffer from the same reactivity issues as Cyrene and is less viscous, potentially making it a more versatile replacement for commonly used solvents of concern.

4 Summary and Conclusions

The aim of this research programme was to address the need for suitable alternatives for polar aprotic solvents within organic and medicinal chemistry. With the outlook that synthetic chemists have the opportunity to influence upstream processes in the manufacture of pharmaceuticals, reaction specific exploration of bio-based alternatives was carried out. Frequently employed transformations, and crucial bond forming tools within synthesis, were selected with the intention that these studies would encourage the uptake of Cyrene and DMI within early-stage drug discovery.

The evaluation of Cyrene was carried out in the context of three transformations; amidation, Suzuki–Miyaura and the Sonogashira reaction (Figure 16). In addition, the Sonogashira methodology was extended in a one-pot annulation reaction, facilitating expedient access to indoles and benzofurans, both of which are privileged structures within medicinal chemistry. Through methodical optimisation, robust condition sets were identified, and the scope of the reactions extensively investigated in the synthesis of small molecules and drug-like fragments.

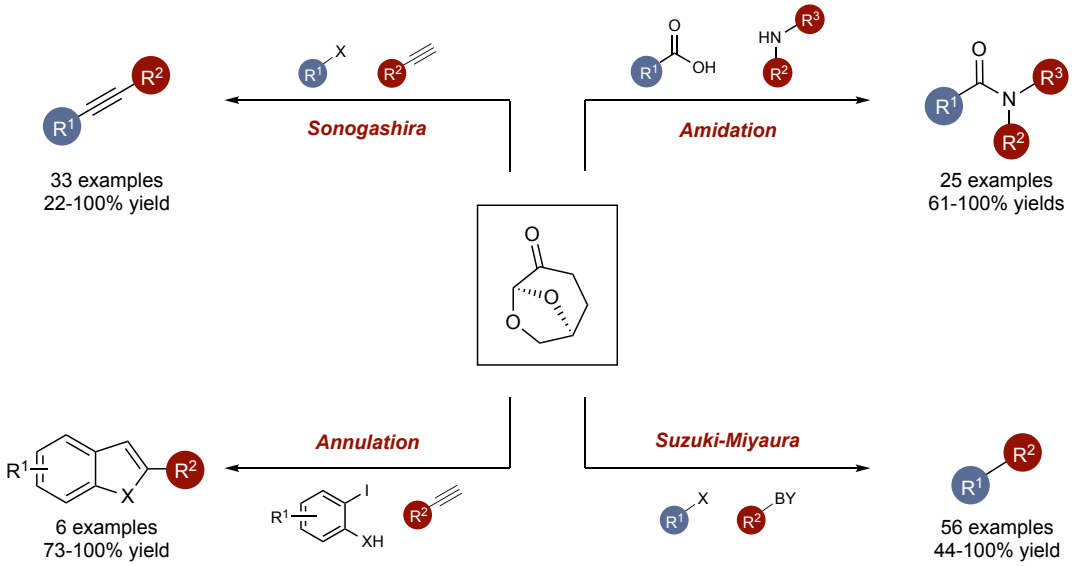


Figure 16 The application of Cyrene in benchmark transformations within organic synthesis

However, during the process of optimisation for the Sonogashira reaction, a sensitivity towards bases was identified which resulted in the formation of a precipitate. Subsequent investigations revealed that this was due to dimerisation of Cyrene *via* an aldol

condensation and subsequent elimination to deliver a highly insoluble dimer (**54**). A survey was carried out to establish the stability of Cyrene towards a range of bases to discern the limitations of Cyrene and how this could affect its capacity as a solvent within organic synthesis. Dimerisation was observed with most bases assessed, with the exception of Et_3N and DIPEA at low temperatures.

The use of DMI within Pd-catalysed cross-couplings, specifically the Suzuki–Miyaura, Mizoroki–Heck, and Sonogashira reactions, was also investigated (Figure 17). The methodologies developed were demonstrated in the synthesis of a range of substrates and broad tolerance of functionality was observed. In addition, no potential limitations of DMI were observed compared to Cyrene, indicating that this is likely to be the preferred choice of replacement solvent in these processes.

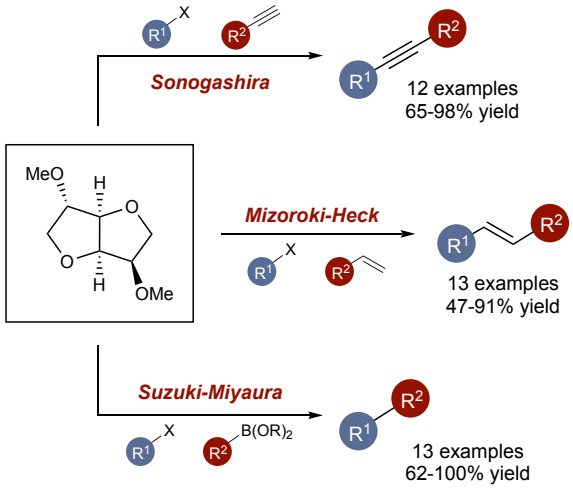


Figure 17 The application of DMI in Pd-catalysed cross-coupling reactions

5 Future Work

The utilisation of Cyrene within amide coupling chemistry delivered promising results in the liquid phase (LP) synthesis of small molecules and peptides. However, when the procedure was translated to SPPS we found that no coupling occurred. The use of Cyrene within SPPS could be investigated further. However, due to the exhibited base sensitivity which could limit the use of Cyrene within an industry setting, it would be more beneficial to investigate the use of DMI within this transformation. In addition to its superior stability, the lower viscosity of DMI may give rise to fewer encountered issues with respect to agitation of the reaction mixture.

Initially, conditions should be established to facilitate the LP amide bond formation. Following a similar optimisation process to that discussed in Section 3.1.5, a variety of bases and coupling agents would be evaluated to assess the practicality of the reaction. Once suitable conditions have been developed, the scope of the LP reaction can be investigated to demonstrate the functional group tolerance. In addition, a study of the solubility of Fmoc-protected amino acids in DMI and the LP coupling of Fmoc-protected amino acids would be required.

If successful, the application to SPPS can be assessed. Based on the published study of resin swelling,[136] a suitable resin, such as ParaMax or HypoGel 200 should be selected. Additionally, the feasibility of deprotection using DMI as the bulk medium would be necessary and can be established by conducting a loading test and comparing with values obtained using DMF (Section 6.9.3). If the use of DMI is not compatible in the deprotection step, other solvents could be considered. Following this, coupling can be attempted.

6 Experimental

6.1 General Techniques

i. All reagents, catalysts, and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated.
ii. Purification was carried out according to standard laboratory methods.[161]

6.1.1 Purification of Solvents

i. Cyrene was supplied directly by Circa and used as obtained.
ii. DMI was supplied directly by Sigma-Aldrich and used as obtained.
iii. DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves.
iv. THF was obtained from a PureSolv SPS-400-5 solvent purification system and transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under N_2.
v. CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

6.1.2 Purification and Drying of Bases

i. Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 h before use.
ii. Et_3N was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves.

6.1.3 Experimental Details

i. Reactions were carried out using conventional glassware or in sealed 5 mL microwave vials (air sensitive reactions).
ii. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure.

iii. Room temperature was generally *ca.* 20 °C.

iv. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

6.1.4 Purification of Products

i. Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using vanillin solution.

ii. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

iii. Reverse phase flash chromatography was carried out manually using IST Isolute C18 cartridges.

6.1.5 Analysis of Products

i. Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1S machine.

ii. ^{1}H, ^{13}C, and ^{19}F spectra were obtained on either a Bruker DRX 500 spectrometer (Avance III HD console, Ascend 500 MHz magnet, BBO smart probe) at 500 MHz, 126 MHz, and 471 MHz respectively, or Bruker AV 400 at 400 MHz, 101 MHz and 376 MHz, respectively.

iii. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.1 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C).

iv. **Amide bond formation:** Samples for quantitative NMR analysis were prepared through the addition of 1 mL of a 0.0625 M 1,4-dinitrobenzene standard to the organics prior to concentration. The conversion to product **4a** was calculated from the peak area ratio of 4-methyl-*N*-phenylbenzamide (δ 2.40 ppm), and 1,4-dinitrobenzene (δ 8.39 ppm).

v. **DMI studies:** Samples for quantitative NMR analysis were prepared through the addition of 1 mL of a 0.0625 M 1,4-dinitrobenzene standard to the organics prior to concentration. The conversion to product was calculated from the peak ratio of the diagnostic product peak and 1,4-dinitrobenzene (δ 8.39 ppm).

vi. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

vii. Optical rotation was performed on a Perkin Elmer 341 polarimeter.

6.2 General Experimental Procedures

6.2.1 General Procedures for Optimised Condition Sets

General Procedure A: Optimized Conditions for the Cyrene-based Sonogashira Reaction

For example, synthesis of 1,2-diphenylethyne, **13**.

To an oven dried 5 mL microwave vessel was added $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%) and CuI (1.9 mg, 0.01 mmol, 4 mol%). The vessel was then capped and purged with N_2 before addition of Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2×20 mL) and brine (2×20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.6 mg, 96%).

ν_{max} (solid): 3068, 1603, 1495, 1446 cm^{-1}.

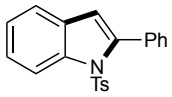
^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (dd, J = 7.2, 1.9 Hz, 4H), 7.38–7.32 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.4, 128.3, 123.3, 89.4.

HRMS: exact mass calculated for [M] ($C_{14}H_{10}$) requires *m/z* 178.0782, found *m/z* 178.0784.

Characterisation data is consistent with literature reported values.[162]

General Procedure B: Cyrene-based Synthesis of Indoles and Benzofurans



For example, synthesis of 2-phenyl-1-tosyl-1*H*-indole, **47**.

To an oven dried 5 mL microwave vessel was added $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), and *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv.). The vessel was then capped and purged with N_2 before addition of Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h. The reaction was subsequently heated to 60 °C and maintained at this temperature for 6 h before the vessel was vented and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2×20 mL) and brine (2×20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (78.4 mg, 90%).

ν_{max} (solid): 3073, 1368, 1169 cm^{-1}.

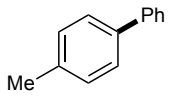
^1H NMR ($CDCl_3$, 500 MHz): δ 8.33 (d, *J* = 8.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.47–7.44 (m, 4H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.5, 142.2, 138.3, 134.7, 132.4, 130.7, 130.4, 129.2, 128.7, 127.5, 126.8, 124.8, 124.3, 120.7, 116.7, 113.4, 21.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}NO_6S$) requires *m/z* 348.1058, found *m/z* 348.1061.

Characterisation data is consistent with literature reported values.[163]

General Procedure C: Optimized Conditions for the Cyrene-based Suzuki–Miyaura Reaction



For example, synthesis of 4-phenyltoluene, **57**.

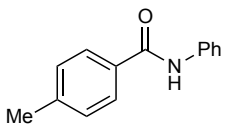
To an oven dried 5 mL microwave vessel was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), and Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.). The vessel was then capped and purged with N_2 before addition of Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). The reaction mixture was heated to 50 °C and maintained at this temperature with stirring for 5 h before the vessel was vented, and decapped. The solution was then diluted with Et_2O (10 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.9 mg, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38–7.33 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 138.5, 137.2, 129.6, 128.9, 127.1 (3C), 21.2.

Characterisation data is consistent with literature reported values.[164]

General Procedure D: Optimized Conditions for the Cyrene-based HATU-mediated Amide Bond Formation



For example, synthesis of 4-methyl-*N*-phenylbenzamide, **126**.

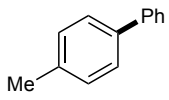
To a 5 mL round-bottomed flask was added *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at room temperature for 10 mins before the addition of aniline (25 µL, 0.275 mmol, 1.1 equiv.) and subsequently maintained at this temperature for 1 h with stirring. The solution was then diluted with EtOAc (20 mL), and washed with 2 M HCl (2 x 20 mL), sat. solution $NaHCO_3$ (2 x 20 mL), H_2O (20 mL), and brine (20 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was subsequently purified by flash chromatography (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (51 mg, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (br s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.8, 142.5, 138.2, 132.3, 129.6, 129.2, 127.2, 124.6, 120.3, 21.6.

Characterisation data is consistent with literature reported values.[165]

General Procedure E: Optimised Conditions for the DMI-based Suzuki–Miyaura Reaction



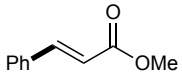
For example, synthesis of 4-phenyltoluene, **57**.

To an oven dried 5 mL microwave vessel was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.). The vessel was then capped and purged with N_2 before addition of DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25 mmol, 5 equiv.). The reaction mixture was heated to 60 °C and maintained at this temperature with stirring for 1 h before the vessel was vented, and decapped. The solution

was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-5% EtOAc in petroleum ether) to afford the title compound as a colourless solid (42.9 mg, >99%).

Characterisation data is consistent with those reported previously and with literature reported values.[164]

General Procedure F: Optimised Conditions for the DMI-based Mizoroki–Heck Reaction



For example, synthesis of methyl cinnamate **157**.

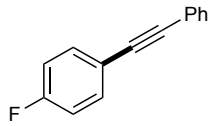
To an oven dried 5 mL microwave vessel was added Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), and iodobenzene (28 μL, 0.25 mmol, 1 equiv.). The vessel was then capped and purged with N_2 before addition of DMI (1 mL, 0.25 M), methyl acrylate (45 μL, 0.5 mmol, 2 equiv.), and Et_3N (105 μL, 0.75 mmol, 3 equiv.). The reaction mixture was heated to 80 °C and maintained at this temperature with stirring for 1 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-5% EtOAc in petroleum ether) to afford the title compound as a colourless solid (40 mg, 99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.53 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.41–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.6, 145.0, 134.6, 130.4, 129.0, 128.2, 117.9, 51.8.

Characterisation data is consistent with literature reported values.[166]

General Procedure G: Conditions for the DMI-based Sonogashira Reaction



For example, synthesis of 1-fluoro-4-(phenylethynyl)benzene, **14**.

To an oven dried 5 mL microwave vessel was added $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 4-fluoroiodobenzene (29 μL, 0.25 mmol, 1 equiv.), and phenylacetylene (29 μL, 0.26 mmol, 1.05 equiv.). The vessel was then capped and purged with N_2 before addition of DMI (0.5 mL, 0.5 M), and Et_3N (38 μL, 0.28 mmol, 1.1 equiv.). The reaction mixture was maintained at room temperature with stirring for 1 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2×20 mL) and brine (20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0-5% EtOAc in petroleum ether) to afford the title compound as a colourless solid (45 mg, 92%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.50 (m, 4H), 7.38–7.33 (m, 3H), 7.05 (t, J = 8.7 Hz, 2H).

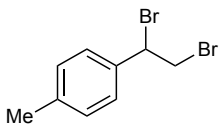
^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.7 (d, $^1J_{CF}$ = 249.6 Hz), 133.6 (d, $^3J_{CF}$ = 8.2 Hz), 131.7, 128.5, 128.5, 123.3, 119.5 (d, $^4J_{CF}$ = 3.4 Hz), 115.8 (d, $^2J_{CF}$ = 22.4 Hz), 89.2, 88.4.

^{19}F NMR ($CDCl_3$, 471 MHz,) δ -110.98.

Characterisation data is consistent with literature reported values.[163]

6.2.2 General Procedures for the Synthesis of Precursors

General Procedure H: Synthesis of Dibromides



For example, synthesis of (1,2-dibromoethyl)toluene, **58**

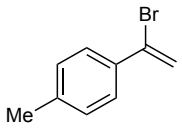
To an oven dried 10 mL round-bottomed flask charged with 4-methylstyrene (224.5 mg, 1.9 mmol, 1 equiv.) and $CHCl_3$ (1 mL, 1.9 M) was added bromine (110 µL, 2.15 mmol, 1.15 equiv.) dropwise under N_2 at 0 °C. The reaction was allowed to reach room temperature before being diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium bisulfite solution (10 mL). The organics were passed through a hydrophobic frit and concentrated to afford (1,2-dibromoethyl)toluene as an off colourless solid (528.2 mg, >99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.15 (dd, *J* = 10.6, 5.5 Hz, 1H), 4.11–3.99 (m, 2H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 139.2, 135.6, 129.6, 127.5, 51.0, 35.0, 21.3.

Characterisation data is consistent with literature reported values.[168]

General Procedure I: Synthesis of Vinyl bromides



For example, synthesis of 1-(1-bromovinyl)-4-methylbenzene, **63**

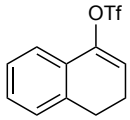
To an oven dried 10 mL round-bottomed flask charged with (1,2-dibromoethyl)toluene (528.2 mg, 1.9 mmol, 1 equiv.) as a solution in a mixture of MeOH/THF (1/1, 2 mL) was added K_2CO_3 (525.2 mg, 3.8 mmol, 2 equiv.). The reaction mixture was stirred at room temperature for 16 h before being quenched with water (10 mL). The volatiles were removed under reduced pressure and the aqueous layer extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (2 x 10 mL), passed through a hydrophobic frit and concentrated to afford the title compound as a yellow oil (294.9 mg, 79%) which was immediately used in subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.08 (d, *J* = 2.0 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 139.2, 135.8, 131.1, 128.9, 127.2, 116.8, 21.1.

Characterisation data is consistent with literature reported values.[169]

General Procedure J: Synthesis of Trifluoromethanesulfonates



For example, synthesis of 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate, **68**

To an oven dried 25 mL round-bottomed flask was added 1-tetralone (600 mg, 4.1 mmol, 1 equiv.). The flask was sealed and purged with N_2 before addition of CH_2Cl_2 (16.5 mL, 0.25 M) and Et_3N (0.86 mL, 6.2 mmol, 1.5 equiv.). The reaction mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (1 mL, 6.2 mmol, 1.5 equiv.) was added dropwise under nitrogen before it was heated to 40 °C and maintained at this temperature with stirring for 24 h. Upon completion of the reaction, the solution was washed with water (2 x 20 mL) and the organics passed through a hydrophobic frit and concentrated under reduced pressure to give a brown oil, which was purified by flash chromatography (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (1.15 g, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.34 (m,1H), 7.30–7.24 (m, 2H), 7.20–7.16 (m, 1H), 6.03 (t, J = 4.8 Hz, 1H), 2.88 (t, J = 8.2 Hz, 2H), 2.52 (td, J = 8.2, 4.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.4, 136.2, 129.2, 128.7, 127.7, 126.9, 121.2, 118.6 (q, $^1J_{CF}$ = 320.5 Hz), 117.7, 26.8, 22.3.

^{19}F NMR (CDCl3, 376 MHz): δ -73.69.

Characterisation data is consistent with literature reported values.[167]

6.3 Reaction Optimisation

6.3.1 Reaction Optimisation Data for the Investigation of Cyrene as an Alternative Solvent in the Sonogashira Cross-Coupling and Cacchi-Type Annulation Reactions

Results from Table 5, Concentration Study

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (**X** M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 5 h at 20 °C, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the desired compound as a colourless solid.

Entry	Concentration (M)	Isolated Yield (%)
1	0.3	98
2	0.1	94
3	0.5	> 99

Results from Table 6, Base Study

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), **Base** (**X** equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 5 h at 20 °C, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the desired compound as a colourless solid.

Entry	Base	Equivalents	Isolated Yield (%)
1	K_3PO_4	3	-

2	Cs_2CO_3	3	-
3	DIPEA	3	85
4	Pyridine	3	0
5	Et_3N	1.1	98
6	Et_3N	1.5	94
7	Et_3N	2	92

[a]Solidification of reaction mixture

Results from Table 7, Temperature Study

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After **T** h at ***t*** °C, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the desired compound as a colourless solid.

Entry	**Temp. (°C)**	**Time (h)**	**Isolated Yield (%)**
1	20	1	86
2	20	3	94
3	20	5	98
4	25	1	91
5	30	1	96

Results from Table 8, Solvent Study

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), **solvent** (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 5 h at 30 °C, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the desired compound as a colourless solid.

Entry	Solvent	Isolated Yield (%)
1	Cyrene	96
2	THF	81
3	DMF	87

6.3.2 Reaction Optimisation Data for the Investigation of Cyrene as an Alternative Solvent in the Suzuki–Miyaura Cross-Coupling

Results from Table 10, Base Study

Reactions were carried out according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), **Base** (3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (22.5 µL, 5 equiv.). After 5 h at 20 °C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid.

Entry	Base	Isolated Yield µ ± σ (%)
1	K_3PO_4	-[b]
2	K_2CO_3	-[b]

3	Cs_2CO_3	82 ± 16
4	Et_3N	13 ± 3
5	KF	7
6	KOAc	1
7	Na_3PO_4	1
8	Na_2CO_3	1

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture.

Results from Table 11, Fixed Concentration Water Study

Reactions were carried out according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (**X** mL), and H_2O (**X** mL, **X** equiv.). After 5 h at 20 °C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid.

Entry	**H_2O volume (mL)**	**Cyrene volume (mL)**	**Isolated yield μ ± σ (%)[a]**
1	0	2	-[b]
2	0.02	1.98	-[b]
3	0.05	1.95	-[b]
4	0.09	1.91	5 ± 0
5	0.23	1.77	6 ± 1
6	0.45	1.55	12 ± 2
7	0.9	1.1	34 ± 1

8	1	1	61 ± 35
9	1.35	0.65	58 ± 1
10	1.8	0.2	31 ± 0

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture.

Results from Table 12, Variable Concentration Water Study

Reactions were carried out according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL), and H_2O (**X** mL, **X** equiv.). After 5 h at 20 °C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid.

Entry	H_2O volume (mL)	Total volume (mL)	Concentration (M)	Isolated yield μ ± σ (%)[a]
1	0	1.00	0.250	-[b]
2	0.02	1.02	0.245	82 ± 16
3	0.05	1.05	0.238	21 ± 4
4	0.09	1.09	0.229	41 ± 26
5	0.23	1.23	0.203	37 ± 21
6	0.45	1.45	0.172	41 ± 27
7	0.9	1.90	0.132	57 ± 30
8	1	2.00	0.125	66 ± 28
9	1.35	2.35	0.106	72 ± 15

10	1.8	2.80	0.089	81 ± 15

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture.

Results from Table 13, Temperature Study

Reactions were carried out according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL), and H_2O (1.8 mL, 400 equiv.). After 5 h at **X** °C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid.

Entry	Temperature (°C)	Isolated yield (%)[a]
1	30	-[b,c]
2	20	81 ± 15
3	30	80 ± 12
4	50	94 ± 5

[a] Yield given as the mean and standard deviation of four reactions. [b]Solidification of reaction mixture. [c] Cyrene (1 mL), H_2O (5 equiv.)

Results from Table 14, Solvent Study

Reactions were carried out according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), **Solvent** (1 mL), and H_2O (1.8 mL, 400 equiv.). After 5 h at 50 °C, the reaction

mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid.

Entry	Solvent	Isolated yield (%)
1	Cyrene	94 ± 5
2	THF	92
3	DMF	98
4	1,4-Dioxane	>99
5	H_2O	31

6.3.3 Reaction Optimisation Data for the Investigation of Cyrene as an Alternative Solvent in Amide Bond Formation

Results from Table 15, Time Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (87 µL, 0.5 mmol, 2 equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After **X** h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure. Note that these experiments were run before stirring rate was identified as a key factor (Table 16).

Entry	Time (h)	Conversion µ ± σ (%)
1	1	84 ± 21
2	2	83 ± 27
3	4	81 ± 0
4	8	98 ± 2

5	16	91 ± 13
6	24	87 ± 13
7	48	86 ± 7

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 16, Stirring Rate Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (87 µL, 0.5 mmol, **2 equiv.**), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at **X** rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	**Stirring Rate (rpm)**	**Conversion µ ± σ (%)[a]**
1	100	51 ± 10
2	200	73 ± 3
3	400	71 ± 3
4	800	96 ± 7
5	1200	91 ± 11

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 17, Base Equivalency Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (**X** equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was

stirred at 400 rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Base (equiv.)	Conversion μ ± σ (%)[a]
1	1	83 ± 4
2	2	96 ± 7
3	3	92 ± 2
4	5	90 ± 6
5	10	96 ± 4
6	20	76 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 18, Stirring Rate Study Using 3 Equiv. Base

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 μL, 0.75 mmol, **3 equiv.**), aniline (25 μL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at **X** rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Stirring Rate (rpm)	Conversion μ ± σ (%)[a]
1	200	92 ± 5
2	400	92 ± 2
3	800	>99 ± 0

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 19, Coupling Reagent Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), **coupling reagent** (0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Coupling Reagent	Conversion µ ± σ (%)[a]
1	HATU	92 ± 2
2	COMU	14 ± 2
3	DIC/HOBt	9 ± 7
4	PyBOP	29 ± 1
5	T3P	4 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 20, Base Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), **base** (0.75 mmol, 3 equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Base	Conversion µ ± σ (%)[a]
1	DIPEA	92 ± 2

2	Et_3N	67 ± 4
3	NMM	43 ± 3
4	Lutidine	35 ± 1

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

Results from Table 21, Solvent Study

Reactions were carried out according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and **Solvent** (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at 20 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	**Solvent**	**Conversion µ ± σ (%)[a]**
1	DMF	94 ± 1
2	Cyrene	92 ± 2
3	CPME	18 ± 2
4	EtOAc	72 ± 6
5	*i*-PrOH	29 ± 4
6	2-MeTHF	28 ± 5

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

6.3.4 Reaction Optimisation Data for the Investigation of DMI as an Alternative Solvent in the Suzuki–Miyaura Cross-Coupling

Results from Table 22, Temperature Study

Reactions were carried out according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (3 equiv.), DMI (1 mL, 0.25 M), and H_2O (22.5 µL, 5 equiv.). After 1 h at **X** °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Temperature (°C)	Conversion (%)[a]
1	20	62
2	30	72
3	40	93
4	60	>99

[a] ^1H NMR % conversion calculated using an internal standard as an average of two reactions.

