Suzuki-Miyaura Mediated Biphenyl Synthesis: A Spotlight on the Boronate Coupling Partner

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NOVARTIS

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ABSTRACT

Suzuki-Miyaura Mediated Biphenyl Synthesis: A Spotlight on the Boronate Coupling Partner

The biaryl motif is found in many natural and synthetic products that display a wide range of biological activities. This explains why biphenyls are widely encountered in medicinal chemistry as a privileged scaffold. The palladium-catalysed Suzuki-Miyaura (SM) coupling is one of the most important and efficient strategies for the synthesis of symmetrical and unsymmetrical biaryl compounds; the arylboronic acid or ester is a key partner in this coupling reaction.

This work presents the synthesis of a library of new molecules containing the biphenyl scaffold; *o*-, *m*- and *p*-(bromomethyl)phenylboronic acid pinacol esters, **2a-c**, were selected as coupling partners. Nucleophilic substitution of the bromide was carried out with amine, thiol, alcohol or phenol nucleophiles. Supported reagents and microwave assisted organic synthesis conditions were employed to enhance this chemistry and made it amenable to parallel synthesis. The resulting arylboronates were used in SM coupling reactions in order to obtain a range of biphenyls.

The use of Boc-piperazine as a nucleophile in the S_N2 reaction, with **2a-c**, and 1-bromo-, 2-, 3- or 4-nitrobenzene or 2-bromo-5-nitropyridine as aryl halides in the SM coupling reaction, allowed two other points of functionalisation to be added to the biaryl motif.

The conditions for the SM coupling of mercaptomethylphenylboronic esters and *ortho*-substituted methylphenylboronic esters were optimised in order to broaden the scope of the biaryl library.

Phosphines were found to be good nucleophiles in the S_N2 reaction with **2a-c**. A Wittig reaction was performed with the resulting phosphonium arylboronates in order to synthesise arylboronic esters containing an alkene function prior the reduction of the resulting double bond of the stilbene derivatives and realising a SM coupling to synthesise arylethylbiphenyls. The stilbene derivatives were also synthesised by using the olefin cross-metathesis reaction of 4-vinylphenylboronic acid pinacol ester.

A solid state crystallographic study was undertaken on a small library of methylbiphenylamides to compare the crystal structures of isomers or biphenyls with different functional groups.

Christine B. BALTUS [B.Sc. Chemistry; M.Sc. Chemistry]

CONTENTS

SCHEMES

Chapter 1

Chapter 4

Chapter 5

Chapter 6

FIGURES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

TABLES

Chapter 6

ABBREVIATIONS

Abbreviation	*meaning*
AIBN	azobisisobutyronitrile
Ar	aryl
Boc	*tert*-butyloxy carbamate
Bu	butyl
CM	cross-metathesis (reaction)
DBU	1,8-diazabicycloundec-7-ene
DIPHOS	1,2-bis(diphenylphosphino)ethane
DMA	dimethylacetamide
DMF	*N*,*N*-dimethylformamide
dmphen	2,9-dimethyl-1,10- phenanthroline
DMSO	dimethylsulphoxide
dppb	1,4-bis(diphenylphosphine)butane
dppf	1,1-bis(diphenylphosphino)ferrocene
dtbpy	di-*tert*-butylbipyridine
DSC	differential scanning calorimetry
FW	formula weight
GPCR	G protein-coupled receptor
LC-MS	liquid chromatography coupled with mass spectrometry
m	meta
MAOS	microwave-assisted organic synthesis
MIDA	*N*-methyliminodiacetic acid
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Ph	phenyl
Pin	pinacolato ($OCMe_2CMe_2O$)

PS	polystyrene supported
Pyr	pyridine
Pyrim	pyrimidine
R_F	retention factor
rt	room temperature
RT	retention time
SM	Suzuki-Miyaura (cross-coupling)
S_N2	2^{nd} order nucleophilic substitution
TBAB	tetrabutylammonium bromide
TLC	thin layer chromatography
TFA	trifluoroacetic acid
TGA	thermogravimetric analysis
THF	tetrahydrofuran
TMS	tetramethylsilane
Ts	tosyl
UV	ultra violet
X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
μw	microwave

OVERVIEW OF THE THESIS

This thesis describes the work I have carried out during the three years of my Ph.D. at the University of Greenwich, which was funded by the pharmaceutical company Novartis U.K. It is based on a boronic ester coupling partner and the ways of functionalising it in order to then synthesise interesting biaryls *via* the Suzuki-Miyaura (SM) coupling reaction. Two types of boronic acids were selected as a starting point, (bromomethyl)phenylboronic acids and 4-vinylphenylboronic acid.