Results from Table 23, Catalyst Loading Study

Reactions were carried out according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (**X** mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (3 equiv.), DMI (1 mL, 0.25 M), and H_2O (22.5 µL, 5 equiv.). After 1 h at 40 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Catalyst loading (mol%)	Conversion (%)[a]
1	4	93
2	2	92

3	1	92
4	0.5	80

[a] ^{1}H NMR % conversion calculated using an internal standard as an average of two reactions.

6.3.5 Reaction Optimisation Data for the Investigation of DMI as an Alternative Solvent in the Mizoroki–Heck Cross-Coupling

Results from Table 24, Time Study for Iodobenzene System

Reactions were carried out according to General Procedure F using $Pd(PPh_3)_2Cl_2$ (8.8 mg, 0.013 mmol, 5 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), Et_3N (105 µL, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M). After **X** h at 80 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Time (h)	Conversion (%)[a]
1	1	>99
2	2	98
3	4	98
4	8	>99

[a] ^{1}H NMR % conversion calculated using an internal standard as an average of two reactions.

Results from Table 25, Temperature Study for Iodobenzene System

Reactions were carried out according to General Procedure F using $Pd(PPh_3)_2Cl_2$ (8.8 mg, 0.013 mmol, 5 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), Et_3N (105 µL, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M). After 1 h at **X** °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Temperature (°C)	Conversion (%)[a]
1	23	0
2	30	<1
3	40	<1
4	60	12
5	80	>99

[a] ^{1}H NMR % conversion calculated using an internal standard as an average of two reactions.

Results from Table 26, Time Study for Bromobenzene System

Reactions were carried out according to General Procedure F using $Pd(PPh_3)_2Cl_2$ (8.8 mg, 0.013 mmol, 5 mol%), bromobenzene (26 µL, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), Et_3N (105 µL, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M). After **X** h at 80 °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Time (h)	Conversion (%)[a]
1	1	<1
2	2	7
3	4	11
4	8	16
5	16	67
6	24	81

[a] ^{1}H NMR % conversion calculated using an internal standard as an average of two reactions.

Results from Table 27, Temperature Study for the Bromobenzene System

Reactions were carried out according to General Procedure F using $Pd(PPh_3)_2Cl_2$ (8.8 mg, 0.013 mmol, 5 mol%), bromobenzene (26 µL, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), Et_3N (105 µL, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M). After 24 h at **X** °C, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Temperature (°C)	Conversion (%)[a]
1	80	81
2	100	89
3	115	98

[a] ^1H NMR % conversion calculated using an internal standard as an average of two reactions.

Results from Table 28, Catalyst Screen for Electron Poor Systems

Reactions were carried out according to General Procedure F using **catalyst** (5 mol%), 4-nitroiodobenzene (31 mg, 0.125 mmol, 1 equiv.), methyl acrylate (23 µL, 0.25 mmol, 2 equiv.), Et_3N (52 µL, 0.38 mmol, 3 equiv.), DMI (0.5 mL, 0.25 M). After 1 h at 80 °C, the reaction mixture was subjected to the purification method outlined in the General Procedure silica gel, 0-15% EtOAc in petroleum ether).

Entry	Catalyst	Isolated Yield (%)
1	$Pd(PPh_3)_2Cl_2$	0
2	$Pd(PPh_3)_4$	0
3	$Pd(dppf)Cl_2$	85

6.4 Investigation of Base Sensitivity

Results from Table 9

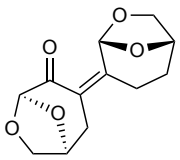
Base (0.07 mmol) was added to a test tube and Cyrene (0.5 mL) was added. The tube was then capped and the mixture stirred at **X** °C. After 24 h the reaction mixture was sampled and analysed by TLC (60% EtOAc in petroleum ether) and ^{1}H NMR and the resulting spectrum compared with that of Cyrene.

Entry	Base	Temp (°C)	Reaction (Y/N)[a]
1	KOAc	25	N
		50	Y
		100	Y
2	Pyridine	25	N
		50	Y
		100	Y
3	K_2CO_3	25	Y
		50	Y
		100	Y
4	DIPEA	25	N
		50	N
		100	Y
5	Cs_2CO_3	25	Y
		50	Y
		100	Y

		25	N
6	Et_3N	50	N
		100	Y
		25	Y
7	K_3PO_4	50	Y
		100	Y
		25	Y
8	DBU	50	Y
		100	Y
		25	Y
9	KOH	50	Y
		100	Y
		25	Y
10	*t*-BuOK	50	Y
		100	Y
		25	Y
11	NaH	50	Y
		100	Y

[a]Analysis by TLC and ^{1}H NMR

6.5 Preparation and Characterisation of Cyrene Adduct, 54



To an oven dried 5 mL microwave vessel was added K_3PO_4 (637 mg, 3 mmol, 3 equiv.). The vessel was then capped and purged with N_2 before addition of THF (4 mL, 0.25 M), and Cyrene (123 µL, 1 mmol, 1 equiv.). The reaction mixture was heated to 70 °C and maintained at this temperature with stirring for 8 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (20 mL) and washed with water (2×20 mL) and brine (2×20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give an off-white solid, which was purified by flash chromatography (silica gel, 0-50% EtOAc in petroleum ether) to afford the title compound as a colourless solid (105 mg, 88%).

ν_{max} (solid): 2898, 1703, 1621, 1098 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 6.76 (s, 1H), 5.18 (s, 1H), 4.79 (t, J = 5.1 Hz, 1H), 4.60 (t, J = 4.0 Hz, 1H), 3.94–3.83 (m, 4H), 2.78 (dd, J = 16.3, 2.6 Hz, 1H), 2.56 (d, J = 16.3 Hz, 1H), 2.41-2.24 (m, 2H), 2.14-2.07 (m, 1H), 1.75 (dd, J = 13.5, 6.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.7, 151.0, 123.4, 101.5, 97.2, 72.6, 72.5, 68.7, 67.8, 34.1, 28.8, 20.4.

HRMS: exact mass calculated for [M] ($C_{12}H_{14}$) requires *m/z* 238.0841, found *m/z* 238.0839.

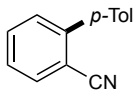
Single Crystal Diffraction. Measurements were made with an Oxford Diffraction Gemini S instrument. Refinement was to convergence against F^2 and used all unique reflections. Programs used were from the SHELX suite.[20] Non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were placed in idealized positions and refined in riding modes. Selected crystallographic and refinement parameters are given in Table 1. CCDC reference number CCDC 1485168 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 29 Selected crystallographic data and refinement parameters for compound 17b.

Compound	**17b**
Formula	$C_{12}H_{14}O_5$
M_r (g mol^{-1})	238.23
Crystal system	monoclinic
Space group	$P2_1$
Temperature (K)	123(2)
a (Å)	6.4668(2)
b (Å)	9.8239(3)
c (Å)	8.5963(2)
β (°)	96.341(3)
V/Å^3	542.78(3)
Z	2
Wavelength (Å)	0.71073
Measured reflections	9884
Unique reflections	3457
R_{int}	0.03024
Observed rflns [$I > 2\sigma(I)$]	3286
μ (mm^{-1})	0.114
No. of parameters	155
2θmax (°)	63.8

R [on *F*, obs rflns only]	0.0329
wR [on F^2, all data]	0.0852
GoF	1.043
Largest diff. peak/hole/e $Å^{-3}$	0.242/–0.191

6.6 Procedure for the large-scale synthesis of 4'-methyl-2-biphenylcarbonitrile (OTBN), 94



To a 1 L round-bottomed flask was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (744 mg, 0.91 mmol, 4 mol%), 2-bromobenzonitrile (4.2 g, 22.8 mmol, 1 equiv.), *p*-tolylboronic acid (3.1 g, 22.8 mmol, 1 equiv.), Cs_2CO_3 (22.3 g, 68.4 mmol, 3 equiv.), and H_2O (166 mL). Cyrene (91 mL) was subsequently added and the reaction vessel sealed with a septum and placed under a N_2 atmosphere. The reaction mixture was heated to 50 °C and maintained at this temperature with stirring for 5 h before being allowed to return to 20 °C.

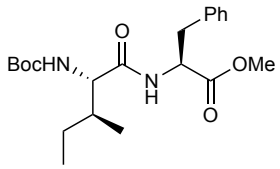
The solution was then diluted with a 40% solution EtOAc in petroleum ether (3 x 200 mL) and stirred at 20 °C for 30 mins before the liquids were decanted (56 g of Cyrene dimer was isolated from the precipitate). The combined liquids were separated, and the organic phase dried over Na_2SO_4 and concentrated. The brown oil was then dissolved in a 15% solution EtOAc in petroleum ether (100 mL) and washed with H_2O (2 x 200 mL). The combined organics were filtered through celite and concentrate to yield a yellow oil (4.4 g, >99%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.75 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.5, 138.7, 135.3, 133.7, 132.7, 129.9, 129.4, 128.6, 127.2, 118.8, 111.2, 21.2

Characterization data is consistent with literature reported values.[164]

6.7 Procedure for the Large-Scale Synthesis of Boc-Ile-Phe-OMe, 144



To a 100 mL round-bottomed flask was added Boc-Ile-OH (1 g, 4.3 mmol, 1 equiv.), HATU (2 g, 5.2 mmol, 1.2 equiv.), DIPEA (2.2 mL, 12.9 mmol, 3 equiv.), and Cyrene (22 mL, 0.2 M). The reaction mixture was stirred at 20 °C for 10 mins before the addition of Phe-OMe.HCl (1 g, 4.8 mmol, 1.1 equiv.) and subsequently maintained at this temperature for 1 h with stirring. The solution was then diluted with EtOAc (40 mL), and washed with 2 M HCl (2 x 100 mL), sat. solution $NaHCO_3$ (2 x 100 mL), H_2O (100 mL), and brine (50 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was subsequently triturated with cold Et_2O to afford the title compound as a colourless solid (1.7 g, >99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–7.21 (m, 3H), 7.13–7.10 (m, 2H), 6.27 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.87 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.96–3.87 (m, 1H), 3.71 (s, 3H), 3.17–3.06 (m, 2H), 1.86–1.79 (m, 1H), 1.58 (br s, 1H), 1.44 (s, 9H), 1.07 (br s, 1H), 0.89 - 0.86 (m, 6H).

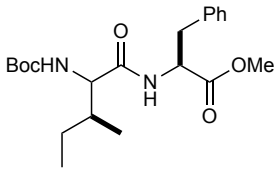
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 171.3, 155.8, 135.8, 129.4, 128.8, 127.3, 80.0, 59.4, 53.2, 52.4, 38.1, 37.4, 28.4, 24.8, 15.6, 11.6.

Characterization data is consistent with literature reported values.[170]

6.8 Evidence of Enantiopurity

The DL-L enantiomers of the following peptides were synthesized and the ^{1}H NMR of the diastereotopic mixture compared to those of the enantiopure analogues.

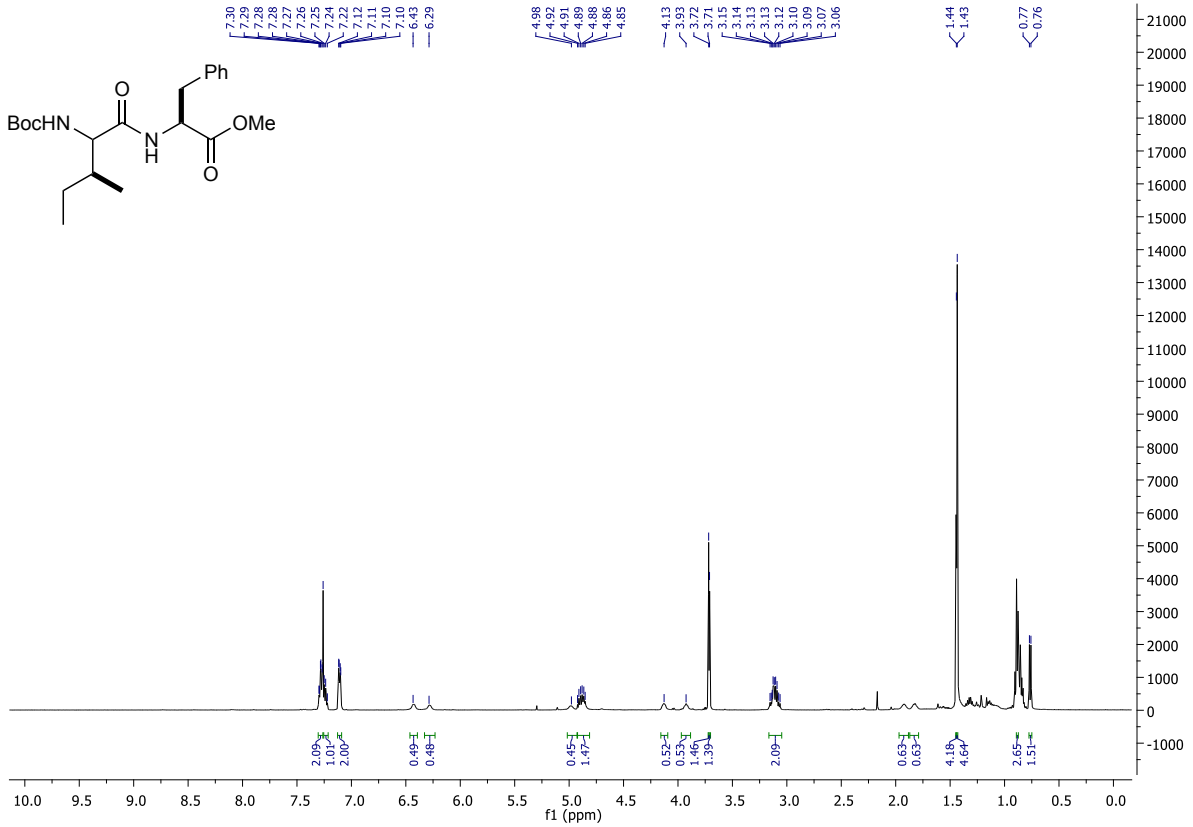
151: Boc-(DL)Ile-Phe-OMe



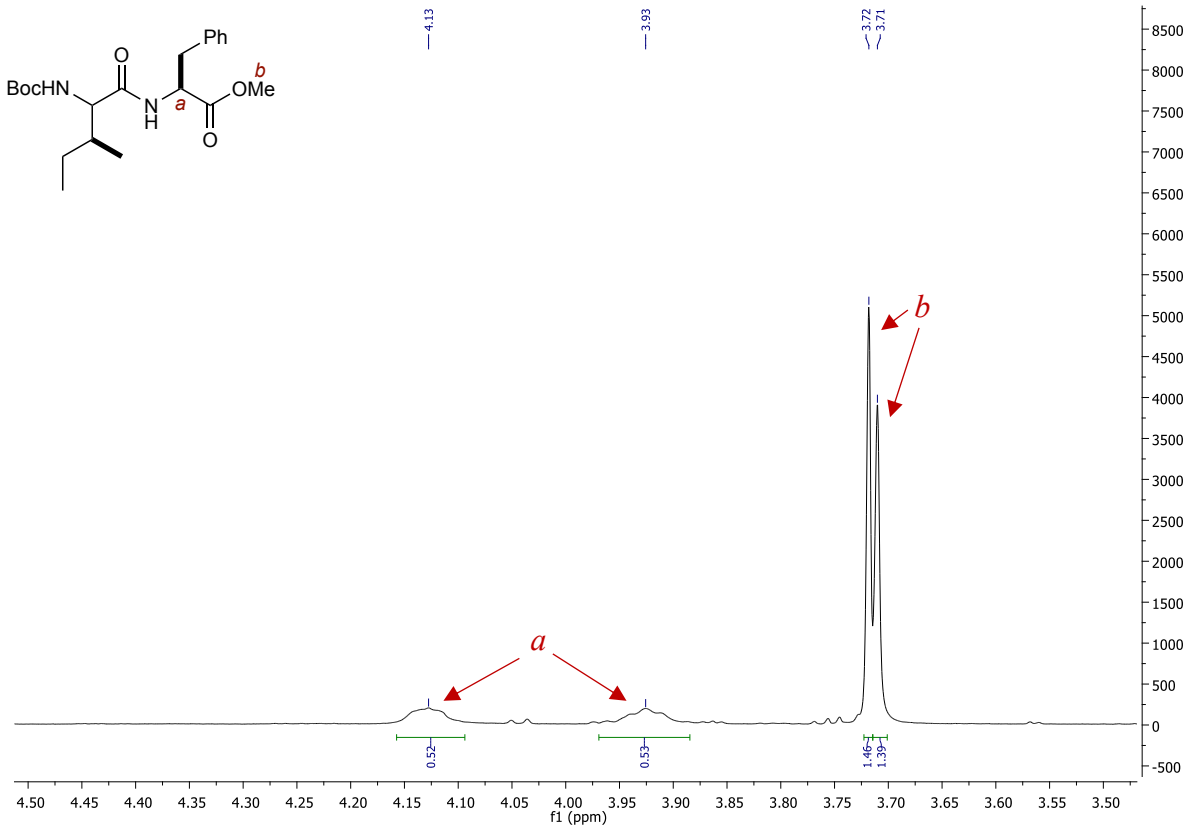
Prepared according to General Procedure D using Boc-(DL)Ile-OH (57.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Phe-OMe.HCl (59.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (102 mg, >99%).

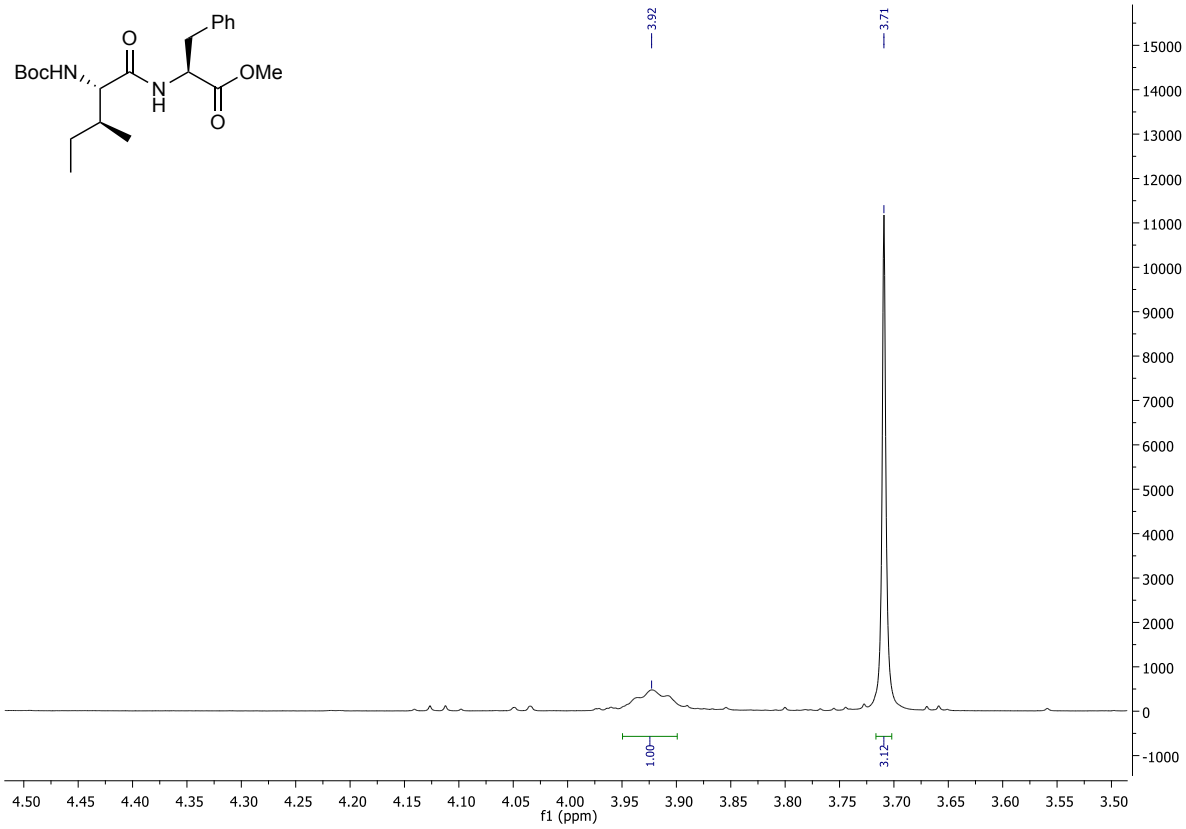
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.31–7.21 (m, 3H), 7.11 (m, 2H), 6.43 (DL br s, 0.5H), 6.29 (LL br s, 0.5H), 4.98 (LL br s, 0.5H), 4.92–4.85 (m, 1.5H), 4.13 (DL br s, 0.5H), 3.93 (LL br s, 0.5H), 3.72 (DL s, 1.5H), 3.71 (LL s, 1.5H), 3.17–3.05 (m, 2H), 1.92 (DL br s, 0.5H), 1.83 (LL br s, 0.5H), 1.44 (LL s, 4.5H), 1.43 (DL s, 4.5H), 0.90–0.83 (m, 6.5H), 0.76 (DL d, J = 6.9 Hz, 1.5H).

^{1}H NMR of Diastereotopic Mixture

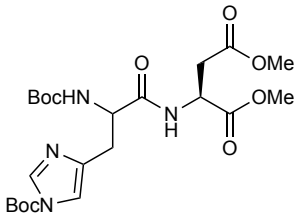


^{1}H Spectra (4.5-3.5 ppm) of diastereotopic mixture vs enantiopure compound





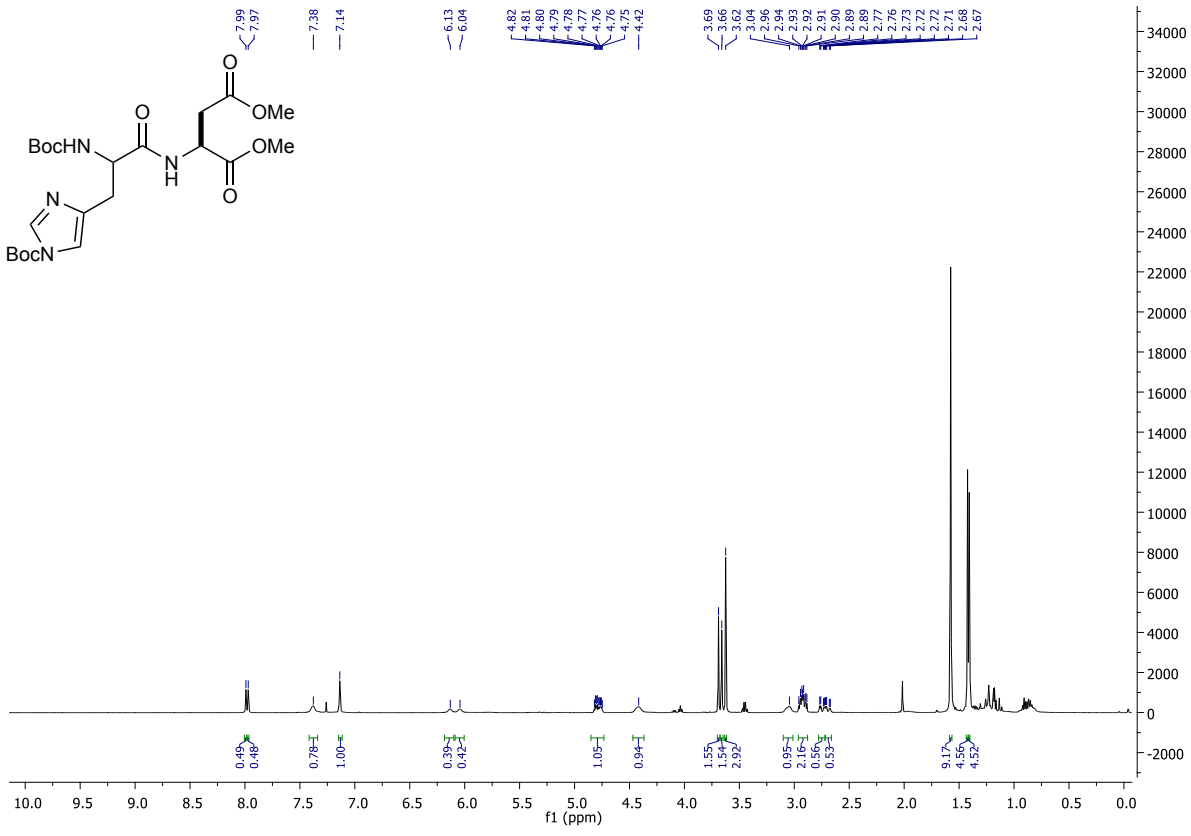
152: Boc-(DL)His(Boc)-Asp(OMe)-OMe



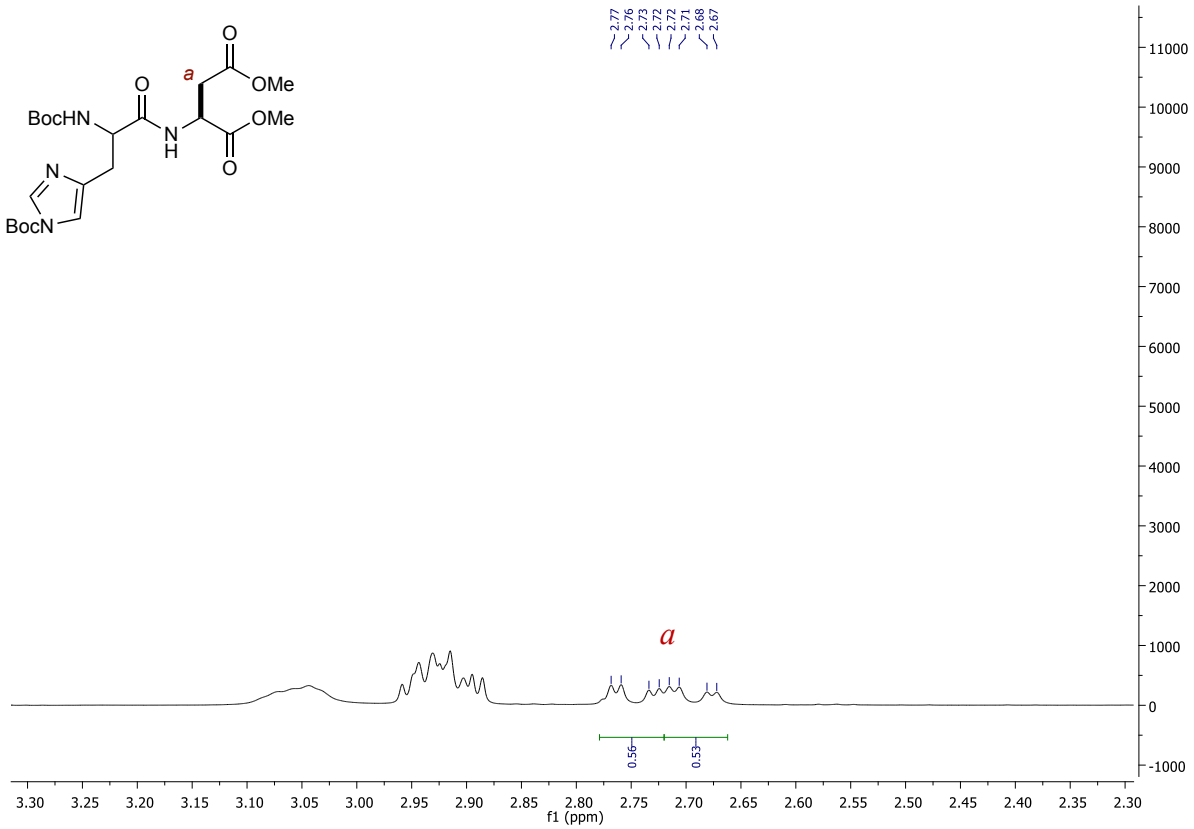
Prepared according to General Procedure D using Boc-(DL)His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Asp(OMe)-OMe.HCl (54.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-70% EtOAc in petroleum ether) to afford the title compound as a colourless oil (74.2 mg, 59%).

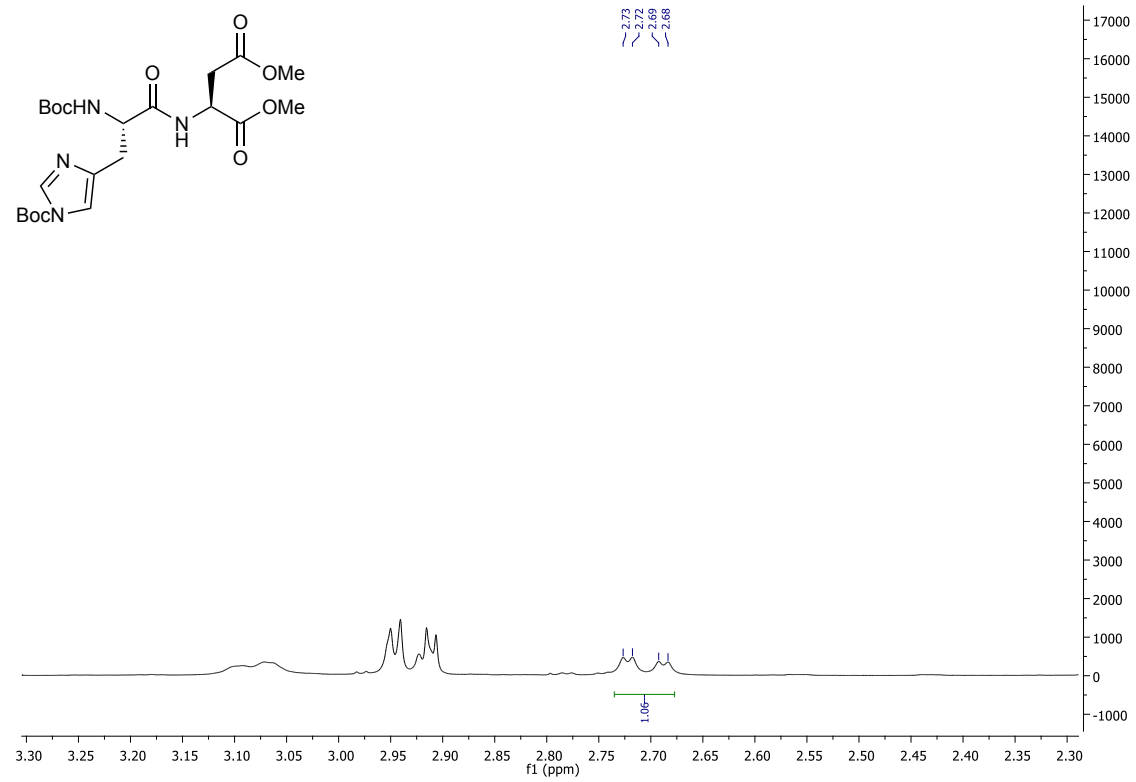
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.99 (DL s, 0.5H), 7.97 (LL s, 0.5H), 7.38 (br s, 1H), 7.14 (s, 1H), 6.13 (DL br s, 0.5H), 6.04 (LL br s, 0.5H), 4.84–4.73 (m, 1H), 4.42 (br s, 1H), 3.69 (LL s, 1.5H), 3.66 (DL s, 1.5H), 3.62 (s, 3H), 3.04 (br s, 1H), 2.92 (m, 2H), 2.75 (DL dd, J = 17.3, 4.6 Hz, 0.5H), 2.69 (LL dd, J = 17.1, 4.5 Hz, 0.5H), 1.58 (s, 9H), 1.42 (LL s, 4.5H), 1.41 (DL s, 4.5H).

^{1}H NMR of Diastereotopic Mixture



^{1}H Spectra (3.3-2.3 ppm) of diastereotopic mixture vs enantiopure compound





6.9 Procedure for the Attempted Solid Phase Synthesis of Leu-Enkephalin

6.9.1 General Procedures for Peptide Coupling

i. Wang resin, supplied by Sigma–Aldrich, was used for the synthesis.

ii. Manual couplings were performed in a Merrifield bubbler attached to a vacuum line, a nitrogen line and a round-bottom flask for waste.

iii. Cleavage of peptides from the resin was carried out using a mixture of TFA/TIPS/H_2O (95:2.5:2.5).

iv. Resin was swollen in DCM (10 mL) for 10 mins prior to synthesis.

v. Unless otherwise stated, a washing procedure using EtOAc (5 x 5 mL x 1 min) was carried out between all steps.

vi. Deprotections were carried out before all couplings using a solution of 20% (v/v) piperidine in EtOAc (3 x 5mL x 5 mins).

vii. *N*-terminal capping was carried out using 15% (v/v) Ac_2O in EtOAc (3 x 5mL x 5 mins).

viii. Fmoc loading test: two 10 mL volumetric flasks were charged with a known mass of resin (~ 5 mg). The flasks were then filled to the 10 mL mark with 20% piperidine in EtOAc solution, stoppered and sealed with parafilm. The flasks were simultaneously sonicated for 15 mins. After this time the UV absorption of each solution at 302 nm was measured. This absorption was then used in the calculation shown in Figure 18, which is derived from the Beer-Lambert law, to give the loading of the resin. The average value of the two tests was taken as the overall loading of the sample resin.

$$Loading = \frac{A\ x\ 10}{m\ x\ 7.8}$$

Figure 18 Fmoc loading test equation. A = absorption at 302 nm, m = mass of resin tested (mg)

ix. Full cleavage reactions were charged with 10 mL of cleavage solution. The resin was agitated for 4 h and then filtered into a 50 mL Falcon tube filled with cold Et_2O (25 mL). The sample was centrifuged for 3 mins and the supernatant discarded. This was repeated twice, and the solvent removed *in vacuo*.

6.9.2 Attaching first Amino Acid Residue to Resin

A 100 mL round-bottom flask, equipped with a stirrer bar, was charged with Fmoc-Leu-OH (2.9 g, 8.25 mmol, 10 equiv.). DCM (25 mL) was added and the flask equipped with a CaCl drying tube before cooling to 0 °C. DIC (635 μL, 4.13 mmol, 5 equiv.) in DCM (1 mL) was added to the flask and the solution stirred at 0 °C for 10 mins. The reaction mixture was allowed to reach 20 °C and stirred for a further 10 mins. DCM was removed and the solid redissolved in DMF (5 mL).

Simultaneously, Wang resin (750 mg, 0.83 mmol, 1 equiv.) was placed in the Merrifield bubbler and swollen in DCM (10 mL) for 10 mins. DCM was evacuated, and the resin washed with DMF (5 x 5 mL x 1 min). The symmetrical anhydride solution formed above was added to the bubbler, followed by 4-dimethylaminopyridine (100 mg, 0.83 mmol, 1 equiv.) in DMF (2 mL). The vessel was agitated for 1 h and the resin then washed with DMF (5 x 5mL x 1 min).

6.9.3 Loading Test

The loading test was carried out according to the General Procedure outlined in Section 6.9.1 using EtOAc or DMF as solvents in the 20% (v/v) piperidine deprotection solution.

Entry	Solvent	Mass Resin (mg)	Absorption	Loading (mmol/g)
1	EtOAc	6.2	2.99	0.62
2	EtOAc	6.5	3.30	0.65
3	DMF	5.2	2.54	0.63
4	DMF	8.9	2.78	0.40

6.9.4 Coupling Procedure

Based on a resin loading of 0.64 mmol/g (EtOAc) = 1.25 mmol (1.95 g) Wang resin.

Preparation of Coupling Mixture

A 10 mL sample vial was charged with amino acid (6.25 mmol, 5 equiv.) and HATU (2.4 g, 6.25 mmol, 5 equiv.). Cyrene (5 mL) and DIPEA (2.2 mL, 12.5 mmol, 10 equiv.) were added and the solution stirred at 20 °C for 30 mins before transfer to the Merrifield bubbler.

Coupling Procedure

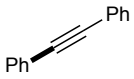
The resin was swollen in DCM, washed, deprotected and washed again according to the General Procedure outlined in Section 6.9.1 using EtOAc. This was followed by washing with Cyrene (2 x 5 mL x 1 min) and addition of the coupling reaction mixture. The resin was then agitated for 1 h. The resin was subsequently washed with Cyrene (2 x 5 mL x 1 min) and EtOAc (5 x 5 mL x 1 min) before subsequent deprotection and coupling steps.

Coupling	Amino Acid	Mass (g)
1	Fmoc-Phe-OH	2.4
2	Fmoc-Gly-OH	1.9
3	Fmoc-Gly-OH	1.9
4	Fmoc-Tyr-OH	2.9

On completion of the coupling steps, the *N*-terminus was capped and the resin cleaved according to the General Procedure outlined in Section 6.9.1. ^{1}H NMR analysis of the crude residue indicated the presence of leucine only.

6.10 Characterisation Data

13: 1,2-Diphenylethyne



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.6 mg, 96%).

ν_{max} (solid): 3068, 1603, 1495, 1446 cm^{-1}.

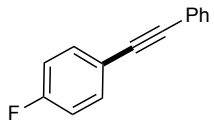
^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.2, 1.9 Hz, 4H), 7.38–7.32 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.4, 128.3, 123.3, 89.4.

HRMS: exact mass calculated for [M] ($C_{14}H_{10}$) requires *m/z* 178.0782, found *m/z* 178.0784.

Characterisation data is consistent with literature reported values.[162]

14: 1-Fluoro-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 4-fluoro-iodobenzene (28.8 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5%

Et_2O in petroleum ether) to afford the title compound as a colourless solid (48.8 mg, >99%).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), DMF (0.5 mL, 0.5 M), Et_3N (38 μL, 0.275 mmol, 1.1 equiv.), 4-fluoro-iodobenzene (28.8 μL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 μL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (46.9 mg, 96%).

Prepared according to General Procedure C using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 4-fluoro-iodobenzene (29 μL, 0.25 mmol, 1 equiv.), phenylacetylene (29 μL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 μL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (45 mg, 92%).

ν_{max} (solid): 2921, 1595, 1508, 1217 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.50 (m, 4H), 7.38–7.33 (m, 3H), 7.05 (t, J = 8.7 Hz, 2H).

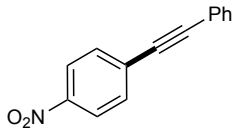
^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.5 (d, $^1J_{CF}$ = 249.6 Hz), 133.5 (d, $^3J_{CF}$ = 8.2 Hz), 131.6, 128.4, 128.4, 123.3, 119.4 (d, J_{CF} = 3.4 Hz), 115.7 (d, $^2J_{CF}$ = 22.4 Hz), 89.1, 88.3.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -110.98.

HRMS: exact mass calculated for [M] ($C_{14}H_9F$) requires *m/z* 196.0688, found *m/z* 196.0689.

Characterisation data is consistent with literature reported values.[163]

15: 1-Nitro-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 4-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as an off-white solid (48.8 mg, >99%).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 4-nitro-bromobenzene (50.5 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as an off-white solid (14.6 mg, 28%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 4-nitro-iodobenzene (62 mg, 0.25 mmol, 1 equiv.), phenylacetylene (29 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (55 mg, 98%).

ν_{max} (solid): 3107, 2926, 2217, 1593, 1511 cm^{-1}.

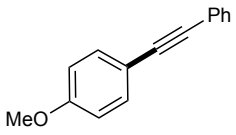
^1H NMR ($CDCl_3$, 500 MHz): δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.58–7.54 (m, 2H), 7.39 (dd, *J* = 5.3, 1.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 147.0, 132.3, 131.9, 130.4, 129.3, 128.6, 123.7, 122.1, 94.7, 87.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NO_2$) requires *m/z* 224.0712, found *m/z* 224.0714.

Characterisation data is consistent with literature reported values.[163]

16: 1-Methoxy-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 4-iodoanisole (58.5 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% Et_2O in petroleum ether) to afford the title compound as an off-white solid (51.9 mg, >99%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 4-iodoanisole (59 mg, 0.25 mmol, 1 equiv.), phenylacetylene (29 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (50 mg, 97%).

ν_{max} (solid): 3014, 2841, 2217, 1509 cm^{-1}.

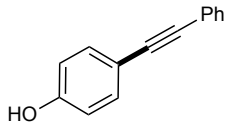
^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dt, *J* = 3.9, 2.1 Hz, 2H), 7.49–7.46 (m, 2H), 7.36–7.29 (m, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 133.1, 131.5, 128.3, 127.9, 123.6, 115.4, 114.0, 89.4, 88.1, 55.3.

HRMS: exact mass calculated for $[2M+H]^+$ ($C_{30}H_{25}O_2$) requires *m/z* 417.1855, found *m/z* 417.1847.

Characterisation data is consistent with literature reported values.[163]

17: 4-(Phenylethynyl)phenol



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (70 µL, 0.5 mmol, 2 equiv.), 4-iodophenol (55 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as an off-white solid (32.6 mg, 68%).

ν_{max} (solid): 3412, 3059, 1513, 1254 cm^{-1}.

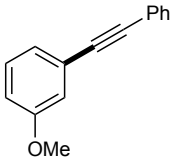
^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.36–7.30 (m, 3H), 6.81 (d, *J* = 8.6 Hz, 2H). Exchangeable proton not observed.

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.7, 133.3, 131.5, 128.3, 127.9, 123.6, 115.7, 115.5, 89.2, 88.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{11}O$) requires *m/z* 195.0810, found *m/z* 195.0813.

Characterisation data is consistent with literature reported values.[171]

18: 1-Methoxy-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 3-iodoanisole (29.8 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the

purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (51.4 mg, 99%).

ν_{max} (liquid film): 2937, 2838 cm^{-1}.

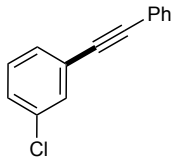
^1H NMR ($CDCl_3$, 500 MHz): δ 7.57–7.53 (m, 2H), 7.35 (dd, *J* = 4.9, 2.4 Hz, 3H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.91 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.4, 131.7, 129.4, 128.4, 128.3, 124.3, 124.2, 123.2, 116.4, 114.9, 89.3, 89.2, 55.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{13}O$) requires *m/z* 209.0966, found *m/z* 209.1008.

Characterisation data is consistent with literature reported values.[162]

19: 1-Chloro-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 3-chloro-iodobenzene (30.9 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (53.5 mg, 82%).

ν_{max} (liquid film): 3064, 2224, 884 cm^{-1}.

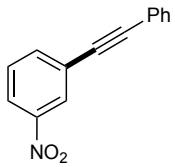
^1H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.51 (m, 3H), 7.41 (dt, *J* = 7.3, 1.4 Hz, 1H), 7.36 (dd, *J* = 4.9, 1.7 Hz, 3H), 7.31 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 134.4, 131.9, 131.6, 129.9, 129.8, 128.8, 128.7, 128.6, 125.2, 122.9, 90.7, 88.1.

HRMS: exact mass calculated for [M] ($C_{14}H_9{}^{35}Cl$) requires *m/z* 212.0393, found *m/z* 212.0395.

Characterisation data is consistent with literature reported values.[172]

20: 1-Nitro-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 3-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (55.2 mg, 99%).

ν_{max} (solid): 3083, 2213, 1517, 1349 cm^{-1}.

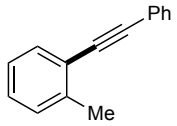
^1H NMR ($CDCl_3$, 500 MHz): δ 8.40–8.37 (m, 1H), 8.20–8.18 (m, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.58–7.53 (m, 3H), 7.41–7.38 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.2, 137.2, 131.8, 129.4, 129.1, 128.5, 126.4, 125.2, 122.9, 122.2, 91.9, 86.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NO_2$) requires *m/z* 224.0712, found *m/z* 224.0710.

Characterisation data is consistent with literature reported values.[173]

21: 1-Methyl-2-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-65% MeCN in water) to afford the title compound as a yellow oil (40 mg, 83%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 2-iodotoluene (32 µL, 0.25 mmol, 1 equiv.), phenylacetylene (29 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (45 mg, 94%).

ν_{max} (liquid film): 3023, 2924, 2855, 2217, 1496 cm^{-1}.

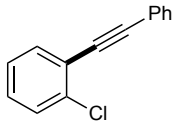
^1H NMR ($CDCl_3$, 500 MHz): δ 7.56–7.53 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.38–7.34 (m, 3H), 7.24 (d, *J* = 3.9 Hz, 2H), 7.19–7.16 (m, 1H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 140.3, 131.9, 131.7, 129.6, 128.5, 128.5, 128.3, 125.7, 123.7, 123.2, 93.5, 88.5, 20.9.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0935.

Characterisation data is consistent with literature reported values.[173]

22: 1-Chloro-2-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-chloro-iodobenzene (30.5 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-65% MeCN in water) to afford the title compound as a yellow oil (54.9 mg, >99%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 2-chloroiodobenzene (31 µL, 0.25 mmol, 1 equiv.), phenylacetylene (29 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (50 mg, 94%).

ν_{max} (liquid film): 3060, 2926, 2224, 1495 cm^{-1}.

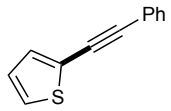
^1H NMR (DMSO-*d*$_6$, 500 MHz): δ 7.69 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.62–7.58 (m, 3H), 7.48–7.41 (m, 5H).

^{13}C NMR (DMSO-*d*$_6$, 126 MHz): δ 135.1, 133.8, 131.9, 130.9, 129.9, 129.8, 129.3, 127.9, 122.4, 122.3, 94.8, 86.4.

HRMS: exact mass calculated for [M] ($C_{14}H_9{}^{35}Cl$) requires *m/z* 212.0393, found *m/z* 212.0385.

Characterisation data is consistent with literature reported values.[162]

23: 2-(Phenylethynyl)thiophene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodothiophene (27.6 µL, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as an off-white solid (41.4 mg, 92%).

ν_{max} (liquid film): 3088, 2204 cm^{-1}.

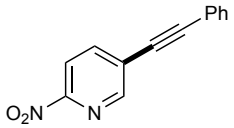
^1H NMR ($CDCl_3$, 500 MHz): δ 7.54–7.50 (m, 2H), 7.39–7.34 (m, 3H), 7.31–7.28 (m, 2H), 7.02 (dd, J = 5.0, 3.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M] ($C_{12}H_8S$) requires *m/z* 184.0347, found *m/z* 184.0348.

Characterisation data is consistent with literature reported values.[162]

24: 2-Nitro-5-(phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 5-bromo-2-nitropyridine (50.8 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15%

Et_2O in petroleum ether) to afford the title compound as a colourless solid (51.4 mg, 92%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 5-bromo-2-nitropyridine (51 mg, 0.25 mmol, 1 equiv.), phenylacetylene (29 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (55 mg). The yield was calculated as an NMR yield (48.4 mg, 84%) from 1:0.15 ratio title compound: 5-bromo-2-nitropyridine.

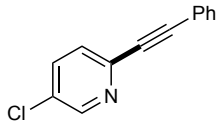
ν_{max} (solid): 3058, 2219, 1532, 1348 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.73 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.44–7.38 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.8, 151.1, 141.8, 131.9, 129.8, 128.7, 126.7, 121.4, 117.7, 97.9, 84.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9N_2O_2$) requires *m/z* 225.0664, found *m/z* 225.0670.

25: 5-Chloro-2-(phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 3-chloro-6-iodopyridine (59.8 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5%

Et_2O in petroleum ether) to afford the title compound as a colourless solid (54.5 mg, >99%).

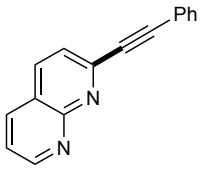
ν_{max} (solid): 3040, 2221, 1493, 1459 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.58 (d, *J* = 1.8 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.40–7.36 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.1, 141.5, 136.0, 132.1, 131.3, 129.2, 128.5, 127.7, 121.9, 90.4, 87.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9N^{35}Cl$) requires *m/z* 214.0418, found *m/z* 214.0421.

26: 2-(Phenylethynyl)-1,8-naphthyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-bromo-1,8-naphthyridine (52.3 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-65% Et_2O in petroleum ether) to afford the title compound as a colourless solid (54.3 mg, 94%).

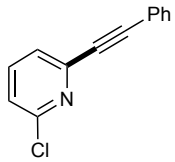
ν_{max} (solid): 3049, 3008, 2211, 1601, 1498 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 9.15 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 2H), 7.69–7.64 (m, 3H), 7.48 (dd, *J* = 7.7, 3.9 Hz, 1H), 7.43–7.37 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.1, 154.3, 146.9, 137.2, 136.6, 132.4, 129.5, 128.5, 125.4, 122.3, 121.9, 91.6, 89.3. Quaternary carbon at ring junction not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{11}N_2$) requires *m/z* 231.0922, found *m/z* 231.0923.

27: 2-Chloro-6-(phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.5 mmol, 1.1 equiv.), 2-bromo-6-chloropyridine (48 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as an off-white solid (52.3 mg, >99%).

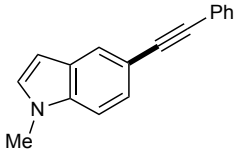
ν_{max} (solid): 3059, 2960, 2226, 1577, 1435 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.63 (t, *J* = 7.8 Hz, 1H), 7.60–7.56 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.37 (q, *J* = 5.7 Hz, 3H), 7.28 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.4, 143.6, 138.7, 132.1, 129.3, 128.5, 125.7, 123.6, 121.8, 90.7, 87.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9N^{35}Cl$) requires *m/z* 214.0424, found *m/z* 214.0427.

28: 1-Methyl-5-(phenylethynyl)-1*H*-indole



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (2.6 mg, 0.004 mmol, 2 mol%), CuI (1.4 mg, 0.007 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (28 µL, 0.20 mmol, 1.1 equiv.), 5-iodo-1-methyl-1*H*-indole (47 mg, 0.18 mmol, 1 equiv.), and phenylacetylene (21 µL, 0.19 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as an off-white solid (27.7 mg, 67%).

ν_{max} (solid): 3051, 2926, 2208, 1597, 1496 cm^{-1}.