Chapter 1 is an introduction to boronates and biphenyls. It describes their synthesis and their application in organic synthesis and in medicinal chemistry. Microwave-assisted organic synthesis (MAOS), which played an important part in this work, is also introduced in this chapter.

Chapter 2 focuses on the microwave-mediated nucleophilic substitution (S_N2) of (bromomethyl)phenylboronic acid pinacol esters with *N*-, *S*- and *O*-nucleophiles. The corresponding substituted methylphenylboronic esters were then coupled with aryl bromides in a SM coupling in order to provide a library of substituted methylbiaryls.

In Chapter 3, the *p*- and *m*-methylphenylboronic esters, which were substituted by Boc-piperazine in the S_N2 reaction (reported in Chapter 2), were chosen as precursors to a highly functionalised (piperazin-1-ylmethyl)biaryl library. They were coupled in a SM reaction with bromonitroaryls and, by using piperazine deprotection and nitro group reduction, the resulting biaryls were then functionalised.

After failing to couple *S*- and *o*-substituted methylphenylboronic esters in the SM reaction reported in Chapter 2, reaction conditions optimisation was attempted in the work reported in Chapter 4 resulting in an interesting sulphur-containing and *o*-(piperazin-1-ylmethyl)- biaryl library as well as unsymmetrical palladacycles.

The S_N2 reaction was also achieved using (bromomethyl)phenylboronic acid pinacol esters in the presence of phosphorus-nucleophiles and is described in Chapter 5. Some resulting phosphonium derivatives were reacted with aldehydes in Wittig reactions to form alkenylarylboronates. The latter were also obtained *via* the cross-metathesis reaction of 4-vinylphenylboronic acid pinacol ester and 4-vinylbiaryls. The alkenylarylboronates obtained were reduced, coupled in SM coupling reactions and led to the synthesis of an arylethylbiaryl library.

During the course of the synthesis of (piperazin-1-ylmethyl)biaryls, reported in Chapter 3, *N*-(4'-methylbiphenyl-4-yl)cyclopropane carboxamide was surprisingly obtained and crystallographic studies revealed an interesting crystal structure. Chapter 6 describes a small study of the synthesis and solid state of methybiphenylamides.

Chapter 1: Introduction

1.1. Organoboranes

Boron is a semi-metallic element which belongs in group 13 in the Periodic Table. It was discovered by Sir Humphry Davy in London, Joseph-Louis Gay-Lussac and Louis Jacques Thenard in Paris in 1808, by the treatment of boric acid (H_3BO_3) with potassium.[1] Pure boron (Figure 1.1) is not found in nature. It is found as orthoboric acid and borates in borax (sodium tetraborate decahydrate $Na_2B_4O_7 \cdot 10H_2O$), colemanite, etc.

Figure 1.1. Picture of boron crystals.[1d]

Organoboron compounds are defined by the presence of a B-C bond. Boron can also form B-O, B-N, B-S or B-P bonds and boronic acids can often dimerise or trimerise (Figure 1.2). Boronic acids and esters are very important compounds because of their reactivity in synthetic organic chemistry and their uses in medicinal chemistry.[2]

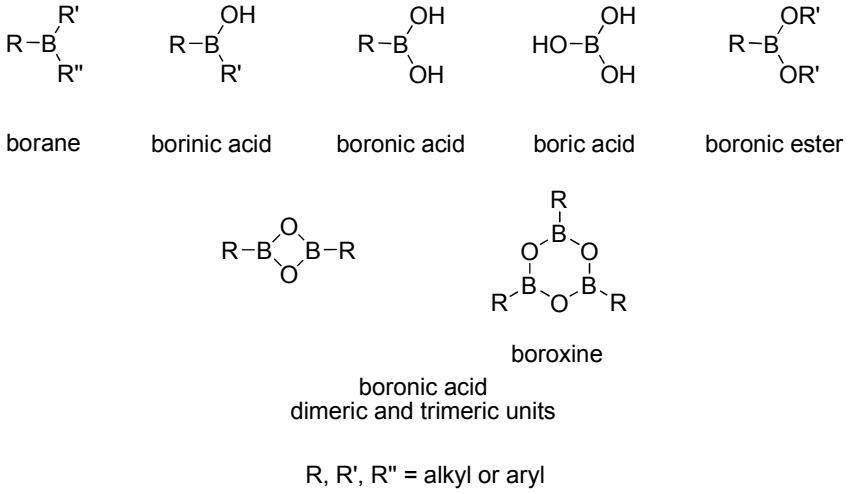


Figure 1.2. Organoborons and acids.