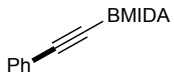
^1H NMR ($CDCl_3$, 500 MHz): δ 7.85 (s, 1H), 7.57–7.54 (m, 2H), 7.41 (dd, J = 8.5, 1.2 Hz, 1H), 7.36–7.30 (m, 4H), 7.08 (d, J = 3.1 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.4, 131.5, 129.8, 128.4, 128.3, 127.7, 125.2, 124.8, 124.1, 113.8, 109.3, 101.3, 91.2, 87.0, 32.9.

HRMS: exact mass calculated for [M] ($C_{17}H_{13}N$) requires *m/z* 231.1048, found *m/z* 231.1057.

Characterisation data is consistent with literature reported values.[174]

29: Phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off-white solid (61.3 mg. 95%).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), DMF (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off-white solid (61.2 mg. 95%).

Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), ethynyl boronic acid, MIDA ester (48 mg, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (57 mg, 88%).

ν_{max} (solid): 3025, 2198, 1768, 1493 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 7.51–7.48 (m, 2H), 7.42–7.37 (m, 3H), 4.32 (d, J = 17.1 Hz, 2H), 4.15 (d, J = 17.1 Hz, 2H), 3.08 (s, 3H).

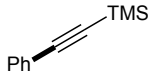
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 132.0, 129.4, 129.1, 129.1, 122.9, 99.9, 61.9, 48.4. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.24.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{13}H_{16}BN_2O_4$) requires *m/z* 275.1202, found *m/z* 275.1198.

Characterisation data is consistent with literature reported values.[175]

30: Trimethyl(phenylethynyl)silane



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and ethynyltrimethylsilane (37 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (44 mg, >99%).

ν_{max} (liquid film): 2962, 2161, 1491, 1251 cm^{-1}.

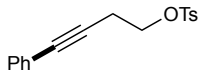
^1H NMR ($CDCl_3$, 500 MHz): δ 7.50–7.47 (m, 2H), 7.34–7.29 (m, 3H), 0.27 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 128.5, 128.2, 123.1, 105.1, 94.1, 0.0.

HRMS: exact mass calculated for [M] ($C_{11}H_{14}Si$) requires *m/z* 174.0865, found *m/z* 174.0866.

Characterisation data is consistent with literature reported values.[176]

31: 4-Phenylbut-3-yn-1-yl 4-methylbenzenesulfonate



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 3-butynyl-*p*-toluenesulfonate (46.3 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (60.7 mg, 81%).

ν_{max} (liquid film): 2924, 2980, 1493, 1361, 1176 cm^{-1}.

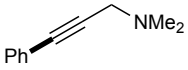
^1H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, J = 8.3 Hz, 2H), 7.32–7.28 (m, 3H), 7.28–7.23 (m, 4H), 4.16 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.9, 132.9, 131.7, 129.9, 128.2, 128.2, 127.9, 122.9, 83.8, 82.7, 67.8, 21.6, 20.4.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}O_3SNa$) requires *m/z* 323.0712, found *m/z* 323.0702.

Characterisation data is consistent with literature reported values.[177]

32: *N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and dimethyl(prop-2-yne)amine (28 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to purification by SCX (MeOH in 3M ammonium MeOH) to afford the title compound as a yellow oil (28.2 mg, 71%).

ν_{max} (liquid film): 3058, 2941, 2824, 2775, 1690, 1493 cm^{-1}.

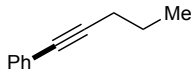
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46–7.42 (m, 2H), 7.32–7.28 (m, 3H), 3.49 (s, 2H), 2.39 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.7, 128.3, 128.1, 123.2, 85.4, 84.4, 48.6, 44.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{14}N$) requires *m/z* 160.1126, found *m/z* 160.1125.

Characterisation data is consistent with literature reported values.[176]

33: Pent-1-yn-1-ylbenzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 1-pentyne (25.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as a yellow oil (34.5 mg, 96%).

ν_{max} (liquid film): 3058, 2963, 2934, 2872, 2237, 1601, 1491 cm^{-1}.

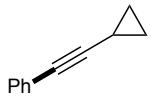
^1H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.22–7.17 (m, 3H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.59–1.52 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.2, 127.5, 124.1, 90.3, 80.7, 22.2, 21.4, 13.6.

HRMS: exact mass calculated for [M] ($C_{11}H_{12}$) requires *m/z* 144.0939, found *m/z* 144.0941.

Characterisation data is consistent with literature reported values.[176]

34: (Cyclopropylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and ethynylcyclopropane (22 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-

1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (30.3 mg, 85%).

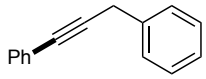
ν_{max} (liquid film): 3034, 2924, 2219, 1597, 1513 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.38 (m, 2H), 7.30–7.26 (m, 3H), 1.50–1.45 (m, 1H), 0.91–0.87 (m, 2H), 0.84–0.82 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.1, 127.4, 123.9, 93.4, 75.8, 8.6, 0.1.

Characterisation data is consistent with values reported in the literature.[176]

35: Prop-1-yne-1,3-diyldibenzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 3-phenyl-1-propyne (32.6 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (38.7 mg, 81%).

ν_{max} (liquid film): 3064, 3032, 2924, 1601, 1493 cm^1.

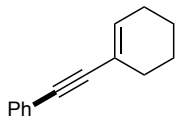
^1H NMR ($CDCl_3$, 500 MHz): δ 7.46 (dd, J = 6.5, 3.0 Hz, 2H), 7.44 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.32–7.29 (m, 3H), 7.26 (dd, J = 8.8, 5.8 Hz, 1H), 3.85 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.8, 131.7, 128.6, 128.3, 127.9, 127.8, 126.7, 123.7, 87.5, 82.7, 25.8.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0932.

Characterisation data is consistent with literature reported values.[178]

36: (Cyclohex-1-en-1-ylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 1-ethynylcyclohexene (30.8 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as an off-white solid (43.3 mg, 95%).

ν_{max} (liquid film): 3062, 2935, 2865, 2204, 1716, 1670 cm^{-1}.

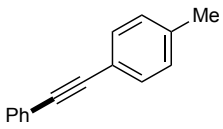
^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.28–7.23 (m, 3H), 6.20–6.16 (m, 1H), 2.20 (dd, *J* = 8.1, 6.0 Hz, 2H), 2.13–2.09 (m, 2H), 1.68–1.63 (m, 2H), 1.61–1.56 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 135.2, 131.4, 128.2, 127.7, 123.8, 120.8, 91.3, 86.8, 29.3, 25.8, 22.4, 21.6.

HRMS: exact mass calculated for [M] ($C_{14}H_{14}$) requires *m/z* 182.1095, found *m/z* 182.1102.

Characterisation data is consistent with literature reported values.[179]

37: 1-Methyl-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and *p*-tolylacetylene

(33.2 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as an off-white solid (46.9 mg, 98%).

ν_{max} (liquid film): 3032, 2921, 2219, 1597, 1511 cm^{-1}.

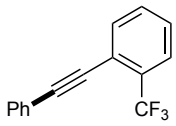
^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.37–7.31 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.4, 131.6, 131.5, 129.1, 128.3, 128.1, 123.5, 120.2, 89.6, 88.7, 21.5.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0942.

Characterisation data is consistent with literature reported values.[162]

38: 1-(Phenylethynyl)-2-(trifluoromethyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 2-ethynyltrifluorotoluene (36.5 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (53 mg, 86%).

ν_{max} (liquid film): 3066, 2224, 1312 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.69 (t, *J* = 8.3 Hz, 2H), 7.57 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.40–7.35 (m, 3H).

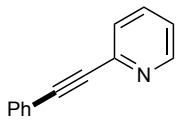
^{13}C NMR ($CDCl_3$, 126 MHz): δ 133.7, 131.7, 131.4, 128.8, 128.4, 127.9, 125.9 (q, $^3J_{CF}$ = 5.2 Hz), 123.6 (q, $^1J_{CF}$ = 273.5 Hz), 122.8, 121.6, 94.9, 85.4. Carbon bearing trifluoromethyl group not observed.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -62.35.

HRMS: exact mass calculated for [M] ($C_{15}H_9F_3$) requires *m/z* 246.0656, found *m/z* 246.0654.

Characterisation data is consistent with literature reported values.[47]

39: 2-(Phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 2-ethynylpyridine (26.5 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a yellow oil (43.3 mg, 97%).

ν_{max} (liquid film): 3053, 2224, 1582, 1493, 1463 cm^{-1}.

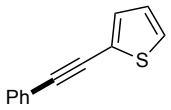
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.62 (d, *J* = 4.4 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.38–7.35 (m, 3H), 7.26–7.22 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.1, 143.5, 136.2, 132.1, 128.9, 128.4, 127.2, 122.8, 122.3, 89.2, 88.6.

HRMS: exact mass calculated for [M] ($C_{13}H_9N$) requires *m/z* 179.0735, found *m/z* 179.0731.

Characterisation data is consistent with literature reported values.[162]

40: 2-(Phenylethynyl)thiophene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv.), and 2-ethynylthiophene (24.9 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as an off-white solid (42.4 mg, 92%).

ν_{max} (liquid film): 3088, 2204 cm^{-1}.

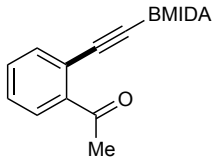
^1H NMR ($CDCl_3$, 500 MHz): δ 7.54–7.50 (m, 2H), 7.39–7.34 (m, 3H), 7.31–7.28 (m, 2H), 7.02 (t, J = 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M] ($C_{12}H_8S$) requires *m/z* 184.0347, found *m/z* 184.0349.

Characterisation data is consistent with literature reported values.[162]

41: 2-Acetyl phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodoacetophenone (35.8 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction

mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-100% EtOAc in petroleum ether) to afford the title compound as an off-white solid (66.5 mg, 89%).

ν_{max} (solid): 2960, 2193, 1770, 1684 cm^{-1}.

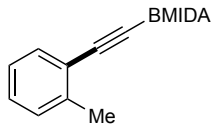
^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.79 (dd, J = 7.7, 0.9 Hz, 1H), 7.63 (dd, J = 7.6, 0.9 Hz, 1H), 7.57 (td, J = 7.5, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.3 Hz, 1H), 4.34 (d, J = 17.1 Hz, 2H), 4.13 (d, J = 17.1 Hz, 2H), 3.11 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 200.1, 169.1, 141.2, 134.6, 131.9, 129.4, 129.2, 120.7, 98.6, 61.9, 48.4, 29.9. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.23.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{15}H_{18}BN_2O_5$) requires *m/z* 317.1305, found *m/z* 317.1303.

42: 2-Methyl-phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off-white solid (62.9 mg, 93%).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), DMF (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was

subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off-white solid (62.3 mg, 92%).

ν_{max} (solid): 3019, 2191, 1770, 1290, 1247 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 7.45 (d, *J* = 7.4 Hz, 1H), 7.31–7.27 (m, 2H), 7.22–7.18 (m, 1H), 4.33 (d, *J* = 17.1 Hz, 2H), 4.15 (d, *J* = 17.1 Hz, 2H), 3.09 (s, 3H), 2.40 (s, 3H).

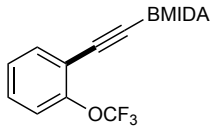
^{13}C NMR (DMSO-*d*$_6$, 126 MHz): δ 169.2, 140.3, 132.4, 129.9, 129.3, 126.3, 122.7, 98.7, 61.9, 48.4, 20.8. Carbon bearing boron not observed.

^{11}B NMR (DMSO-*d*$_6$, 160 MHz): δ 6.37.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{14}H_{18}BN_2O_4$) requires *m/z* 289.1355, found *m/z* 289.1354.

Characterisation data is consistent with literature reported values.[180]

43: 2-Trifluoromethoxy-phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-(trifluoromethoxy)iodobenzene (38.8 µL, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off-white solid (71.8 mg, 85%).

ν_{max} (solid): 3016, 2922, 2965, 2198, 1772, 1217, 1024 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.69 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.47–7.42 (m, 2H), 4.35 (d, J = 17.2 Hz, 2H), 4.15 (d, J = 17.2 Hz, 2H), 3.09 (s, 3H).

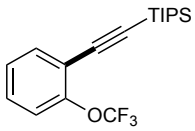
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.0, 148.9, 134.5, 131.3, 128.3, 121.9, 120.6 (q, $^{1}J_{CF}$ = 257.4 Hz), 117.3, 93.5, 62.1, 48.3. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.29.

^{19}F NMR (DMSO-d_6, 471 MHz): δ -56.54.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}BF_3NO_5$) requires *m/z* 342.0763, found *m/z* 342.0767.

44: Triisopropyl((2-(trifluoromethoxy)phenyl)ethynyl)silane



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-(trifluoromethoxy)iodobenzene (38.8 µL, 0.25 mmol, 1 equiv.), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% Et_2O in petroleum ether) to afford the title compound as a colouless oil (58.3 mg, 68%).

ν_{max} (liquid film): 2947, 2868, 2167, 1491, 1258, 1219, 1169 cm^{-1}.

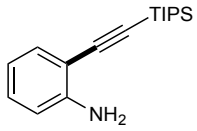
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (dd, J = 7.6, 1.3 Hz, 1H), 7.28–7.24 (m, 1H), 7.19–7.14 (m, 2H), 1.06 (app s, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.8, 134.1, 129.4, 126.6, 121.2, 120.6 (q, $^{1}J_{CF}$ = 258.1 Hz), 118.3, 100.4, 97.1, 18.5, 11.2.

^{19}F NMR (471 MHz, $CDCl_3$): δ -57.50.

HRMS: exact mass calculated for [M] ($C_{18}H_{25}F_3SiO$) requires *m/z* 342.1627, found *m/z* 342.1626.

45: 2-((Triisopropylsilyl)ethynyl)aniline



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-iodoaniline (54.8 mg, 0.25 mmol, 1 equiv.), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (45.3 mg, 66%).

ν_{max} (liquid film): 3487, 3388, 2945, 2867, 2146, 1616, 1318 cm^{-1}.

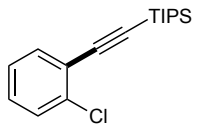
^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.14–7.09 (m, 1H), 6.71–6.64 (m, 2H), 4.25 (s, 2H), 1.14 (app s, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.3, 132.4, 129.7, 117.7, 114.1, 108.3, 103.7, 95.9, 18.7, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{28}NSi$) requires *m/z* 274.1986, found *m/z* 274.1986.

Characterisation data is consistent with literature reported values.[181]

46: ((2-Chlorophenyl)ethynyl)triisopropylsilane



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv.), 2-chloro-iodobenzene (30.5 µL, 0.25 mmol, 1 equiv.), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv.). After 1 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-100% MeCN in water) to afford the title compound as a yellow oil (47.7 mg, 65%).

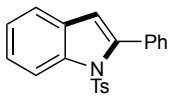
ν_{max} (liquid film): 2945, 2867, 2163, 1472, 1225 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.23 (td, *J* = 7.7, 1.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 1.15 (app s, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.5, 133.9, 129.4 (2C), 126.4, 123.6, 103.3, 96.9, 18.8, 11.5.

HRMS: exact mass calculated for [M] ($C_{17}H_{25}{}^{35}ClSi$) requires *m/z* 292.1414, found *m/z* 292.1431.

47: 2-Phenyl-1-tosyl-1*H*-indole



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (78.4 mg, 90%).

Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), DMF (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1

equiv.), and phenylacetylene (28.8 μL, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (78.4 mg, 90%).

ν_{max} (solid): 3073, 1368, 1169 cm^{-1}.

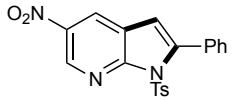
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.33 (d, *J* = 8.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.47–7.44 (m, 4H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.5, 142.2, 138.3, 134.7, 132.4, 130.7, 130.4, 129.2, 128.7, 127.5, 126.8, 124.8, 124.3, 120.7, 116.7, 113.4, 21.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}NO_6S$) requires *m/z* 348.1058, found *m/z* 348.1061.

Characterisation data is consistent with literature reported values.[163]

48: 5-Nitro-2-phenyl-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 μL, 0.75 mmol, 3 equiv.), *N*-(3-iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide (104 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 μL, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as an off-white solid (71.4 mg, 73%).

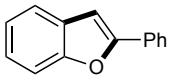
ν_{max} (solid): 3070, 2935, 1593, 1517, 1394, 1346, 1184 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.32 (d, *J* = 2.4 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.55–7.48 (m, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.63 (s, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.3, 145.8, 145.8, 141.4, 140.3, 135.3, 131.5, 129.9, 129.6, 129.6, 128.2, 127.9, 124.3, 121.4, 108.3, 21.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{16}N_3O_4S$) requires *m/z* 394.0862, found *m/z* 394.0869.

49: 2-Phenylbenzofuran



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), 2-iodophenol (55 mg, 0.25 mmol, 1 equiv.), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-1% EtOAc in petroleum ether) to afford the title compound as a colourless solid (43.3 mg, 89%).

ν_{max} (solid): 3038, 2924, 2855 cm^{-1}.

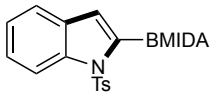
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.6, 124.9, 124.3, 122.9, 120.9, 111.2, 101.3

HRMS: exact mass calculated for [M] ($C_{14}H_{10}O$) requires *m/z* 194.0732, found *m/z* 194.0737.

Characterisation data is consistent with literature reported values.[181]

50: (1-Tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-80% EtOAc in petroleum ether) to afford the title compound as a colourless solid (87.4 mg, 82%).

ν_{max} (solid): 2928, 1763, 1450, 1176, 1038 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.39–7.34 (m, 3H), 7.25 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 4.47 (d, J = 17.5 Hz, 2H), 4.23 (d, J = 17.4 Hz, 2H), 2.96 (s, 3H), 2.32 (s, 3H).

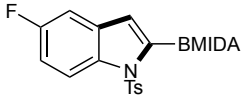
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 145.72, 138.9, 135.5, 130.4, 130.1, 127.08, 125.7, 123.9, 122.2, 122.0, 114.7, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.28.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{20}BN_2O_6S$) requires *m/z* 427.1139, found *m/z* 427.1139.

Characterisation data is consistent with literature reported values.[182]

51: (5-Fluoro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv.), *N*-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (98 mg, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-80% EtOAc in petroleum ether) to afford the title compound as a colourless solid (98 mg, 88%).

ν_{max} (solid): 2930, 1750, 1305, 1174, 1040 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 8.13 (dd, J = 9.2, 4.3 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 8.8, 2.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.22 (td, J = 9.2, 2.6 Hz, 1H), 7.06 (s, 1H), 4.48 (d, J = 17.5 Hz, 2H), 4.24 (d, J = 17.5 Hz, 2H), 2.96 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 159.3 (d, $^1J_{CF}$ = 238.2 Hz), 145.9, 135.4, 135.3, 131.2 (d, $^3J_{CF}$ = 10.4 Hz), 130.5, 127.1, 121.9, 116.1 (d, $^3J_{CF}$ = 9.4 Hz), 113.5 (d, $^2J_{CF}$ = 25.5 Hz), 107.1 (d, $^2J_{CF}$ = 23.5 Hz), 64.8, 49.9, 21.5. Carbon bearing boron not observed.

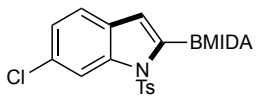
^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.09.

^{19}F NMR (DMSO-d_6, 471 MHz): δ -120.04.

HRMS: exact mass calculated for [M] ($C_{21}H_{18}BF_3N_2O_6SNa$) requires *m/z* 444.2966, found *m/z* 444.0951.

Characterisation data is consistent with literature reported values.[182]

52: (6-Chloro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75

mmol, 3 equiv.), *N*-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (102 mg, 0.25 mmol, 1 equiv.), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv.). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-80% EtOAc in petroleum ether) to afford the title compound as a colourless solid (116 mg, >99%).

ν_{max} (solid): 2922, 1763, 1455, 1267, 1173, 1038 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.11 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 8.4, 1.7 Hz, 1H), 7.09 (s, 1H), 4.48 (d, J = 17.5 Hz, 2H), 4.23 (d, J = 17.4 Hz, 2H), 2.94 (s, 3H), 2.34 (s, 3H).

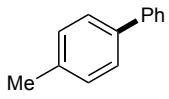
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.1, 139.3, 135.2, 130.6, 130.4, 128.9, 127.0, 124.4, 123.4, 121.9, 114.4, 64.7, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.21.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{20}H_{18}{}^{35}ClN_2O_6SB$) requires *m/z* 460.0671, found *m/z* 460.0658.

Characterisation data is consistent with literature reported values.[182]

57: 4-Phenyltoluene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.9 mg, >99%).

Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (38.6 mg, 92%).

Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), phenylboronic acid MIDA ester (58.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (36 mg, 86%).

Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), potassium phenyltrifluoroborate (46 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (41.2 mg, 98%).

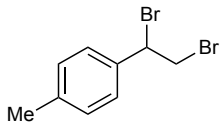
Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (30.5 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 μL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (43.2 mg, >99%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (dd, J = 8.3, 1.2 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.38–7.33 (m, 1H), 7.29 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 138.5, 137.2, 129.6, 128.9, 127.1 (3C), 21.2.

Characterization data is consistent with literature reported values.[164]

58: (1,2-Dibromoethyl)toluene



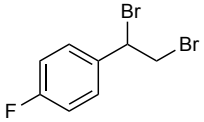
Prepared according to General Procedure H using 4-methylstyrene (224.5 mg, 1.9 mmol, 1 equiv.), $CHCl_3$ (1 mL, 1.9 M), and bromine (110 µL, 2.15 mmol, 1.15 equiv.). After the reaction mixture had reached room temperature it was subjected to the purification method outlined in the General Procedure to afford (1,2-dibromoethyl)toluene as an off-white solid (528.2 mg, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.15 (dd, *J* = 10.6, 5.5 Hz, 1H), 4.11–3.99 (m, 2H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.2, 135.6, 129.6, 127.5, 51.0, 35.0, 21.3.

Characterisation data is consistent with literature reported values.[168]

59: (1,2-Dibromoethyl)-4-fluorobenzene



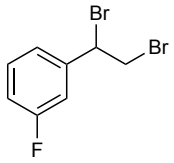
Prepared according to General Procedure H using 4-fluorostyrene (1 g, 8.2 mmol, 1 equiv.), $CHCl_3$ (4 mL, 1.9 M), and bromine (482 µL, 9.4 mmol, 1.15 equiv.). After the reaction mixture had reached room temperature it was subjected to the purification method outlined in the General Procedure to afford (1,2-dibromoethyl)-4-fluorobenzene as an off-white solid (2.3 g, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 5.14 (dd, *J* = 11.0, 5.1 Hz, 1H), 4.08 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.98 (dd, *J* = 11.0, 10.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.8 (d, $^{1}J_{CF}$ = 249.3 Hz), 134.5 (d, $^{4}J_{CF}$ = 3.1 Hz), 129.5 (d, $^{3}J_{CF}$ = 8.1 Hz), 115.9 (d, $^{2}J_{CF}$ = 22.3 Hz), 49.8, 34.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -111.65.

60: (1,2-Dibromoethyl)-3-fluorobenzene



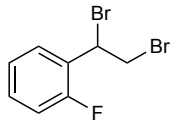
Prepared according to General Procedure H using 3-fluorostyrene (232.1 mg, 1.9 mmol, 1 equiv.), $CHCl_3$ (1 mL, 1.9 M), and bromine (110 µL, 2.15 mmol, 1.15 equiv.). After the reaction mixture had reached room temperature it was subjected to the purification method outlined in the General Procedure to afford (1,2-dibromoethyl)-3-fluorobenzene as an off-white solid (549.9 mg, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.33 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.13 (dd, *J* = 9.5, 1.2 Hz, 1H), 7.05 (t, *J* = 8.4 Hz, 1H), 5.10 (dd, *J* = 10.9, 5.2 Hz, 1H), 4.08–3.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.8 (d, $^{1}J_{CF}$ = 247.2 Hz), 141.0 (d, $^{3}J_{CF}$ = 7.2 Hz), 130.4 (d, $^{3}J_{CF}$ = 8.2 Hz), 123.5 (d, $^{4}J_{CF}$ = 2.1 Hz), 116.2 (d, $^{2}J_{CF}$ = 21.2 Hz), 114.7 (d, $^{2}J_{CF}$ = 22.7 Hz), 49.4, 34.6.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -111.81.

61: (1,2-Dibromoethyl)-2-fluorobenzene



Prepared according to General Procedure H using 2-fluorostyrene (232.1 mg, 1.9 mmol, 1 equiv.), $CHCl_3$ (1 mL, 1.9 M), and bromine (110 µL, 2.15 mmol, 1.15 equiv.). After the reaction mixture had reached room temperature it was subjected to the purification

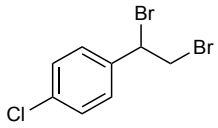
method outlined in the General Procedure to afford (1,2-dibromoethyl)-2-fluorobenzene as an off-white solid (512.4 mg, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (t, J = 7.4 Hz, 1H), 7.34 (dd, J = 12.5, 6.7 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.08 (dd, J = 9.8, 9.0 Hz, 1H), 5.44 (dd, J = 10.6, 5.6 Hz, 1H), 4.15–4.03 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.2 (d, $^{1}J_{CF}$ = 250.1 Hz), 130.8 (d, $^{3}J_{CF}$ = 8.6 Hz), 128.8, 125.9 (d, $^{2}J_{CF}$ = 12.5 Hz), 124.6, 116.0 (d, $^{2}J_{CF}$ = 21.7 Hz), 42.7, 33.6.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.29.

62: (1,2-Dibromoethyl)-4-chlorobenzene



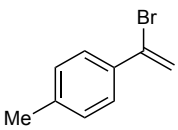
Prepared according to General Procedure H using 4-chlorostyrene (1 g, 7.2 mmol, 1 equiv.), $CHCl_3$ (3.6 mL, 1.9 M), and bromine (425 µL, 8.3 mmol, 1.15 equiv.). After the reaction mixture had reached room temperature it was subjected to the purification method outlined in the General Procedure to afford (1,2-dibromoethyl)-4-chlorobenzene as an off-white solid (2.2 g, >99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.32 (m, 4H), 5.11 (dd, J = 11.0, 5.1 Hz, 1H), 4.07 (dd, J = 10.3, 5.1 Hz, 1H), 4.00–3.94 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.1, 134.9, 129.1, 129.0, 49.5, 34.6.

Characterisation data is consistent with literature reported values.[168]

63: 1-(1-Bromovinyl)-4-methylbenzene



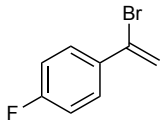
Prepared according to General Procedure I using (1,2-dibromoethyl)toluene (528.2 mg, 1.9 mmol, 1 equiv.), MeOH/THF (1/1, 2 mL), and K_2CO_3 (525.2 mg, 3.8 mmol, 2 equiv.). After 16 h, the reaction mixture was subjected to the purification method outlined in the General Procedure to afford the title compound as a yellow oil (294.9 mg, 79%) which was immediately used in subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.08 (d, J = 2.0 Hz, 1H), 5.73 (d, J = 2.0 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.2, 135.8, 131.1, 128.9, 127.2, 116.8, 21.1.

Characterisation data is consistent with literature reported values.[169]

64: 1-(1-Bromovinyl)-4-fluorobenzene



Prepared according to General Procedure I using (1,2-dibromoethyl)-4-fluorobenzene (500 mg, 1.77 mmol, 1 equiv.), MeOH/THF (1/1, 2 mL), and K_2CO_3 (489.2 mg, 3.54 mmol, 2 equiv.). After 16 h, the reaction mixture was subjected to the purification method outlined in the General Procedure to afford the title compound as a yellow oil (246.2 mg, 69%) which was immediately used in subsequent reactions without further purification.

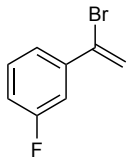
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.54 (m, 2H), 7.07–6.99 (m, 2H), 6.05 (d, J = 2.0 Hz, 1H), 5.76 (d, J = 2.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.1 (d, $^1J_{CF}$ = 249.5 Hz), 134.8 (d, $^4J_{CF}$ = 3.0 Hz), 129.7, 129.2 (d, $^3J_{CF}$ = 8.0 Hz), 117.6, 115.2 (d, $^2J_{CF}$ = 21.8 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz): δ -112.27.

Characterisation data is consistent with literature reported values.[169]

65: 1-(1-Bromovinyl)-3-fluorobenzene



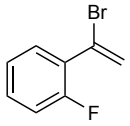
Prepared according to General Procedure I using (1,2-dibromoethyl)-3-fluorobenzene (371 mg, 1.32 mmol, 1 equiv.), MeOH/THF (1/1, 2 mL), and K_2CO_3 (490.2 mg, 3.55 mmol, 2 equiv.). After 16 h, the reaction mixture was subjected to the purification method outlined in the General Procedure to afford the title compound as a yellow oil (160.9 mg, 61%) which was immediately used in subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, J = 7.9 Hz, 1H), 7.34–7.28 (m, 2H), 7.03 (tdd, J = 8.3, 2.6, 1.1 Hz, 1H), 6.15 (d, J = 2.2 Hz, 1H), 5.82 (d, J = 2.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.5 (d, $^1J_{CF}$ = 246.1 Hz), 140.7 (d, $^3J_{CF}$ = 7.9 Hz), 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 129.3 (d, $^4J_{CF}$ = 2.3 Hz), 122.9 (d, $^4J_{CF}$ = 2.5 Hz), 118.7, 115.9 (d, $^2J_{CF}$ = 21.2 Hz), 114.5 (d, $^2J_{CF}$ = 23.4 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz): δ -112.99.

66: 1-(1-Bromovinyl)-2-fluorobenzene



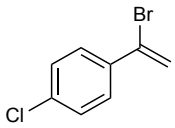
Prepared according to General Procedure I using (1,2-dibromoethyl)-2-fluorobenzene (510 mg, 1.8 mmol, 1 equiv.), MeOH/THF (1/1, 2 mL), and K_2CO_3 (500 mg, 3.6 mmol, 2 equiv.). After 16 h, the reaction mixture was subjected to the purification method outlined in the General Procedure to afford the title compound as a yellow oil (364 mg, >99%) which was immediately used in subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (td, J = 7.7, 1.8 Hz, 1H), 7.33–7.27 (m, 1H), 7.15 (td, J = 7.6, 1.2 Hz, 1H), 7.06 (ddd, J = 10.8, 8.2, 1.2 Hz, 1H), 6.14 (dd, J = 1.8, 1.2 Hz, 1H), 6.02 (dd, J = 1.8, 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.1 (d, $^1J_{CF}$ = 252.2 Hz), 131.3, 130.5 (d, $^3J_{CF}$ = 8.7 Hz), 123.9 (d, $^4J_{CF}$ = 4.0 Hz), 123.0 (d, $^3J_{CF}$ = 6.6 Hz), 122.8, 116.9 (d, $^2J_{CF}$ = 24.5 Hz), 115.9 (d, $^2J_{CF}$ = 22.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.31.

67: 1-(1-Bromovinyl)-4-chlorobenzene



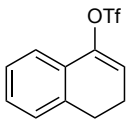
Prepared according to General Procedure I using (1,2-dibromoethyl)-4-chlorobenzene (538 mg, 1.8 mmol, 1 equiv.), MeOH/THF (1/1, 2 mL), and K_2CO_3 (498 mg, 3.6 mmol, 2 equiv.). After 16 h, the reaction mixture was subjected to the purification method outlined in the General Procedure to afford the title compound as a yellow oil (392 mg, >99%) which was immediately used in subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30 (dddd, *J* = 8.2, 7.3, 5.0, 1.8 Hz, 1H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (ddd, *J* = 10.8, 8.2, 1.2 Hz, 1H), 6.14 (dd, *J* = 1.8, 1.2 Hz, 1H), 6.02 (dd, *J* = 1.8, 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.0, 135.1, 129.6, 128.6, 128.4, 118.2.

Characterisation data is consistent with literature reported values.[169]

68: 3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate



Prepared according to General Procedure J using 1-tetralone (600 mg, 4.1 mmol, 1 equiv.), CH_2Cl_2 (16.5 mL, 0.25 M), Et_3N (0.86 mL, 6.2 mmol, 1.5 equiv.), and trifluoromethanesulfonic anhydride (1 mL, 6.2 mmol, 1.5 equiv.). After 24 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica

gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (1.15 g, >99%).

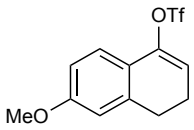
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.34 (m,1H), 7.30–7.24 (m, 2H), 7.20–7.16 (m, 1H), 6.03 (t, J = 4.8 Hz, 1H), 2.88 (t, J = 8.2 Hz, 2H), 2.52 (td, J = 8.2, 4.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.4, 136.2, 129.2, 128.7, 127.7, 126.9, 121.2, 118.6 (q, $^1J_{CF}$ = 320.5 Hz), 117.7, 26.8, 22.3.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -73.69.

Characterisation data is consistent with literature reported values.[167]

69: 7-Methoxy-4-(trifluoromethylsulfonyloxy)-1,2-dihydronaphthalene



Prepared according to General Procedure J using 6-methoxy-1-tetralone (2 g, 13.7 mmol, 1 equiv.), CH_2Cl_2 (54.7 mL, 0.25 M), Et_3N (3.8 mL, 27.4 mmol, 2 equiv.), and trifluoromethanesulfonic anhydride (4.6 mL, 27.4 mmol, 2 equiv.). After 24 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (4.2 g, >99%).

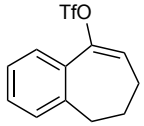
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (d, J = 8.5 Hz, 1H), 6.82–6.68 (m, 2H), 5.86 (t, J = 4.8 Hz, 1H), 3.82 (s, 3H), 2.84 (t, J = 8.1 Hz, 2H), 2.48 (td, J = 8.1, 4.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.3, 146.3, 138.3, 122.7, 121.6, 118.6 (q, $^1J_{CF}$ = 320.6 Hz), 114.7, 114.2, 111.3, 55.3, 27.4, 22.3.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -73.73.

Characterisation data is consistent with literature reported values.[167]

70: 9-(Trifluoromethylsulfonyloxy)-6,7-dihydro-5*H*-benzo[7]annulene



Prepared according to General Procedure J using 1-benzosuberone (500 mg, 3.1 mmol, 1 equiv.), CH_2Cl_2 (12.5 mL, 0.25 M), Et_3N (0.35 mL, 3.4 mmol, 1.1 equiv.), and trifluoromethanesulfonic anhydride (1.8 mL, 6.2 mmol, 2 equiv.). After 24 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (912 mg, >99%).

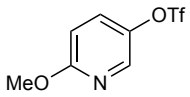
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53–7.49 (m, 1H), 7.33–7.27 (m, 2H), 7.24–7.20 (m, 1H), 6.22 (t, J = 6.2 Hz, 1H), 2.81–2.76 (m, 2H), 2.27–2.20 (m, 2H), 2.12–2.03 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.1, 141.6, 132.0, 129.5, 129.3, 126.5, 126.4, 123.3, 118.5 (q, $^1J_{CF}$ = 320.4 Hz), 33.4, 30.5, 25.4.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -73.96.

Characterisation data is consistent with literature reported values.[167]

72: 6-Methoxypyridin-3-yl trifluoromethanesulfonate



Prepared according to General Procedure J using 6-methoxypyridin-3-ol (33 mg, 0.26 mmol, 1 equiv.), CH_2Cl_2 (1.5 mL, 0.25 M), Et_3N (72.3 µL, 0.52 mmol, 2 equiv.), and trifluoromethanesulfonic anhydride (87 µL, 0.52 mmol, 2 equiv.). After 24 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (38 mg, 57%).

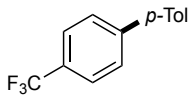
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (d, *J* = 3.0 Hz, 1H), 7.49 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.80 (d, *J* = 9.1 Hz, 1H), 3.95 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 163.2, 141.6, 139.5, 132.0, 112.2, 54.2. Carbon bearing fluorine not observed.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -72.50.

Characterisation data is consistent with literature reported values.[183]

73: 4'-Methyl-4-trifluoromethylbiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 4-(trifluoromethyl)phenylboronic acid (47.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (45.1 mg, 76%).

Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 4-chlorobenzotrifluoride (45.1 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.9 mg, 73%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), 4-(trifluoromethyl)phenylboronic acid (48 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75

mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (47 mg, 80%).

ν_{max} (solid): 2919, 2954, 1604, 1323 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (app s, 4H), 7.51 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H).

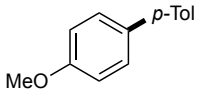
^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.7, 138.2, 136.9, 129.7, 129.0 (q, $^2J_{CF}$ = 32.5 Hz), 127.2, 127.1, 125.2 (q, $^4J_{CF}$ = 3.9 Hz), 124.0 (q, $^1J_{CF}$ = 272.0 Hz), 21.1.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -62.36.

HRMS: exact mass calculated for [M] ($C_{14}H_{11}F_3$) requires *m/z* 236.0813, found *m/z* 236.0813.

Characterization data is consistent with literature reported values.[184]

74: 4'-Methyl-4-methoxybiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 4-(methoxy)phenylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (47.6 mg, 96%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), 4-(methoxy)phenylboronic

acid (38 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 μL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (44 mg, 88%).

ν_{max} (solid): 3021, 2911, 1606, 1500, cm^{-1}.

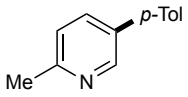
^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.9, 137.9, 136.3, 133.8, 129.4, 127.9, 126.6, 114.2, 55.3, 21.0.

HRMS: exact mass calculated for [M] ($C_{14}H_{14}O$) requires *m/z* 198.1045, found *m/z* 198.1046.

Characterization data is consistent with literature reported values.[185]

75: 2-Methyl-5-(*p*-tolyl)pyridine



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 2-methylpyridine-5-boronic acid (34.2 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a colourless solid (35.88 mg, 78%).

ν_{max} (solid): 2919, 2850, 1599, 1490 cm^{-1}.

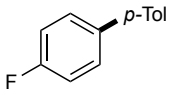
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (d, *J* = 2.1 Hz, 1H), 7.75 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 2.59 (s, 3H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.9, 147.4, 137.7, 135.0, 134.5, 133.7, 129.7, 126.8, 123.1, 24.0, 21.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}N$) requires *m/z* 184.1121, found *m/z* 184.1116.

Characterization data is consistent with literature reported values.[186]

76: 4-Fluoro-4'-methylbiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 4-fluorophenylboronic acid (35 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (43.9 mg, 94%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-fluorophenyl trifluoromethanesulfonate (61 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (31 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (30 mg, 69%).

ν_{max} (solid): 2921, 1597, 1500 cm^{-1}.

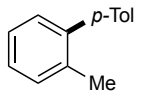
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.13–7.09 (m, 2H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.3 (d, $^{1}J_{CF}$ = 245.5 Hz), 137.4, 137.3 (d, $^{4}J_{CF}$ = 3.4 Hz), 137.0, 129.5, 128.5 (d, $^{3}J_{CF}$ = 7.8 Hz), 126.9, 115.5 (d, $^{2}J_{CF}$ = 21.6 Hz), 21.1.

HRMS: exact mass calculated for [M] ($C_{13}H_{11}F$) requires *m/z* 186.0845, found *m/z* 186.0849.

Characterization data is consistent with literature reported values.[164]

77: 2,4'-Dimethylbiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), *o*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless oil (45.8 mg, >99%).

Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), *o*-tolyl trifluoromethanesulfonate (60.1 mg, 0.25 mmol, 1 equiv.), tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless oil (46.6 mg, >99%).

ν_{max} (liquid film): 3015, 2917, 1483 cm^{-1}.

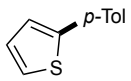
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.27 (m, 8H), 2.47 (s, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.9, 139.0, 136.3, 135.4, 130.3, 129.8, 129.1, 128.8, 127.0, 125.7, 21.1, 20.5.

HRMS: exact mass calculated for [M] ($C_{14}H_{14}$) requires *m/z* 182.1095, found *m/z* 182.1096.

Characterization data is consistent with literature reported values.[164]

78: 2-(*p*-Tolyl)thiophene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 2-thienylboronic acid (32 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (33.5 mg, 77%).

ν_{max} (solid): 3021, 2909, 2850, 1500 cm^{-1}.

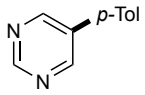
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.31 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.28 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.6, 137.3, 131.6, 129.5, 127.9, 125.9, 124.2, 122.6, 21.1.

HRMS: exact mass calculated for [M] ($C_{11}H_{10}S$) requires *m/z* 174.0503, found *m/z* 174.0504.

Characterization data is consistent with literature reported values.[184]

79: 5-(*p*-Tolyl)pyrimidine



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), pyrimidine-5-boronic acid (31 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a brown solid (18.9 mg, 44%).

ν_{max} (solid): 2919, 2852, 1548, 1411 cm^{-1}.

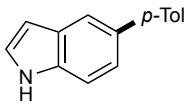
^1H NMR ($CDCl_3$, 400 MHz): δ 9.18 (s, 1H), 8.93 (s, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.2, 154.7, 139.1, 134.2, 131.3, 130.1, 126.8, 21.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{11}N_2$) requires *m/z* 171.0917, found *m/z* 171.0913.

Characterization data is consistent with literature reported values.[186]

80: 5-(*p*-Tolyl)-1*H*-indole



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 5-indolylboronic acid (40.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-50% MeCN in water) to afford the title compound as a brown oil (37.1 mg, 72%).

ν_{max} (liquid film): 3406, 3015, 2913, 1468 cm^{-1}.

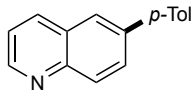
^1H NMR ($CDCl_3$, 400 MHz): δ 8.15 (s, 1H), 7.85 (d, *J* = 0.7 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.45 (m, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.23 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.61 (dd, *J* = 2.8, 2.3 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.7, 135.9, 135.1, 133.4, 129.4, 128.4, 127.2, 124.7, 121.8, 118.9, 111.1, 102.9, 21.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{14}N$) requires *m/z* 208.1121, found *m/z* 208.1121.

Characterization data is consistent with literature reported values.[187]

81: 6-(*p*-Tolyl)quinoline



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 6-quinolineboronic acid (43.2 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-50% MeCN in water) to afford the title compound as an off-white solid (47.8 mg, 87%).

ν_{max} (solid): 2921, 1495 cm^{-1}.

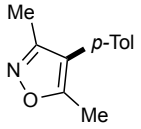
^1H NMR ($CDCl_3$, 400 MHz): δ 8.91 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (m, 2H), 7.99–7.95 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.4, 147.7, 139.4, 137.8, 137.6, 136.3, 129.9, 129.8, 129.3, 128.7, 127.4, 125.2, 121.6, 21.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}N$) requires *m/z* 220.1121, found *m/z* 220.1118.

Characterization data is consistent with literature reported values.[188]

82: 3,5-Dimethyl-4-(*p*-tolyl)isoxazole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 3,5-dimethylisoxazoleboronic acid (35.2 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless oil (36.2 mg, 83%).

ν_{max} (liquid film): 2922, 1422 cm^{-1}.

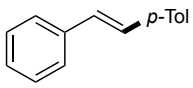
^1H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.23 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.9, 158.8, 137.3, 129.5, 128.9, 127.4, 116.5, 21.2, 11.5, 10.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}NO$) requires *m/z* 188.1070, found *m/z* 188.1066.

Characterization data is consistent with literature reported values.[189]

83: *trans*-1-Methyl-4-styrylbenzene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), *trans*-2-phenylvinylboronic acid (37 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (40.3 mg, 83%).

ν_{max} (solid): 3023, 2913, 2854, 1449 cm^{-1}.

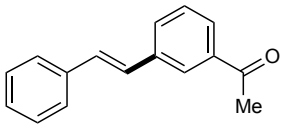
^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, J = 7.3 Hz, 2H), 7.43 (d, J = 18.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 18.0 Hz, 2H), 7.09 (d, J = 2.5 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.5, 134.6, 132.8, 129.4, 128.6, 127.7, 127.6, 127.4, 126.4, 126.4, 21.2.

HRMS: exact mass calculated for [M] ($C_{15}H_{14}$) requires *m/z* 194.1095, found *m/z* 194.1097.

Characterization data is consistent with literature reported values.[190]

84: *trans*-1-(3-Styrylphenyl)ethan-1-one



Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 3-chloroacetophenone (38.6 mg, 0.25 mmol, 1 equiv.), *trans*-2-phenylvinylboronic acid (37 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the

General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (42.2 mg, 76%).

Prepared according to General Procedure E using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 3-chloroacetophenone (39 mg, 0.25 mmol, 1 equiv.), *trans*-2-phenylvinylboronic acid (37 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (36 mg, 65%).

ν_{max} (solid): 2958, 2917, 1680, 1589 cm^{-1}.

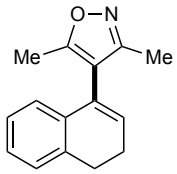
^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (t, *J* = 1.7 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32–7.27 (m, 1H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.14 (d, *J* = 16.4 Hz, 1H), 2.65 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.1, 137.9, 137.6, 136.9, 130.9, 130.1, 128.9, 128.8, 128.0, 127.6, 127.4, 126.6, 126.1, 26.7.

HRMS: exact mass calculated for [M] ($C_{16}H_{14}O$) requires *m/z* 222.1045, found *m/z* 222.1051.

Characterization data is consistent with literature reported values.[191]

85: 4-(3,4-Dihydronaphthalen-1-yl)-3,5-dimethylisoxazole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (69.6 mg, 0.25 mmol, 1 equiv.), 3,5-dimethylisoxazoleboronic acid (35.2 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400

equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% Et_2O in petroleum ether) to afford the title compound as a colourless oil (43.3 mg, 76%).

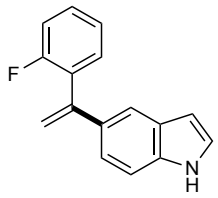
ν_{max} (liquid film): 2930, 1725, 1651, 1422 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.20–7.10 (m, 3H), 6.78 (d, *J* = 7.2 Hz, 1H), 5.99 (t, *J* = 4.6 Hz, 1H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.48–2.39 (m, 2H), 2.28 (s, 3H), 2.07 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.1, 159.8, 135.9, 133.8, 131.1, 127.9, 127.8, 127.4, 126.6, 124.3, 114.8, 27.8, 23.4, 11.4, 10.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}NO$) requires *m/z* 226.1226, found *m/z* 226.1228.

86: 5-(1-(2-Fluorophenyl)vinyl)-1*H*-indole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 1-(1-bromovinyl)-2-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv.), 5-indolylboronic acid (40.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% Et_2O in petroleum ether) to afford the title compound as a colourless oil (32.6 mg, 56%).

ν_{max} (liquid film): 3421, 2921, 1604, 1450, 1221 cm^{-1}.

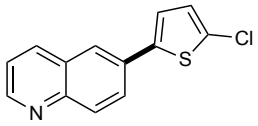
^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1H), 7.55 (d, *J* = 0.5 Hz, 1H), 7.35–7.30 (m, 3H), 7.24 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.20–7.18 (m, 1H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 7.08 (m, 1H), 6.52–6.50 (m, 1H), 5.75 (d, *J* = 1.2 Hz, 1H), 5.36 (d *J* = 1.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.3 (d, $^{1}J_{CF}$ = 248.1 Hz), 144.9, 135.5, 132.8, 131.7 (d, $^{3}J_{CF}$ = 3.9 Hz), 130.3 (d, $^{2}J_{CF}$ = 14.5 Hz), 129.0 (d, $^{3}J_{CF}$ = 8.3 Hz), 127.83, 124.6, 123.8 (d, $^{4}J_{CF}$ = 3.3 Hz), 121.4, 119.4, 115.7 (d, $^{2}J_{CF}$ = 22.2 Hz), 115.3, 110.7, 103.1.

^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.54.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{13}FN$) requires *m/z* 238.1027, found *m/z* 238.1026.

87: 6-(5-Chlorothiophen-2-yl)quinoline



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 2-bromo-5-chlorothiophene (49.4 mg, 0.25 mmol, 1 equiv.), 6-quinolineboronic acid (43.2 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as an off-white solid (58.3 mg, 95%).

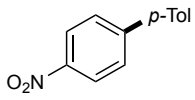
ν_{max} (solid): 2921, 2850, 1589, 1496, 1429 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 9.5 Hz, 1H), 7.90–7.86 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (d, *J* = 3.9 Hz, 1H), 6.95 (d, *J* = 3.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.5, 147.8, 141.9, 135.9, 131.8, 130.3, 130.1, 128.5, 127.4, 127.3, 123.5, 123.3, 121.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9{}^{35}ClNS$) requires *m/z* 246.0139, found *m/z* 246.0141.

88: 4-Methyl-4'-nitrobiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-nitrophenyl trifluoromethanesulfonate (67.8 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (48.9 mg, 92%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), bromotoluene (43 mg, 0.25 mmol, 1 equiv.), 4-nitrophenylboronic acid (42 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (43 mg, 81%).

ν_{max} (solid): 2921, 2844, 1595, 1511, 1327, 1290 cm^{-1}.

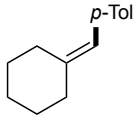
^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.6, 146.9, 139.1, 135.8, 129.9, 127.5, 127.2, 124.1, 21.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}NO_2$) requires *m/z* 214.0868, found *m/z* 214.0870.

Characterization data is consistent with literature reported values.[184]

89: 1-(Cyclohexylidenemethyl)-4-methylbenzene



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), (bromomethylene)cyclohexane (43.8 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-100% MeCN in water) to afford the title compound as a colourless oil (28.3 mg, 61%).

ν_{max} (liquid film): 3086, 2913, 1489, 1307 cm^{-1}.

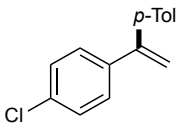
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15–7.07 (m, 4H), 6.21 (s, 1H), 2.40–2.37 (m, 2H), 2.34 (s, 3H), 2.28–2.23 (m, 2H), 1.68–1.53 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.8, 135.5, 135.3, 128.8, 128.7, 121.8, 37.6, 29.4, 28.6, 27.8, 26.7, 21.1.

HRMS: exact mass calculated for [M] ($C_{14}H_{18}$) requires *m/z* 186.1403, found *m/z* 186.1406.