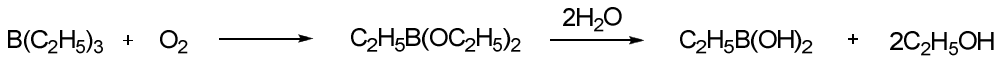
1.1.1. Boronic acids

1.1.1.1. Introduction

A boronic acid is an organoboron compound which contains a B-C bond and two B-OH bonds. It is a mild organic Lewis acid and, generally, boronic acids are stable in air which makes them easy to handle. They have a low toxicity, are degradable and can be considered to be environmentally friendly ("green" compounds). Sp^1 and sp^2-hybridised boronic acids are very important in synthetic chemistry, mainly for being one of the precursors for the Suzuki-Miyaura (SM) coupling reaction in the synthesis of biaryls.

1.1.1.2. Synthesis of boronic acids

Frankland and Duppa first reported the synthesis of a boronic acid in 1860.[3] They obtained ethylboronic acid by oxidation of triethylboron then hydrolysis (Scheme 1.1).

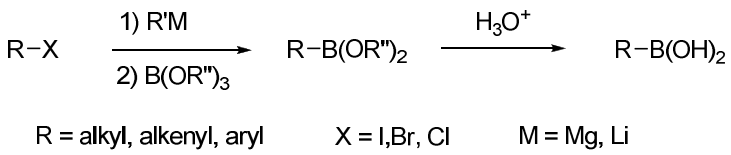


Scheme 1.1. Synthesis of ethylboronic acid by Frankland and Duppa.

Since then, many chemists have reported a number of ways for the synthesis of boronic acids.[2,4]

1.1.1.2.1. Electrophilic trapping of organometallic intermediates with borates

The reaction of an organometallic compound (mercury, lithium or magnesium) with a borate is one of the most used methods to synthesise boronic acids. The organometallic derivatives are generally obtained by metal-halogen exchange. Using this method, alkyl,[5] alkenyl[6] and arylboronic acids[7] can be synthesised (Scheme 1.2).

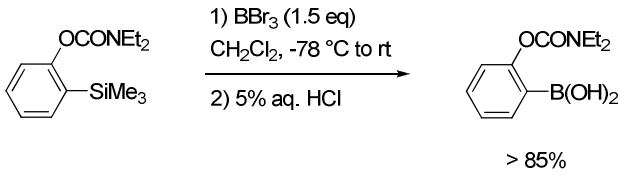


Scheme 1.2. Synthesis of boronic acids from alkyl, alkenyl and aryl halides.

Aromatic organometallic derivatives can also be obtained by *ortho*-metallation, generally lithiation.[8]

1.1.1.2.2. Transmetallation of alkenyl and aryl silanes and stannanes

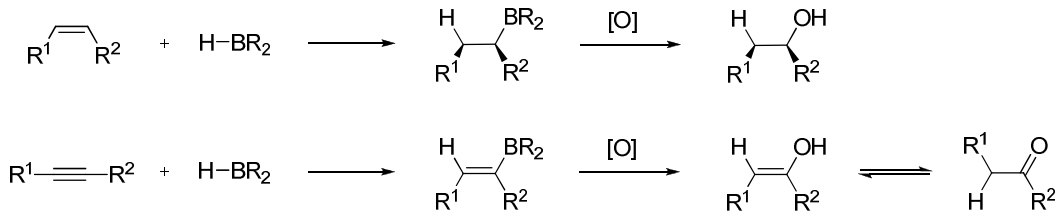
An example of a transmetallation process (Scheme 1.3) includes the treatment of alkenyl or aryl silanes or stannanes with a boron halide which gives the corresponding alkenyl or arylboron dihalide product.[9] The alkenyl and aryl boronic acids are then obtained after the hydrolysis of this organoboron dihalide product.