Characterization data is consistent with literature reported values.[190]

90: 1-Chloro-4-(1-(*p*-tolyl)vinyl)benzene



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 1-(1-bromovinyl)-4-chlorobenzene (54.4 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture

was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as an off-white solid (56 mg, 98%).

ν_{max} (solid): 2028, 2917, 2854, 1511, 1487 cm^{-1}.

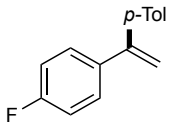
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.24 (m, 4H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 5.42 (d, *J* = 1.1 Hz, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 148.8, 140.2, 138.1, 137.8, 133.5, 129.6, 128.9, 128.3, 128.1, 113.9, 21.2.

HRMS: exact mass calculated for [M] ($C_{15}H_{13}{}^{35}Cl$) requires *m/z* 228.0706, found *m/z* 228.0716.

Characterization data is consistent with literature reported values.[192]

91: 1-Fluoro-4-(1-(*p*-tolyl)vinyl)benzene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 1-(1-bromovinyl)-4-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless oil (43.9 mg, 83%).

ν_{max} (liquid film): 2921, 1602, 1506, 1223 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.28 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.05–6.98 (m, 2H), 5.41 (d, *J* = 1.1 Hz, 1H), 5.36 (d, *J* = 1.1 Hz, 1H), 2.38 (s, 3H).

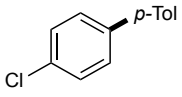
^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.5 (d, $^{1}J_{CF}$ = 246.4 Hz), 148.9, 138.4, 137.7 (d, $^{4}J_{CF}$ = 3.2 Hz), 137.7, 129.9 (d, $^{3}J_{CF}$ = 7.8 Hz), 128.9, 128.1, 114.9 (d, $^{2}J_{CF}$ = 21.5 Hz), 113.5, 21.1.

^{19}F NMR ($CDCl_3$, 376 MHz) δ -114.90.

HRMS: exact mass calculated for [M] ($C_{15}H_{13}F$) requires *m/z* 212.1001, found *m/z* 212.1002.

Characterization data is consistent with literature reported values.[193]

92: 4-Chloro-4'-methylbiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-chlorobromobenzene (47.9 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless oil (48.6 mg, 96%).

ν_{max} (liquid film): 2917, 2952, 1481 cm^{-1}.

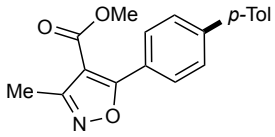
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.6, 137.4, 137.1, 133.0, 129.6, 128.8, 128.2, 126.8, 21.1.

HRMS: exact mass calculated for [M] ($C_{13}H_{11}{}^{35}Cl$) requires *m/z* 202.0549, found *m/z* 202.0544.

Characterization data is consistent with literature reported values.[194]

93: Methyl-3-methyl-5-(4'-methyl-[1,1'-biphenyl]-4-yl)isoxazole-4-carboxylate



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), methyl 5-(4-bromophenyl)-3-methylisoxazole-4-carboxylate (74.1 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% Et_2O in petroleum ether) to afford the title compound as a colourless solid (71.8 mg, 93%).

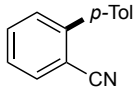
ν_{max} (solid): 2954, 1723, 1591, 1314, 1089 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.87 (s, 3H), 2.52 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.9, 162.7, 160.8, 143.9, 138.0, 137.1, 129.7, 129.5, 127.0, 126.7, 125.4, 107.9, 51.8, 21.1, 12.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}NO_3$) requires *m/z* 308.1281, found *m/z* 308.1281.

94: 4'-Methyl-2-biphenylcarbonitrile



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 2-bromobenzonitrile (45.5 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to

the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as an off-white solid (50 mg, >99%).

ν_{max} (solid): 2917, 2852, 2225, 1480 cm^1.

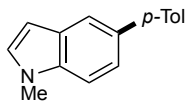
^1H NMR ($CDCl_3$, 400 MHz): δ 7.75 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.5, 138.7, 135.3, 133.7, 132.7, 129.9, 129.4, 128.6, 127.2, 118.8, 111.2, 21.2

HRMS: exact mass calculated for [M] ($C_{14}H_{11}N$) requires *m/z* 193.0891, found *m/z* 193.0891.

Characterization data is consistent with literature reported values.[184]

95: 1-Methyl-5-(*p*-tolyl)-1*H*-indole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 5-bromo-1-methylindole (52.5 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% Et_2O in petroleum ether) to afford the title compound as a colourless solid (29.2 mg, 53%).

ν_{max} (solid): 3015, 2919, 1485 cm^{-1}.

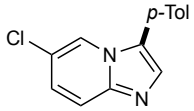
^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.48 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.26 (dd, *J* = 8.4, 0.5 Hz, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.54 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.82 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.8, 136.1, 135.8, 132.8, 129.4, 129.3, 128.9, 127.2, 121.3, 119.2, 109.3, 101.3, 32.9, 21.0.

HRMS: exact mass calculated for [M] ($C_{16}H_{15}N$) requires *m/z* 221.1205, found *m/z* 221.1202.

Characterization data is consistent with literature reported values.[164]

96: 6-Chloro-3-(*p*-tolyl)imidazo[1,2-*a*]pyridine



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-bromo-6-chloroimidazo[1,2-*a*]pyridine (57.9 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-50% MeCN in water) to afford the title compound as an off-white solid (59.4 mg, 98%).

ν_{max} (solid): 3086, 2917, 2852, 1489 cm^{-1}.

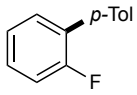
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, *J* = 1.6 Hz, 1H), 7.67 (s, 1H), 7.60 (d, *J* = 9.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 9.5, 1.9 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.8, 138.2, 132.6, 129.6, 127.6, 125.9, 125.2, 124.9, 120.8, 120.4, 118.1, 20.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}{}^{35}ClN_2$) requires *m/z* 243.0684, found *m/z* 243.0685.

Characterization data is consistent with literature reported values.[195]

97: 2-Fluoro-4'-methylbiphenyl



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 2-fluorophenyl trifluoromethanesulfonate (61 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless oil (46.9 mg, >99%).

ν_{max} (liquid film): 2917, 2852, 1483 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.43 (m, 3H), 7.35–7.28 (m, 3H), 7.19 (m, 2H), 2.44 (s, 3H).

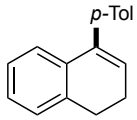
^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.8 (d, $^1J_{CF}$ = 247.1 Hz), 137.5, 132.9, 130.7 (d, $^4J_{CF}$ = 3.9 Hz), 129.3 (d, $^2J_{CF}$ = 23.4 Hz), 129.2, 128.9 (d, $^4J_{CF}$ = 3.1 Hz), 128.6 (d, $^3J_{CF}$ = 8.2 Hz), 124.3 (d, $^3J_{CF}$ = 4.5 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 21.2.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -117.99.

HRMS: exact mass calculated for [M] ($C_{13}H_{11}F$) requires *m/z* 186.0845, found *m/z* 186.0843.

Characterization data is consistent with literature reported values.[196]

98: 4-(*p*-Tolyl)-1,2-dihydronaphthalene



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-(trifluoromethylsulfonyloxy)-1,2-dihydronaphthalene (69.6 mg, 0.25

mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (50.9 mg, 93%).

ν_{max} (liquid film): 3017, 2928, 2826 cm^{-1}.

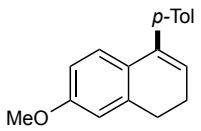
^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, *J* = 9.8 Hz, 2H), 7.25–7.14 (m, 5H), 7.10–7.06 (m, 1H), 6.13 (t, *J* = 4.7 Hz, 1H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.49–2.43 (m, 5H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.7, 137.8, 136.8, 136.7, 135.2, 128.9, 128.6, 127.5, 127.2, 126.9, 126.1, 125.4, 28.3, 23.5, 21.2.

HRMS: exact mass calculated for [M] ($C_{17}H_{16}$) requires *m/z* 220.1252, found *m/z* 220.1262.

Characterization data is consistent with literature reported values.[197]

99: 7-Methoxy-4-(*p*-tolyl)-1,2-dihydronaphthalene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 7-methoxy-4-(trifluoromethylsulfonyloxy)-1,2-dihydronaphthalene (77.1 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (48.2 mg, 77%).

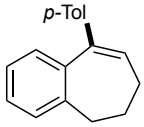
ν_{max} (liquid film): 2921, 2833, 1714, 1606, 1495 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.21 (dd, *J* = 7.1, 1.3 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.97 (t, *J* = 4.7 Hz, 1H), 3.83 (s, 3H), 2.88–2.82 (m, 2H), 2.43–2.38 (m, 5H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.5, 139.3, 138.7, 138.1, 136.6, 128.9, 128.6, 128.4, 126.6, 124.7, 113.7, 110.7, 55.2, 28.8, 23.5, 21.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{19}O$) requires *m/z* 251.1436, found *m/z* 251.1436.

100: 9-(*p*-Tolyl)-6,7-dihydro-5*H*-benzo[7]annulene



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 9-(trifluoromethylsulfonyloxy)-6,7-dihydro-5*H*-benzo[7]annulene (73.1 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (54.1 mg, 92%).

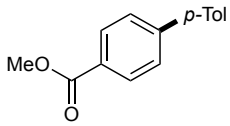
ν_{max} (liquid film): 3017, 2922, 2852, 1448 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.37–7.33 (m, 1H), 7.32–7.28 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.54 (t, *J* = 7.4 Hz, 1H), 2.78 (t, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 2.29 (q, *J* = 7.1 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.8, 142.2, 140.5, 139.5, 136.7, 129.2, 128.8, 128.5, 127.8, 127.6, 126.9, 125.8, 35.3, 32.3, 25.3, 21.1.

HRMS: exact mass calculated for [M] ($C_{18}H_{18}$) requires *m/z* 234.1409, found *m/z* 234.1413.

101: Methyl-4'-methylbiphenyl-4-carboxylate



Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), methyl 4-chlorobenzoate (42.6 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (53 mg). The yield was calculated as an NMR yield (44.9 mg, 79%) from 1:0.24 ratio title compound: methyl 4-chlorobenzoate.

ν_{max} (solid): 2943, 2844, 1712, 1437 cm^{-1}.

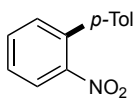
^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.94 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.0, 145.6, 138.1, 137.1, 130.1, 129.6, 128.6, 127.1, 126.8, 52.1, 21.1.

HRMS: exact mass calculated for [M] ($C_{15}H_{14}O_2$) requires *m/z* 226.0994, found *m/z* 226.0992.

Characterization data is consistent with literature reported values.[196]

102: 4'-Methyl-2-nitrobiphenyl



Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 2-chloronitrobenzene (39.4 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75

mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (47.6 mg, 89%).

ν_{max} (liquid film): 2921, 2859, 1521, 1478, 1353 cm^{-1}.

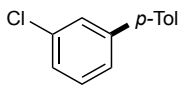
^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.60 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48–7.42 (m, 2H), 7.25–7.20 (m, 4H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.6, 138.3, 136.4, 134.5, 132.3, 132.1, 129.6, 128.0, 127.9, 124.2, 21.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}NO_2$) requires *m/z* 214.0868, found *m/z* 214.0871.

Characterization data is consistent with literature reported values.[184]

103: 3-Chloro-4'-methylbiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-chloroiodobenzene (59.6 mg, 0.25 mmol, 1 equiv.), *p*-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (40.6 mg, 80%).

ν_{max} (solid): 3028, 2915, 1561 cm^{-1}.

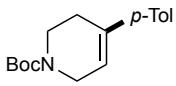
^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (t, *J* = 1.8 Hz, 1H), 7.48–7.44 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.31–7.28 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.0, 137.7, 136.9, 134.6, 129.9, 129.6, 129.4, 127.1, 126.9, 125.1, 21.1.

HRMS: exact mass calculated for [M] ($C_{13}H_{11}{}^{35}Cl$) requires *m/z* 202.0549, found *m/z* 202.0553.

Characterization data is consistent with literature reported values.[184]

104: *tert*-Butyl-4-(*p*-tolyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (77.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% Et_2O in petroleum ether) to afford the title compound as an off-white solid (64.9 mg, 95%).

Prepared according to General Procedure E using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (43 mg, 0.25 mmol, 1 equiv.), *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (77 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% Et_2O in petroleum ether) to afford the title compound as an off-white solid (56 mg, 81%).

ν_{max} (solid): 2971, 2926, 1690, 1158 cm^{-1}.

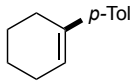
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.99 (app s, 1H), 4.07 (dd, *J* = 5.8, 2.8 Hz, 2H), 3.64 (t, *J* = 5.7 Hz, 2H), 2.53–2.50 (m, 2H), 2.35 (s, 3H), 1.51 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 154.9, 138.0, 136.9, 135.5, 129.1, 124.9, 120.1, 79.6, 43.8, 40.6, 28.5, 27.6, 20.9.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{17}H_{22}NO_2$) requires *m/z* 272.1645, found *m/z* 272.1645.

Characterization data is consistent with literature reported values.[198]

105: 4'-Methyl-2,3,4,5-tetrahydrobiphenyl



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 1-cyclohexen-1-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless oil (35.8 mg, 83%).

ν_{max} (liquid film): 2921, 2855, 1513 cm^{-1}.

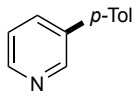
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.10–6.08 (m, 1H), 2.43–2.37 (m, 2H), 2.34 (s, 3H), 2.23–2.18 (m, 2H), 1.82–1.75 (m, 2H), 1.70–1.64 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 139.9, 136.4, 136.1, 128.9, 124.8, 123.9, 27.4, 25.8, 23.1, 22.2, 20.9.

HRMS: exact mass calculated for [M] ($C_{13}H_{16}$) requires *m/z* 172.1252, found *m/z* 172.1257.

Characterization data is consistent with literature reported values.[199]

106: 3-(*p*-Tolyl)pyridine



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), pyridine-3-boronic acid pinacol ester (51.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless oil (35.3 mg, 83%).

ν_{max} (liquid film): 3025, 2919, 1470 cm^{-1}.

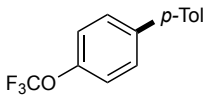
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (dd, *J* = 2.3, 0.6 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.86 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.34 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 148.1, 138.0, 136.6, 134.9, 134.2, 129.8, 126.9, 125.5, 123.5, 21.1.

HRMS: exact mass calculated for [M] ($C_{12}H_{11}N$) requires *m/z* 169.0891, found *m/z* 169.0893.

Characterization data is consistent with literature reported values.[184]

107: 4-Methyl-4'-(trifluoromethoxy)-biphenyl



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 4-(trifluoromethoxy)phenylboronic acid pinacol ester (72 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400

equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (51.7 mg, 82%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (43 mg, 0.25 mmol, 1 equiv.), 4-(trifluoromethoxy)phenylboronic acid pinacol ester (72 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (49 mg, 78%).

ν_{max} (solid): 3030, 2922, 1495, 1154 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.56 (m, 2H), 7.48–7.44 (m, 2H), 7.29–7.25 (m, 4H), 2.41 (s, 3H).

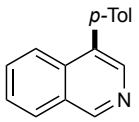
^{13}C NMR ($CDCl_3$, 101 MHz): δ 148.4, 139.9, 137.5, 136.9, 129.6, 128.2, 126.9, 121.2, 120.5 (q, $^1J_{CF}$ = 256.8 Hz), 21.1.

^{19}F NMR ($CDCl_3$, 376 MHz) δ -57.82.

HRMS: exact mass calculated for [M] ($C_{14}H_{11}F_3O$) requires *m/z* 252.0762, found *m/z* 252.0763.

Characterization data is consistent with literature reported values.[200]

108: 4-(*p*-Tolyl)isoquinoline



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), 4-isoquinolineboronic acid pinacol ester (63.8 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3

equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a brown oil (51.6 mg, 94%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (43 mg, 0.25 mmol, 1 equiv.), 4-isoquinolineboronic acid pinacol ester (64 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a brown oil (47 mg, 86%).

ν_{max} (liquid film): 3021, 2919, 1390 cm^{-1}.

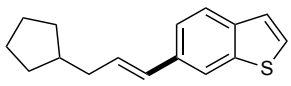
^1H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 8.48 (s, 1H), 8.03 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.68–7.59 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 2.47 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.7, 142.8, 137.7, 134.3, 134.0, 133.3, 130.4, 129.9, 129.3, 128.4, 127.8, 127.1, 124.8, 21.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{14}N$) requires *m/z* 220.1121, found *m/z* 220.1122.

Characterization data is consistent with literature reported values.[201]

109: *trans*-6-(3-Cyclopentylprop-1-en-1-yl)benzo[*b*]thiophene



Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-chlorobenzothiophene (42.2 mg, 0.25 mmol, 1 equiv.), *trans*-3-(cyclopentyl)-1-propenylboronic acid pinacol ester (59 mg, 0.25

mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (47.4 mg, 78%).

Prepared according to General Procedure E using $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2 mol%), SPhos (4.1 mg, 0.01 mmol, 4 mol%), 6-chlorobenzothiophene (42 mg, 0.25 mmol, 1 equiv.), *trans*-3-(cyclopentyl)-1-propenylboronic acid pinacol ester (59 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether) to afford the title compound as a colourless solid (56 mg, 92%).

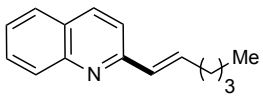
ν_{max} (solid): 2943, 2861 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 0.7 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.40 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.37 (d, *J* = 5.4 Hz, 1H), 7.28 (dd, *J* = 5.4, 0.7 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.25 (td, *J* = 7.1, 1.3 Hz, 2H), 2.03–1.91 (m, 1H), 1.84–1.76 (m, 2H), 1.68–1.49 (m, 4H), 1.28–1.17 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.3, 138.5, 134.5, 130.7, 130.0, 126.0, 123.7, 123.4, 122.4, 119.8, 40.1, 39.5, 32.3, 25.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}S$) requires *m/z* 242.1129, found *m/z* 242.1123.

110: *trans*-2-(Hex-1-en-1-yl)quinoline



Prepared according to General Procedure C using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 5-chloroquinoline (40.9 mg, 0.25 mmol, 1 equiv.), *trans*-1-hexen-1-ylboronic acid pinacol ester (52.5 mg, 0.25 mmol, 1 equiv.),

Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-70% MeCN in water) to afford the title compound as a colourless oil (42.1 mg, 80%).

ν_{max} (liquid film): 2952, 2922, 2852, 1597 cm^{-1}.

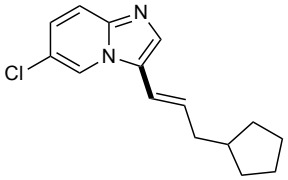
^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J* = 8.7 Hz, 1H), 8.02 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.46 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.83 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.71 (dt, *J* = 15.9, 1.1 Hz, 1H), 2.38–2.30 (m, 2H), 1.59–1.50 (m, 2H), 1.46–1.37 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.5, 148.1, 138.0, 136.1, 131.0, 129.5, 129.1, 127.4, 127.1, 125.8, 118.7, 32.7, 31.0, 22.3, 13.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N$) requires *m/z* 212.1434, found *m/z* 212.1433.

Characterization data is consistent with literature reported values.[202]

111: *trans*-6-Chloro-3-(3-cyclopentylprop-1-en-1-yl)imidazo[1,2-*a*]pyridine



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-bromo-6-chloroimidazo[1,2-*a*]pyridine (57.9 mg, 0.25 mmol, 1 equiv.), *trans*-3-(cyclopentyl)-1-propenylboronic acid pinacol ester (59 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-100% MeCN in water) to afford the title compound as a colourless oil (53.9 mg, 83%).

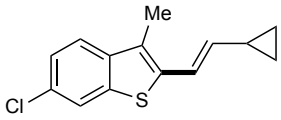
ν_{max} (liquid film): 2948, 2865, 1656, 1498 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.69 (s, 1H), 7.54 (dd, *J* = 9.5, 0.7 Hz, 1H), 7.10 (dd, *J* = 9.5, 1.9 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 15.8, 7.0 Hz, 1H), 2.29 (td, *J* = 7.1, 1.1 Hz, 2H), 2.04–1.93 (m, 1H), 1.85–1.77 (m, 2H), 1.68–1.60 (m, 2H), 1.59–1.51 (m, 2H), 1.24–1.17 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.8, 133.2, 131.8, 124.7, 124.5, 121.1, 120.8, 118.4, 114.7, 39.9, 39.8, 32.3, 25.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}{}^{35}ClN_2$) requires *m/z* 261.1153, found *m/z* 261.1156.

112: *trans*-5-Chloro-2-(2-cyclopropylvinyl)-3-methylbenzo[*b*]thiophene



Prepared according to General Procedure C using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 5-chloro-2-bromo-3-methylbenzo[*b*]thiophene (65.4 mg, 0.25 mmol, 1 equiv.), (*trans*)-2-cyclopropylvinylboronic acid pinacol ester (48.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, petroleum ether to afford the title compound as a colourless solid (28.3 mg, 46%).

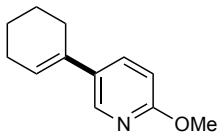
ν_{max} (solid): 3013, 2915, 1578, 1437 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.76 (d, *J* = 15.4 Hz, 1H), 5.65 (dd, *J* = 15.4, 9.0 Hz, 1H), 2.33 (s, 3H), 1.65–1.55 (m, 1H), 0.91–0.84 (m, 2H), 0.61–0.54 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.7, 138.7, 138.2, 135.6, 130.3, 126.2, 124.5, 122.9, 121.1, 119.4, 14.9, 11.5, 7.7.

HRMS: exact mass calculated for [M] ($C_{14}H_{13}{}^{35}ClS$) requires *m/z* 248.0426, found *m/z* 248.0423.

113: 5-(Cyclohex-1-en-1-yl)-2-methoxypyridine



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (4.9 mg, 0.006 mmol, 4 mol%), 6-methoxypyridin-3-yl trifluoromethanesulfonate (38 mg, 0.15 mmol, 1 equiv.), 1-cyclohexen-1-yl-boronic acid pinacol ester (31.2 mg, 0.15 mmol, 1 equiv.), Cs_2CO_3 (146.7 mg, 0.45 mmol, 3 equiv.), Cyrene (0.6 mL, 0.25 M), and H_2O (1.08 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% Et_2O in petroleum ether to afford the title compound as a yellow oil (26.1 mg, 92%).

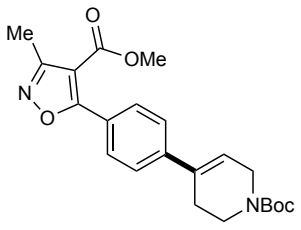
ν_{max} (liquid film): 2924, 2855, 1602, 1495, 1383, 1286 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, *J* = 2.4 Hz, 1H), 7.59 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.68 (dd, *J* = 8.7, 0.6 Hz, 1H), 6.04–6.01 (m, 1H), 3.93 (s, 3H), 2.37–2.34 (m, 2H), 2.21–2.17 (m, 2H), 1.81–1.75 (m, 2H), 1.68–1.62 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.0, 143.0, 135.5, 133.5, 131.4, 124.3, 110.1, 53.4, 27.2, 25.8, 22.9, 22.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}NO$) requires *m/z* 190.1226, found *m/z* 190.1223.

114: Methyl 5-(4-(1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-methylisoxazole-4-carboxylate



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), methyl 5-(4-bromophenyl)-3-methylisoxazole-4-carboxylate (74.1 mg,

0.25 mmol, 1 equiv.), *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (77.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-40% Et_2O in petroleum ether) to afford the title compound as a colourless gum (88.9 mg, 89%).

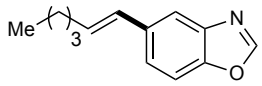
ν_{max} (solid): 2974, 1719, 1695, 1591, 1418, 1095 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 6.17 (app s, 1H), 4.11 (d, *J* = 2.7 Hz, 2H), 3.84 (s, 3H), 3.65 (t, *J* = 5.7 Hz, 2H), 2.55 (app s, 2H), 2.50 (s, 3H), 1.49 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.8, 162.7, 160.7, 154.8, 143.3, 134.7, 129.2, 125.6, 124.7, 122.7, 107.9, 79.8, 51.7, 43.8, 30.3, 28.5, 27.1, 12.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{27}N_2O_5$) requires *m/z* 399.1914, found *m/z* 399.1912.

115: *trans*-6-(Hex-1-en-1-yl)benzo[*d*]oxazole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 5-bromobenzoxazole (49.5 mg, 0.25 mmol, 1 equiv.), *trans*-1-hexen-1-ylboronic acid pinacol ester (52.5 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-40% EtOAc in petroleum ether) to afford the title compound as a pink oil (43.2 mg, 86%).

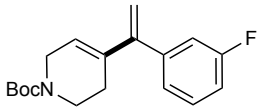
ν_{max} (liquid film): 2954, 2924, 2854, 1673, 1519 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.26–2.21 (m, 2H), 1.52–1.44 (m, 2H), 1.43–1.35 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.8, 149.1, 140.5, 135.3, 131.5, 129.1, 123.9, 117.4, 110.6, 32.7, 31.5, 22.3, 13.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}NO$) requires *m/z* 202.1226, found *m/z* 202.1225.

116: *tert*-Butyl 4-(1-(3-fluorophenyl)vinyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 1-(1-bromovinyl)-3-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv.), *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (77.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-40% Et_2O in petroleum ether) to afford the title compound as a colourless oil (53.7 mg, 71%).

ν_{max} (liquid film): 2971, 2924, 1692, 1422, 1364, 1158 cm^{-1}.

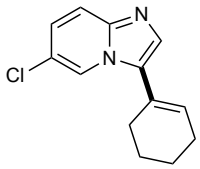
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.26 (m, 1H), 7.06–6.91 (m, 3H), 5.54 (app s, 1H), 5.25 (s, 1H), 5.09 (s, 1H), 3.97 (app s, 2H), 3.58 (t, *J* = 5.7 Hz, 2H), 2.35 (app s, 2H), 1.47 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.52 (d, $^{1}J_{CF}$ = 245.4 Hz), 154.8, 148.9, 143.4 (d, $^{3}J_{CF}$ = 7.5 Hz), 135.5, 129.5 (d, $^{3}J_{CF}$ = 8.5 Hz), 124.4, 115.6 (d, $^{2}J_{CF}$ = 21.5 Hz), 114.2 (d, $^{2}J_{CF}$ = 20.9 Hz), 113.0, 79.7, 43.7, 40.8, 39.7, 28.5, 26.34.

^{19}F NMR ($CDCl_3$, 376 MHz) δ -113.83.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}FNNaO_2$) requires *m/z* 326.1527, found *m/z* 326.1519.

117: 6-Chloro-3-(cyclohex-1-en-1-yl)imidazo[1,2-*a*]pyridine



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-bromo-6-chloroimidazo[1,2-*a*]pyridine (57.9 mg, 0.25 mmol, 1 equiv.), 1-cyclohexen-1-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-100% MeCN in water) to afford the title compound as a colourless oil (48.3 mg, 83%).

Prepared according to General Procedure E using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-bromo-6-chloroimidazo[1,2-*a*]pyridine (58 mg, 0.25 mmol, 1 equiv.), 1-cyclohexen-1-yl-boronic acid pinacol ester (52 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20-50% MeCN in water) to afford the title compound as a colourless oil (36 mg, 62%).

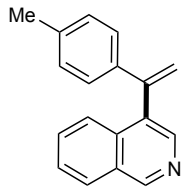
ν_{max} (liquid film): 2928, 2855, 1721, 1649, 1498 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.30 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.54 (dd, *J* = 9.5, 0.7 Hz, 1H), 7.51 (s, 1H), 7.09 (dd, *J* = 9.5, 2.0 Hz, 1H), 6.12–6.08 (m, 1H), 2.40–2.36 (m, 2H), 2.32–2.27 (m, 2H), 1.86–1.80 (m, 2H), 1.78–1.72 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.1, 132.2, 127.8, 127.7, 126.4, 124.8, 122.7, 120.4, 118.4, 28.7, 25.5, 22.7, 21.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}{}^{35}ClN_2$) requires *m/z* 233.0840, found *m/z* 233.0842.

118: 4-(1-(*p*-Tolyl)vinyl)isoquinoline



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-(1-bromovinyl)-toluene (49.3 mg, 0.25 mmol, 1 equiv.), 4-isoquinolineboronic acid pinacol ester (63.8 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a colourless oil (46.3 mg, 75%).

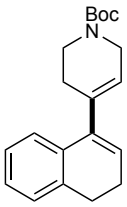
ν_{max} (liquid film): 3025, 2921, 1623, 1500 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 9.26 (s, 1H), 8.50 (s, 1H), 7.99 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.57–7.50 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.97 (s, 1H), 5.40 (s, 1H), 2.33 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.4, 144.9, 143.1, 137.9, 137.6, 134.6, 133.1, 130.3, 129.2, 128.4, 127.8, 127.0, 126.5, 125.4, 116.6, 21.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N$) requires *m/z* 246.1277, found *m/z* 246.1277.

119: *tert*-Butyl 4-(3,4-dihydronaphthalen-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 4-(trifluoromethylsulfonyloxy)-1,2-dihydronaphthalene (69.6 mg, 0.25 mmol, 1 equiv.), *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (77.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% Et_2O in petroleum ether) to afford the title compound as a yellow oil (79.1 mg, >99%).

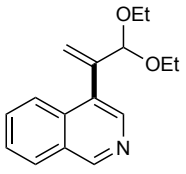
ν_{max} (liquid film): 2973, 2930, 1693, 1415, 1366, 1164 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.21–7.12 (m, 3H), 7.10–7.05 (m, 1H), 5.93 (t, *J* = 4.7 Hz, 1H), 5.70 (s, 1H), 4.02 (d, *J* = 1.9 Hz, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.27 (td, *J* = 7.8, 4.8 Hz, 4H), 1.50 (s, 9H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.0, 140.5, 136.9, 136.4, 133.8, 127.6, 126.9, 126.3, 125.3, 124.8, 121.9, 79.6, 43.4, 28.6, 28.5, 28.2, 23.1. Carbon adjacent to nitrogen not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}NO_3$) requires *m/z* 312.1958, found *m/z* 312.1959.

120: 4-(3,3-Diethoxyprop-1-en-2-yl)isoquinoline



Prepared according to General Procedure C using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 2-bromopropenal diethyl acetal (52.3 mg, 0.25 mmol, 1 equiv.), 4-

isoquinolineboronic acid pinacol ester (63.8 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% Et_2O in petroleum ether) to afford the title compound as a brown oil (46.7 mg, 73%).

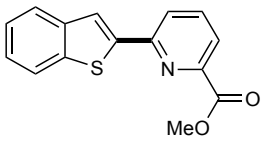
ν_{max} (liquid film): 2973, 2872, 1383, 1058 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 9.18 (s, 1H), 8.41 (s, 1H), 8.02 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.70–7.65 (m, 1H), 7.61–7.57 (m, 1H), 5.93 (d, *J* = 1.5, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.15 (s, 1H), 3.73–3.69 (m, 2H), 3.57–3.53 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.9, 142.4, 142.1, 134.8, 130.8, 130.1, 128.3, 127.7, 126.9, 124.9, 119.9, 102.9, 62.4, 15.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}NO_2$) requires *m/z* 258.1489, found *m/z* 258.1489.

121: Methyl 6-(benzo[*b*]thiophen-2-yl)picolinate



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), methyl 6-bromopicolinate (54 mg, 0.25 mmol, 1 equiv.), 2-benzothiopheneboronic acid MIDA ester (72.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% EtOAc in petroleum ether) to afford the title compound as a colourless solid (38.7 mg, 57%).

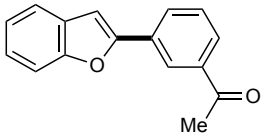
ν_{max} (solid): 2948, 2846, 1716, 1588, 1316 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.95–7.93 (m, 2H), 7.91–7.81 (m, 3H), 7.40–7.34 (m, 2H), 4.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.6, 152.8, 148.1, 143.6, 140.9, 140.3, 137.7, 125.4, 124.6, 124.3, 123.8, 122.8, 122.6, 122.3, 52.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{12}NO_2S$) requires *m/z* 270.0583, found *m/z* 270.0586.

122: 2-(3-Acetylphenyl)benzo[b]furan



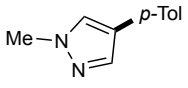
Prepared according to the General Procedure using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 3-bromoacetonphenone (49.8 mg, 0.25 mmol, 1 equiv.), 2-benzofuranylboronic acid MIDA ester (68.3 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether) to afford the title compound as an off-white solid (55.1 mg, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (t, *J* = 1.6 Hz, 1H), 8.05 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.93 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.57-7.53 (m, 2H), 7.32 (td, *J* = 7.5, 1.0 Hz 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 7.12 (d, *J* = 0.8 Hz, 1H), 2.69 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.9, 155.1, 154.9, 137.8, 131.2, 129.3, 129.3, 129.1, 128.3, 124.9, 124.8, 123.3, 121.3, 111.4, 102.5, 26.9.

Characterisation data is consistent with literature reported values.[203]

123: 1-Methyl-4-(*p*-tolyl)-1*H*-pyrazole



Prepared according to General Procedure C using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), 4-bromotoluene (42.8 mg, 0.25 mmol, 1 equiv.), potassium (1-methyl-1*H*-pyrazol-3-yl)trifluoroborate (47 mg, 0.25 mmol, 1 equiv.), Cs_2CO_3 (244.5 mg, 0.75 mmol, 3 equiv.), Cyrene (1 mL, 0.25 M), and H_2O (1.8 mL, 400 equiv.). After 5 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% Et_2O in petroleum ether) to afford the title compound as an off-white solid (32.1 mg, 75%).

ν_{max} (solid): 3108, 2915, 2846, 1721, 1567 cm^{-1}.

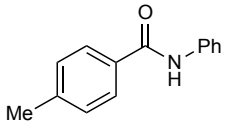
^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (s, 1H), 7.57 (s, 1H), 7.38–7.33 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 3.94 (s, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.6, 136.0, 129.7, 129.5, 126.7, 125.4, 123.2, 38.9, 21.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{13}N_2$) requires *m/z* 173.1073, found *m/z* 173.1071.

Characterization data is consistent with literature reported values.[204]

126: 4-Methyl-*N*-phenylbenzamide



Prepared according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), aniline (25 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General

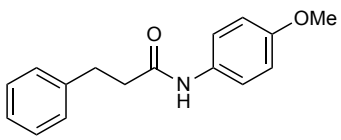
Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (51 mg, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (br s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.8, 142.5, 138.2, 132.3, 129.6, 129.2, 127.2, 124.6, 120.3, 21.6.

Characterization data is consistent with literature reported values.[165]

127: *N*-(4-Methoxyphenyl)-3-phenylpropanamide



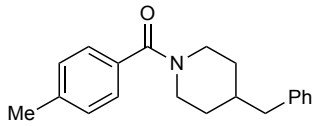
Prepared according to General Procedure D using 3-phenylpropanoic acid (37.5 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 4-methoxyaniline (33.9 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (60.5 mg, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.20 (m, 7H), 6.89 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.78 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.3, 156.6, 140.9, 130.9, 128.8, 128.6, 126.5, 122.0, 114.3, 55.6, 39.5, 31.8.

Characterization data is consistent with literature reported values.[205]

128: (4-Benzylpiperidin-1-yl)(*p*-tolyl)methanone



Prepared according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 4-benzylpiperidine (48 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% EtOAc in petroleum ether) to afford the title compound as a colourless oil (73.7 mg, >99%).

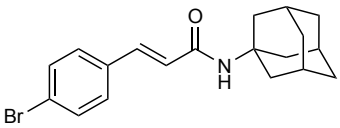
ν_{max} (liquid film): 2916, 2849, 1625, 1434 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.29–7.21 (m, 6H), 7.20–7.16 (m, 3H), 4.00 (s, 2H), 2.87 (t, J = 12.6 Hz, 2H), 2.57 (d, J = 7.1 Hz, 2H), 2.34 (s, 3H), 1.88–1.79 (m, 1H), 1.62 (d, J = 12.6 Hz, 2H), 1.17 (qd, J = 12.6, 4.2 Hz, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.6, 139.5, 138.2, 133.4, 128.3, 128.2, 127.5, 126.1, 125.2, 43.9, 41.5, 36.7, 31.2, 20.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}NO$) requires *m/z* 294.1852, found *m/z* 294.1852.

129: (*E*)-*N*-((3s,5s,7s)-Adamantan-1-yl)-3-(4-bromophenyl)acrylamide



Prepared according to General Procedure D using (*E*)-3-(4-bromophenyl)acrylic acid (56.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 1-adamantylamine (41.6 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method

outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (83.8 mg, 93%).

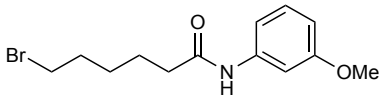
ν_{max} (solid): 3304, 2901, 2854, 1659, 1616, 1536 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.50–7.45 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.32 (d, *J* = 15.5 Hz, 1H), 5.36 (br s, 1H), 2.10 (app s, 3H), 2.07 (app s, 6H), 1.70 (app s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 164.6, 139.0, 134.1, 132.1, 129.2, 123.6, 123.0, 52.4, 41.8, 36.5, 29.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}{}^{79}BrNO$) requires *m/z* 362.0937, found *m/z* 352.0940.

130: 6-Bromo-*N*-(3-methoxyphenyl)hexanamide



Prepared according to General Procedure D using 6-bromohexanoic acid (48.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 3-methoxyaniline (31 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (70.4 mg, 94%).

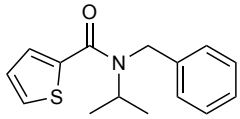
ν_{max} (liquid film): 3291, 2929, 2856, 1659, 1597, 1543 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.42 (br s, 1H), 7.31 (s, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 3.78 (s, 3H), 3.40 (t, *J* = 6.7 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.91–1.84 (m, 2H), 1.77–1.71 (m, 2H), 1.54–1.48 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2, 160.3, 139.3, 129.8, 112.0, 110.2, 105.7, 55.4, 37.6, 33.7, 32.6, 27.8, 24.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}{}^{79}BrNO_2$) requires *m/z* 302.0573, found *m/z* 302.0574.

131: *N*-Benzyl-*N*-isopropylthiophene-2-carboxamide



Prepared according to General Procedure D using 2-thiophenecarboxylic acid (32 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), *N*-isopropylbenzylamine (46 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless oil (61.3 mg, 95%).

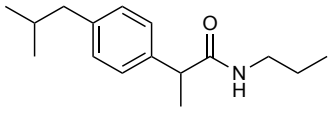
ν_{max} (liquid film): 2966, 2931, 1601 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 7.67 (d, *J* = 5.0 Hz, 1H), 7.35–7.28 (m, 5H), 7.23 (t, *J* = 6.9 Hz, 1H), 7.07 (t, *J* = 8.7 Hz, 1H), 4.68 (s, 2H), 4.48 (sept, *J* = 6.7 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 163.6, 138.9, 138.1, 128.4, 127.8, 127.4, 126.5, 126.2, 126.2, 49.1, 45.7, 20.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NOS$) requires *m/z* 260.1104, found *m/z* 260.1104.

132: 2-(4-Isobutylphenyl)-*N*-propylpropanamide



Prepared according to General Procedure D using 2-(4-isobutylphenyl)propanoic acid (51.6 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 μL, 0.75 mmol, 3 equiv.), propylamine (23 μL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (48.4 mg, 78%).

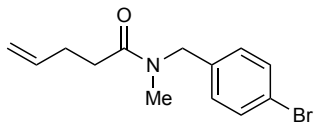
ν_{max} (liquid film): 3286, 2955, 2927, 2867, 1644, 1547 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.33 (br s, 1H), 3.52 (q, *J* = 7.2 Hz, 1H), 3.14 (q, *J* = 7.0 Hz, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.91–1.79 (m, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.45–1.37 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.6, 140.8, 138.8, 129.7, 127.5, 46.9, 45.1, 41.4, 30.3, 22.9, 22.5, 18.6, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{26}NO$) requires *m/z* 248.2009, found *m/z* 248.2011.

133: *N*-(4-Bromobenzyl)-*N*-methylpent-4-enamide



Prepared according to General Procedure D using 4-pentenoic acid (25.5 μL, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 μL, 0.75 mmol, 3 equiv.), (4-bromobenzyl)methylamine (55 μL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (67.1 mg, 95%).

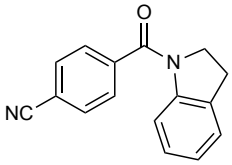
ν_{max} (liquid film): 2920, 1634, 1488, 1400 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.51 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 5.91–5.81 (m, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.51 (s, 2H), 2.90 (s, 3H), 2.45 (t, J = 7.3 Hz, 2H), 2.32 (q, J = 7.1 Hz, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 171.1, 137.4, 136.9, 130.8, 128.9, 119.5, 114.2, 49.6 (br s), 33.9 (br s), 31.3, 28.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}{}^{79}BrNO$) requires *m/z* 284.0468, found *m/z* 248.0467.

134: 4-(Indoline-1-carbonyl)benzonitrile



Prepared according to General Procedure D using 4-cyanobenzoic acid (36.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), indoline (28.1 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (57 mg, 92%).

ν_{max} (solid): 2921, 2226, 1640, 1597, 1398 cm^{-1}.

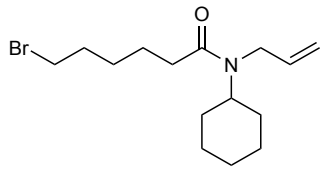
^{1}H NMR (DMSO-d_6, 500 MHz, 300 K): δ 8.10 (app s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.79 (app s, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.23 (app s, 1H), 7.08 (app s, 1H), 3.95 (app s, 2H), 3.09 (t, J = 8.1 Hz, 2H).

^{1}H NMR (DMSO-d_6, 500 MHz, 355 K): δ 7.94 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 3.98 (t, J = 8.3 Hz, 2H), 3.11 (t, J = 8.3 Hz, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz, 355 K): δ 165.9, 141.9, 140.9, 132.3, 132.1, 127.4, 126.4, 124.6, 123.6, 117.7, 115.9, 112.3, 49.6, 27.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{13}N_2O$) requires *m/z* 249.1022, found *m/z* 249.1022.

135: *N*-Allyl-6-bromo-*N*-cyclohexylhexanamide



Prepared according to General Procedure D using 6-bromohexanoic acid (48.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), allylcyclohexylamine (40 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless oil (70.6 mg, 90%).

ν_{max} (liquid film): 2925, 2853, 1633, 1413 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 5.87–5.70 (m, 1H), 5.19–5.02 (m, 2H), 4.47–4.37 (m, 0.58H), 3.88 (app d, *J* = 5.6 Hz, 0.74H), 3.83–3.79 (m, 1.23H), 3.56 (tt, *J* = 11.8, 3.6 Hz, 0.38H), 3.40 (app q, *J* = 7.0 Hz, 2H), 2.38–2.33 (m, 0.73H), 2.28–2.24 (m, 1.23H), 1.93–1.60 (m, 9H), 1.54–1.24 (m, 6H), 1.14–0.99 (m, 1H). Rotamers observed.

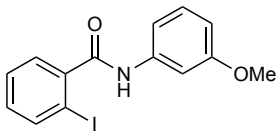
^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 172.1, 135.9, 135.8, 116.2, 115.6, 57.4, 53.4, 45.6, 44.1, 33.9, 33.5, 33.4, 32.8, 32.8, 32.1, 30.9, 28.1, 28.1, 26.1, 25.9, 25.7, 25.4, 24.6. Rotamers observed.

^1H NMR (DMSO-d_6, 500 MHz, 373 K): δ 5.86–5.76 (m, 1H), 5.16–5.04 (m, 2H), 3.86 (d, *J* = 5.0 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.29 (app s, 2H), 1.87–1.80 (m, 2H), 1.76 (d, *J* = 13.2 Hz, 2H), 1.65–1.55 (m, 6H), 1.50–1.40 (m, 4H), 1.35–1.27 (m, 2H), 1.15–1.05 (m, 1H).

^{13}C NMR (DMSO-d_6, 126 MHz, 373 K): δ 171.0, 136.2, 114.6, 60.3, 49.1, 34.0, 32.1, 31.7, 30.3, 26.9, 25.1, 24.5, 23.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{27}{}^{79}BrNO$) requires *m/z* 316.1271, found *m/z* 316.1273.

136: 2-Iodo-*N*-(3-methoxyphenyl)benzamide



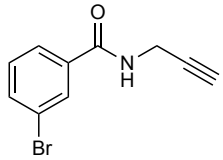
Prepared according to General Procedure D using 2-iodobenzoic acid (62 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 3-methoxyaniline (31 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (62.9 mg, 71%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.45–7.40 (m, 3H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.15 (td, *J* = 7.8, 1.5 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 160.4, 142.3, 140.2, 138.9, 131.7, 129.9, 128.7, 128.53, 112.3, 110.9, 105.9, 92.4, 55.6.

Characterization data is consistent with literature reported values.[206]

137: 3-Bromo-*N*-(prop-2-yn-1-yl)benzamide



Prepared according to General Procedure D using 3-bromobenzoic acid (50.3 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), propargylamine (17.6 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in

the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (37.6 mg, 63%).

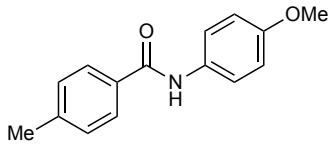
ν_{max} (solid): 3280, 3065, 2914, 2847, 1638, 1536 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.93 (t, *J* = 1.8 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 6.23 (br s, 1H), 4.25 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.30 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 165.8, 135.9, 134.9, 130.4, 130.4, 125.7, 123.0, 79.3, 72.4, 30.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_9{}^{79}BrNO$) requires *m/z* 239.9842, found *m/z* 239.9845.

138: *N*-(4-Methoxyphenyl)-4-methylbenzamide



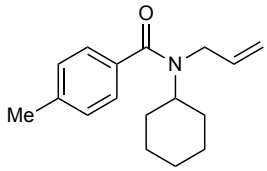
Prepared according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 µL, 0.75 mmol, 3 equiv.), 4-methoxyaniline (33.9 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (61.5 mg, 95%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (br s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.7, 156.7, 142.3, 132.3, 131.3, 129.5, 127.1, 122.2, 114.4, 55.6, 21.6.

Characterization data is consistent with literature reported values.[207]

139: *N*-Allyl-*N*-cyclohexyl-4-methylbenzamide



Prepared according to General Procedure D using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), DIPEA (131 μL, 0.75 mmol, 3 equiv.), allylcyclohexylamine (40 μL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (41.5 mg, 63%).

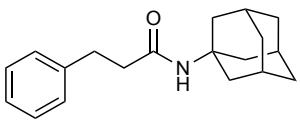
ν_{max} (solid): 2925, 2853, 1625, 1409 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.22 (app s, 4H), 5.84 (m, 1H), 5.14 (d, J = 17.2 Hz, 1H), 5.07 (dd, J = 10.3, 1.5 Hz, 1H), 3.92 (d, J = 5.2 Hz, 2H), 3.71 (app s, 1H), 2.34 (s, 3H), 1.76–1.65 (m, 4H), 1.63–1.51 (m, 3H), 1.08 (m, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 170.2, 137.9, 135.8, 134.5, 128.3, 125.6, 115.1, 56.5, 44.8, 30.4, 25.1, 24.4, 20.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO$) requires *m/z* 258.1852, found *m/z* 258.1853.

140: *N*-((3s,5s,7s)-Adamantan-1-yl)-3-phenylpropanamide



Prepared according to General Procedure D using 3-phenylpropanoic acid (37.5 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv.), 1-adamantylamine (41.6 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was diluted with EtOAc (20

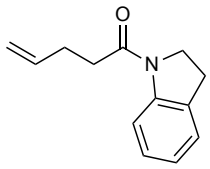
mL), and washed with 2 M HCl (2 x 20 mL), sat. solution NaHCO3 (2 x 20 mL), H_2O (20 mL), and brine (20 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was recrystallized from EtOAc/petroleum ether to afford the title compound as a colourless solid (71.6 mg, >99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–7.25 (m, 2H), 7.21–7.17 (m, 3H), 4.99 (br s, 1H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.04 (app s, 3H), 1.92 (app d, *J* = 2.7 Hz, 6H), 1.65 (app s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.3, 141.2, 128.6, 126.2, 51.9, 41.7, 39.7, 36.5, 31.9, 29.5.

Characterization data is consistent with literature reported values.[208]

141: 1-(Indolin-1-yl)pent-4-en-1-one



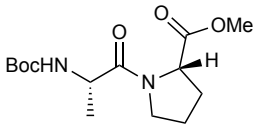
Prepared according to General Procedure D using 4-pentenoic acid (25.5 µL, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), indoline (28.1 µL, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% EtOAc in petroleum ether) to afford the title compound as a colourless solid (47.8 mg, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.21–7.16 (m, 2H), 7.01 (td, *J* = 7.5, 0.7 Hz, 1H), 5.98–5.89 (m, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.06 (t, *J* = 8.5 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.52 (app s, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.6, 143.2, 137.6, 131.1, 127.7, 124.6, 123.7, 117.2, 115.5, 48.1, 35.4, 28.7, 28.2.

Characterization data is consistent with literature reported values.[209]

142: Boc-Ala-Pro-OMe



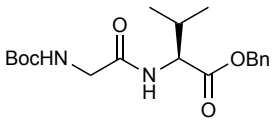
Prepared according to General Procedure D using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Pro-OMe.HCl (45.5 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (67.2 mg, 89%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.33 (d, *J* = 7.8 Hz, 1H), 4.56–4.41 (m, 2H), 3.71 (s, 3H), 3.74–3.67 (m, 1H), 3.63–3.56 (m, 1H), 2.27–2.17 (m, 1H), 2.10–1.95 (m, 3H), 1.42 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.6, 171.9, 155.4, 79.7, 58.8, 52.4, 47.9, 46.9, 29.1, 28.5, 25.1, 18.5.

Characterization data is consistent with literature reported values.[210]

143: Boc-Gly-Val-OBn



Prepared according to General Procedure D using Boc-Gly-OH (43.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Val-OBn.HCl (67 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a colouless oil (50 mg, 56%).

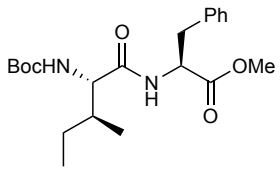
Prepared according to General Procedure D using Boc-Gly-OH (43.8 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Val-OBn.HCl (67 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a colouless oil (50 mg, 77%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.31 (m, 5H), 6.60 (d, *J* = 7.9 Hz, 1H), 5.17 (q, *J* = 12.2 Hz, 2H), 5.15 (br s, 1H), 4.61 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.82 (ddd, *J* = 44.0, 16.7, 5.8 Hz, 2H), 2.24–2.16 (m, 1H), 1.45 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 169.6, 156.2, 135.4, 128.8, 128.6, 128.5, 80.5, 67.2, 57.1, 44.7, 31.5, 28.4, 19.1, 17.6.

Characterization data is consistent with literature reported values.[211]

144: Boc-Ile-Phe-OMe



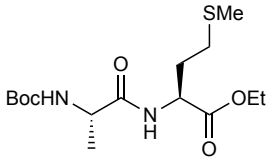
Prepared according to General Procedure D using Boc-Ile-OH (57.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Phe-OMe.HCl (59.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (93 mg, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–7.21 (m, 3H), 7.13–7.10 (m, 2H), 6.27 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.87 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.96–3.87 (m, 1H), 3.71 (s, 3H), 3.17–3.06 (m, 2H), 1.86–1.79 (m, 1H), 1.58 (br s, 1H), 1.44 (s, 9H), 1.07 (br s, 1H), 0.89 - 0.86 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 171.3, 155.8, 135.8, 129.4, 128.8, 127.3, 80.0, 59.4, 53.2, 52.4, 38.1, 37.4, 28.4, 24.8, 15.6, 11.6.

Characterization data is consistent with literature reported values.[170]

145: Boc-Ala-Met-OEt



Prepared according to General Procedure D using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Met-OEt.HCl (58.8 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless solid (47.3 mg, 54%).

Prepared according to General Procedure D using (*tert*-butoxycarbonyl)-*L*-alanine (47.3 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), ethyl *L*-methioninate hydrochloride (58.8 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless solid (87.3 mg, >99%).

$[\alpha]_D^{20}$ = -6.97 (c 0.01, CH_2Cl_2).

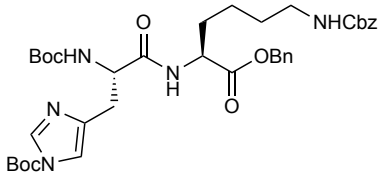
ν_{max} (solid): 3331, 3308, 2975, 2927, 1746, 1679, 1651, 1515, 1158 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* = 7.3 Hz, 1H), 5.02 (br s, 1H), 4.65 (td, *J* = 7.6, 5.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.16 (br s, 1H), 2.52–2.47 (m, 2H), 2.20–2.11 (m, 1H), 2.08 (s, 3H), 2.03–1.93 (m, 1H), 1.44 (s, 9H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). Exchangeable protons not observed.

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.6, 171.8, 155.6, 80.3, 61.8, 51.7, 50.2, 31.9, 30.0, 28.4, 18.2, 15.6, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{30}N_2O_5S$) requires *m/z* 349.1792, found *m/z* 349.1792.

146: Boc-His(Boc)-Lys(CBz)-OBn



Prepared according to General Procedure D using Boc-His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Lys(CBz)-OBn.HCl (111.9 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-50% EtOAc in petroleum ether) to afford the title compound as a colourless gum (140.8 mg, 80%).

$[\alpha]_D^{20}$ = +3.7 (c 0.01, CH_2Cl_2).

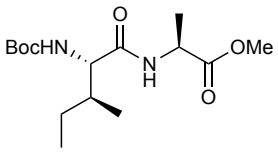
ν_{max} (solid): 3331, 3282, 3308, 2977, 2927, 1748, 1681, 1651, 1517, 1158 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.36–7.28 (m, 11H), 7.14 (s, 1H), 6.08 (s, 1H), 5.17–5.08 (m, 4H), 4.91 (s, 1H), 4.59–4.53 (m, 1H), 4.43 (s, 1H), 3.12–2.88 (m, 4H), 1.86 (s, 1H), 1.80–1.71 (m, 1H), 1.67–1.59 (m, 2H), 1.58 (s,9H), 1.43 (s, 9H), 1.20 - 1.14 (m, 2H). Exchangeable protons not observed.

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.89, 171.49, 156.6, 155.8, 147.1, 139.3, 136.9, 136.8, 135.4, 128.7, 128.6, 128.5, 128.3, 128.2, 114.9, 85.9, 80.2, 67.2, 66.7, 54.3, 52.0, 40.7, 32.1, 30.2, 29.2, 28.4, 28.0, 22.1. CBz carbonyl not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{37}H_{50}N_5O_9$) requires *m/z* 708.3603, found *m/z* 708.3598.

147: Boc-Ile-Ala-OMe



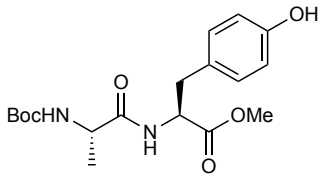
Prepared according to General Procedure D using Boc-Ile-OH (57.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Ala-OMe.HCl (38.4 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (55.4 mg, 72%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.46 (d, *J* = 5.8 Hz, 1H), 5.06 (d, *J* = 5.4 Hz, 1H), 4.58 (q, *J* = 7.2 Hz, 1H), 3.98–3.91 (m, 1H), 3.74 (s, 3H), 1.86 (s, 1H), 1.50 (s, 1H), 1.44 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.19–1.09 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.3, 171.2, 155.9, 80.1, 59.3, 52.6, 48.1, 37.5, 28.4, 24.9, 18.5, 15.6, 11.6.

Characterization data is consistent with literature reported values.[212]

148: Boc-Ala-Tyr-OMe



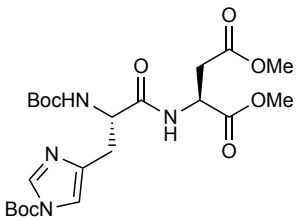
Prepared according to General Procedure D using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Tyr-OMe.HCl (63.7 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (64.4 mg, 70%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.93 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 7.1 Hz, 1H), 6.15 (s, 1H), 5.01 (s, 1H), 4.81 (dt, *J* = 7.9, 5.8 Hz, 1H), 4.14 (s, 1H), 3.72 (s, 3H), 3.11–2.96 (m, 2H), 1.44 (s, 9H), 1.30 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.5, 172.0, 155.4, 130.6, 127.4, 115.7, 80.5, 53.5, 52.5, 50.3, 37.3, 28.5, 18.4. C=O of carbamate overlaps with OH bearing carbon.

Characterization data is consistent with literature reported values.[213]

149: Boc-His(Boc)-Asp(OMe)-OMe



Prepared according to General Procedure D using Boc-His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Asp(OMe)-OMe.HCl (54.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-70% EtOAc in petroleum ether) to afford the title compound as a colourless oil (78.1 mg, 63%).

$[\alpha]_D^{20}$ = +40.3 (c 0.002, CH_2Cl_2).

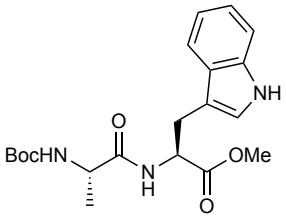
ν_{max} (liquid film): 3338, 2977, 2953, 2927, 1752, 1391, 1255, 1160 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.39 (br s, 1H), 7.15 (s, 1H), 6.06 (br s, 1H), 4.83–4.73 (m, 1H), 4.45 (br s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.08 (d, *J* = 10.8 Hz, 1H), 2.93 (dd, *J* = 17.2, 4.6 Hz, 2H), 2.71 (dd, *J* = 17.1, 4.5 Hz, 1H), 1.60 (s, 9H), 1.45 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.4, 171.2, 170.9, 155.7, 147.1, 139.1, 136.9, 114.9, 85.8, 80.2, 54.4, 52.8, 52.1, 48.7, 36.2, 30.3, 28.4, 28.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{35}N_4O_9$) requires *m/z* 499.2399, found *m/z* 499.2391.

150: Boc-Ala-Trp-OMe



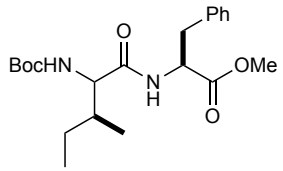
Prepared according to General Procedure D using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Trp-OMe.HCl (70 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a colourless solid (85.6 mg, 88%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (br s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.94 (br s, 1H), 4.90 (dt, *J* = 7.7, 5.4 Hz, 1H), 4.13 (br s, 1H), 3.66 (s, 3H), 3.32 (d, *J* = 5.4 Hz, 2H), 1.41 (s, 9H), 1.29 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.4, 172.2, 155.5, 136.2, 127.8, 123.1, 122.4, 119.8, 118.7, 111.4, 110.0, 80.1, 60.5, 53.1, 52.5, 28.4, 27.7, 18.5.

Characterization data is consistent with literature reported values.[214]

151: Boc-(DL)Ile-Phe-OMe

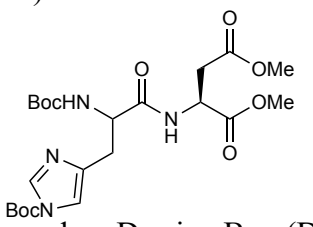


Prepared according to General Procedure D using Boc-(DL)Ile-OH (57.8 mg, 0.25 mmol, 1 equiv.), HATU (114 mg, 0.3 mmol, 1.2 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Phe-OMe.HCl (59.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method

outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless solid (102 mg, >99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.31–7.21 (m, 3H), 7.11 (m, 2H), 6.43 (DL br s, 0.5H), 6.29 (LL br s, 0.5H), 4.98 (LL br s, 0.5H), 4.92–4.85 (m, 1.5H), 4.13 (DL br s, 0.5H), 3.93 (LL br s, 0.5H), 3.72 (DL s, 1.5H), 3.71 (LL s, 1.5H), 3.17–3.05 (m, 2H), 1.92 (DL br s, 0.5H), 1.83 (LL br s, 0.5H), 1.44 (LL s, 4.5H), 1.43 (DL s, 4.5H), 0.90–0.83 (m, 6.5H), 0.76 (DL d, J = 6.9 Hz, 1.5H).

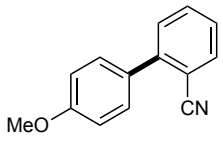
152: Boc-(DL)His(Boc)-Asp(OMe)-OMe



Prepared according to General Procedure D using Boc-(DL)His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv.), HATU (238 mg, 0.625 mmol, 2.5 equiv.), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv.), Asp(OMe)-OMe.HCl (54.3 mg, 0.275 mmol, 1.1 equiv.), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-70% EtOAc in petroleum ether) to afford the title compound as a colourless oil (74.2 mg, 59%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.99 (DL s, 0.5H), 7.97 (LL s, 0.5H), 7.38 (br s, 1H), 7.14 (s, 1H), 6.13 (DL br s, 0.5H), 6.04 (LL br s, 0.5H), 4.84–4.73 (m, 1H), 4.42 (br s, 1H), 3.69 (LL s, 1.5H), 3.66 (DL s, 1.5H), 3.62 (s, 3H), 3.04 (br s, 1H), 2.92 (m, 2H), 2.75 (DL dd, J = 17.3, 4.6 Hz, 0.5H), 2.69 (LL dd, J = 17.1, 4.5 Hz, 0.5H), 1.58 (s, 9H), 1.42 (LL s, 4.5H), 1.41 (DL s, 4.5H).

154: 4'-Methoxy-2-biphenylcarbonitrile



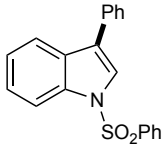
Prepared according to General Procedure E using Pd(dppf)Cl_2·CH_2Cl_2 (4.1 mg, 0.005 mmol, 2 mol%), 2-bromobenzonitrile (46 mg, 0.25 mmol, 1 equiv.), 4-(methoxy)phenylboronic acid (38 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (52 mg, >99%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.2 Hz, 1H), 7.53–7.48 (m, 3H), 7.40 (td, *J* = 7.7, 1.0 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.2, 145.4, 133.9, 132.9, 130.7, 130.2, 130.0, 127.2, 119.1, 114.4, 111.2, 55.5.

Characterisation data is consistent with literature reported values.[216]

155: 3-phenyl-1-(phenylsulfonyl)-1*H*-indole



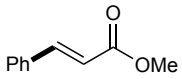
Prepared according to General Procedure E using Pd(dppf)Cl_2·CH_2Cl_2 (8.2 mg, 0.01 mmol, 4 mol%), 3-bromo-1-(phenylsulfonyl)-1H-indole (84 mg, 0.25 mmol, 1 equiv.), phenylboronic acid (36 mg, 0.3 mmol, 1.2 equiv.), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv.), DMI (1 mL, 0.25 M), and H_2O (23 µL, 1.25mmol, 5 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (73 mg, 87%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 7.7 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.50–7.43 (m, 4H), 7.38 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.3, 135.7, 134.0, 133.1, 129.5, 129.1, 128.8, 128.1, 127.7, 126.9, 125.1, 124.3, 123.8, 123.1, 120.6, 113.9.

Characterisation data is consistent with literature reported values.[201]

157: Methyl (*E*)-3-(3-methoxyphenyl)acrylate



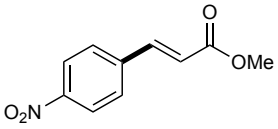
Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a colourless solid (44 mg, 91%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.53 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.41–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.6, 145.0, 134.6, 130.4, 129.0, 128.2, 117.9, 51.8.

Characterisation data is consistent with literature reported values.[166]

160: Methyl (*E*)-3-(4-nitrophenyl)acrylate



Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 4-nitroiodobenzene (62 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined

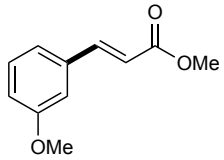
in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a pale yellow solid (44 mg, 85%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 16.1 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 16.1 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.6, 148.7, 142.1, 140.6, 128.8, 124.3, 122.3, 52.2.

Characterisation data is consistent with literature reported values.[218]

161: Methyl (*E*)-3-(3-methoxyphenyl)acrylate



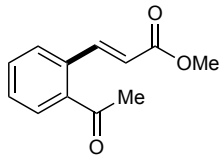
Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 3-iodoanisole (59 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (44 mg, 91%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.5, 160.1, 144.9, 135.9, 130.0, 120.9, 118.3, 116.3, 113.1, 55.4, 51.8.

Characterisation data is consistent with literature reported values.[166]

162: Methyl (*E*)-3-(2-acetylphenyl)acrylate



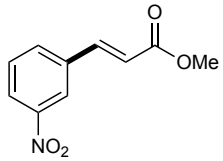
Prepared according to General Procedure F using Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), 2-iodoacetophenone (62 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a yellow oil (35 mg, 68%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15 (d, *J* = 15.9 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.0 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 3.81 (s, 3H), 2.62 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 200.9, 167.1, 144.3, 138.4, 135.0, 132.1, 129.6, 129.4, 128.5, 120.7, 51.9, 29.4.

Characterisation data is consistent with literature reported values.[217]

163: Methyl (*E*)-3-(3-nitrophenyl)acrylate



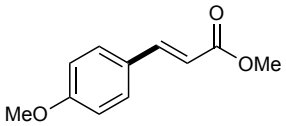
Prepared according to General Procedure F using Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), 3-nitroiodobenzene (62 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as an off-white solid (43 mg, 83%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.38 (t, *J* = 1.7 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 16.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.7, 148.9, 142.1, 136.3, 133.8, 130.1, 124.7, 122.6, 121.2, 52.2.

Characterisation data is consistent with literature reported values.[166]

164: Methyl (*E*)-3-(4-methoxyphenyl)acrylate



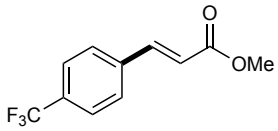
Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 4-bromoanisole (47 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 24 h at 115°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (33 mg, 68%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.9, 161.6, 144.7, 129.9, 127.3, 115.4, 114.5, 55.5, 51.7.

Characterisation data is consistent with literature reported values.[166]

165: Methyl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate



Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 4-bromobenzotrifluoride (56 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 24 h at 115°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless solid (42 mg, 72%).

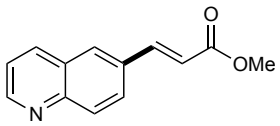
^1H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, J = 16.0 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.0, 143.1, 137.9, 132.0 (q, $^2J_{CF}$ = 32.5 Hz), 128.3, 126.0 (q, $^3J_{CF}$ = 3.7 Hz), 124.0 (q, $^1J_{CF}$ = 272.3 Hz), 120.6, 52.1.

^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.90.

Characterisation data is consistent with literature reported values.[166]

166: Methyl (*E*)-3-(quinolin-6-yl)acrylate



Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 6-bromoquinoline (52 mg, 0.25 mmol, 1 equiv.), methyl acrylate (45 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 24 h at 115°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as a colourless solid (46 mg, 86%).

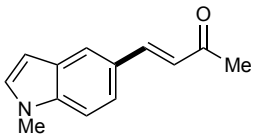
ν_{max} (solid): 2922, 1705, 1583, 1321, 1284 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.93 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 9.3 Hz, 1H), 7.93–7.89 (m, 2H), 7.86 (d, J = 16.0 Hz, 1H), 7.45 (dd, J = 8.3, 4.3 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 151.2, 148.9, 143.9, 136.9, 132.9, 130.2, 129.4, 128.4, 127.6, 122.0, 119.4, 52.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}NO_2$) requires *m/z*214.0863, found *m/z* 214.0863.

167: (*E*)-4-(1-Methyl-1*H*-indol-5-yl)but-3-en-2-one



Prepared according to General Procedure F using Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), 5-bromo-1-methylindole (53 mg, 0.25 mmol, 1 equiv.), methyl vinyl ketone (41 μL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 μL, 0.78 mmol, 3 equiv.). After 24 h at 115°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-40% EtOAc in petroleum ether) to afford the title compound as a brown solid (25 mg, 50%).

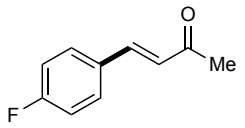
ν_{max} (solid): 2922, 1660, 1635, 1604, 1242 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (s, 1H), 7.67 (d, *J* = 16.2 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.73 (d, *J* = 16.2 Hz, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 3.81 (s, 3H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.7, 145.8, 138.2, 130.2, 128.9, 126.1, 124.7, 123.1, 121.4, 110.0, 102.2, 33.1, 27.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}NO$) requires *m/z* 200.1070, found *m/z* 200.1069.

168: (*E*)-4-(4-Fluorophenyl)but-3-en-2-one



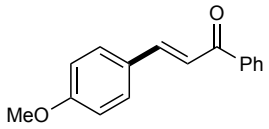
Prepared according to General Procedure F using Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), 4-fluorobromobenzene (44 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.78 mmol, 3 equiv.). methyl vinyl ketone (41 µL, 0.5 mmol, 2 equiv.), and DMI (1 mL, 0.25 M). After 24 h at 115°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether) to afford the title compound as a brown oil (26 mg, 63%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.41 (d, *J* = 16.3 Hz, 1H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 16.3 Hz, 1H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.3, 164.2 (d, $^1J_{CF}$ = 251.8 Hz), 142.2, 130.8 (d, $^4J_{CF}$ = 3.3 Hz), 130.3(d, $^3J_{CF}$ = 8.6 Hz), 127.0, 116.3 (d, $^2J_{CF}$ = 22.0 Hz), 27.8.

Characterisation data is consistent with literature reported values.[219]

169: (*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one



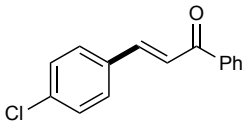
Prepared according to General Procedure F using Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 0.013 mmol, 5 mol%), 4-iodoanisole (59 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.78 mmol, 3 equiv.). phenyl vinyl ketone (66 mg, 0.5 mmol, 2 equiv.), and DMI (1 mL, 0.25 M). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether) to afford the title compound as a colourless solid (51 mg, 86%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, *J* = 7.1 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 15.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.8, 161.9, 144.9, 138.7, 132.7, 130.4, 128.7, 128.6, 127.8, 120.0, 114.6, 55.6.

Characterisation data is consistent with literature reported values.[220]

170: (*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one



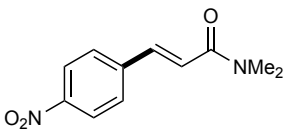
Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 4-chloroiodobenzene (60 mg, 0.25 mmol, 1 equiv.), K_3PO_4 (159 mg, 0.78 mmol, 3 equiv.). phenyl vinyl ketone (66 mg, 0.5 mmol, 2 equiv.), and DMI (1 mL, 0.25 M). After 1 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether) to afford the title compound as a colourless solid (45 mg, 76%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 15.7 Hz, 1H), 7.62–7.56 (m, 3H), 7.53–7.48 (m, 3H), 7.40 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.4, 143.5, 138.2, 136.6, 133.6, 133.1, 129.7, 129.4, 128.8, 128.7, 122.7.

Characterisation data is consistent with literature reported values.[220]

171: (*E*)-*N*,*N*-Dimethyl-3-(4-nitrophenyl)acrylamide



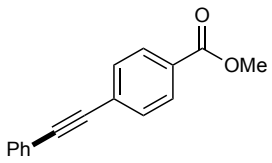
Prepared according to General Procedure F using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.2 mg, 0.013 mmol, 5 mol%), 4-nitroiodobenzene (62 mg, 0.25 mmol, 1 equiv.), dimethyl acrylamide (52 µL, 0.5 mmol, 2 equiv.), DMI (1 mL, 0.25 M), and Et_3N (105 µL, 0.78 mmol, 3 equiv.). After 24 h at 80°C, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a brown solid (26 mg, 47%).

^1H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, J = 8.6 Hz, 2H), 7.70 - 7.65 (m, 3H), 7.02 (d, J = 15.5 Hz, 1H), 3.20 (s, 3H), 3.09 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 165.8, 148.2, 141.8, 139.7, 128.5, 124.3, 121.9, 37.6, 36.2.

Characterisation data is consistent with literature reported values.[221]

172: methyl 4-(phenylethynyl)benzoate



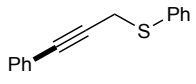
Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), methyl-4-ethynylbenzoate (42 mg, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless solid (51 mg, 87%).

^1H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.55 (dd, J = 6.6, 3.0 Hz, 2H), 7.38–7.36 (m, 3H), 3.93 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.7, 131.9, 131.7, 129.7, 129.6, 128.9, 128.6, 128.2, 122.9, 92.5, 88.8, 52.4.

Characterisation data is consistent with literature reported values.[223]

173: phenyl(3-phenylprop-2-yn-1-yl)sulfane



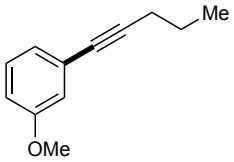
Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), iodobenzene (28 µL, 0.25 mmol, 1 equiv.), phenylpropargylsulfide (39 mg, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (36 mg, 65%).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, J = 7.3 Hz, 2H), 7.29–7.24 (m, 4H), 7.22–7.16 (m, 4H), 3.77 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 135.3, 131.8, 130.8, 129.1, 128.4, 128.3, 127.1, 123.1, 85.4, 83.8, 24.0.

Characterisation data is consistent with literature reported values.[224]

174: 1-methoxy-3-(pent-1-yn-1-yl)benzene



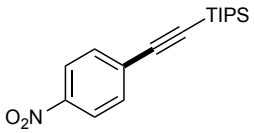
Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 3-iodoanisole (59 mg, 0.25 mmol, 1 equiv.), 1-pentyne (26 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a colourless oil (41 mg, 94%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.94–6.93 (m, 1H), 6.83 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.79 (s, 3H), 2.39 (t, J = 7.0 Hz, 2H), 1.67–1.60 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.4, 129.4, 125.3, 124.3, 116.6, 114.3, 90.3, 80.8, 55.4, 22.4, 21.5, 13.7.

Characterisation data is consistent with literature reported values.[225]

175: triisopropyl((4-nitrophenyl)ethynyl)silane



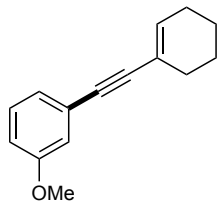
Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 4-nitroiodobenzene (56 mg, 0.25 mmol, 1 equiv.), TIPS acetylene (56 µL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 µL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (70 mg, 93%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 1.17–1.11 (m, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 147.2, 132.9, 130.4, 123.6, 104.9, 97.7, 18.8, 11.4.

Characterisation data is consistent with literature reported values.[226]

176: 1-(cyclohex-1-en-1-ylethynyl)-3-methoxybenzene



Prepared according to General Procedure G using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (1.9 mg, 0.01 mmol, 4 mol%), 3-iodoanisole (59 mg, 0.25 mmol, 1 equiv.), 1-ethynylcyclohexene (31 μL, 0.26 mmol, 1.05 equiv.), DMI (0.5 mL, 0.5 M), and Et_3N (38 μL, 0.28 mmol, 1.1 equiv.). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (44 mg, 83%).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.20 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.95 (dd, *J* = 2.3, 1.4 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.23–6.20 (m, 1H), 3.80 (s, 3H), 2.26–2.20 (m, 2H), 2.17–2.12 (m, 2H), 1.71–1.65 (m, 2H), 1.65–1.59 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.4, 135.5, 129.4, 124.9, 124.2, 120.8, 116.3, 114.6, 91.2, 86.8, 55.4, 29.4, 25.9, 22.5, 21.7.

Characterisation data is consistent with literature reported values.[227]

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