Scheme 1.3. Example of a transmetallation of an aryl silane to a boronic acid.

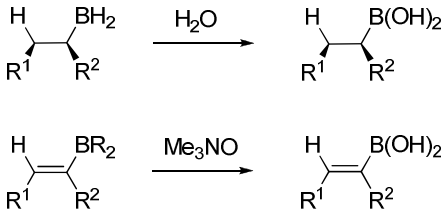
1.1.1.2.3. Hydroboration

Hydroboration (Scheme 1.4) is a very well-known reaction for the synthesis of organoborons and was developed by Brown and Rao.[10] This reaction implies a regioselective *cis*-addition of a hydroborane onto an alkene or an alkyne.



Scheme 1.4. Hydroboration reaction

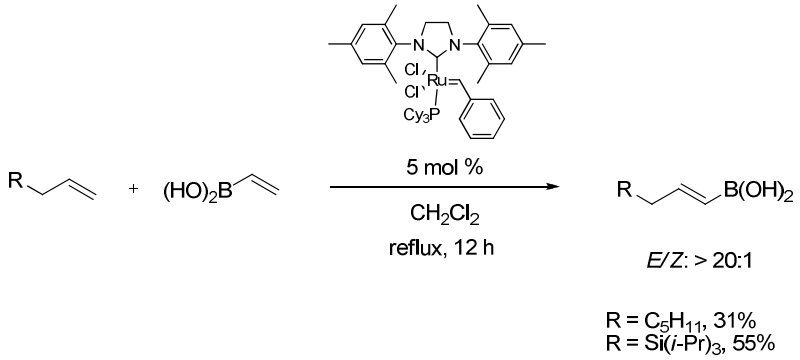
This reaction is known mainly for the preparation of alcohols by the oxidation of an organoboron. However, the organoboron from the *cis*-addition can be hydrolysed to afford the boronic acid (Scheme 1.5).[11]



Scheme 1.5. Synthesis of boronic acids *via* the hydroboration reaction.

1.1.1.2.4. Cross-metathesis reaction

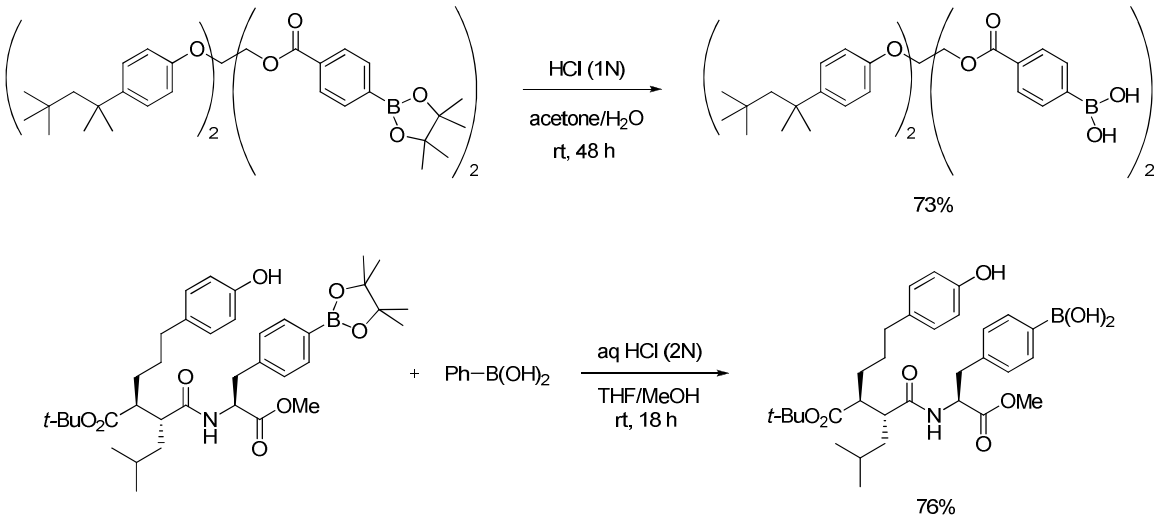
Grubbs *et al.* synthesised alkenylboronic acids (Scheme 1.6) using the cross-metathesis reaction of vinylboronic acid with terminal olefins.[12]



Scheme 1.6. Synthesis of alkenylboronic acids *via* the cross-metathesis reaction.

1.1.1.2.4. Hydrolysis of boronic esters

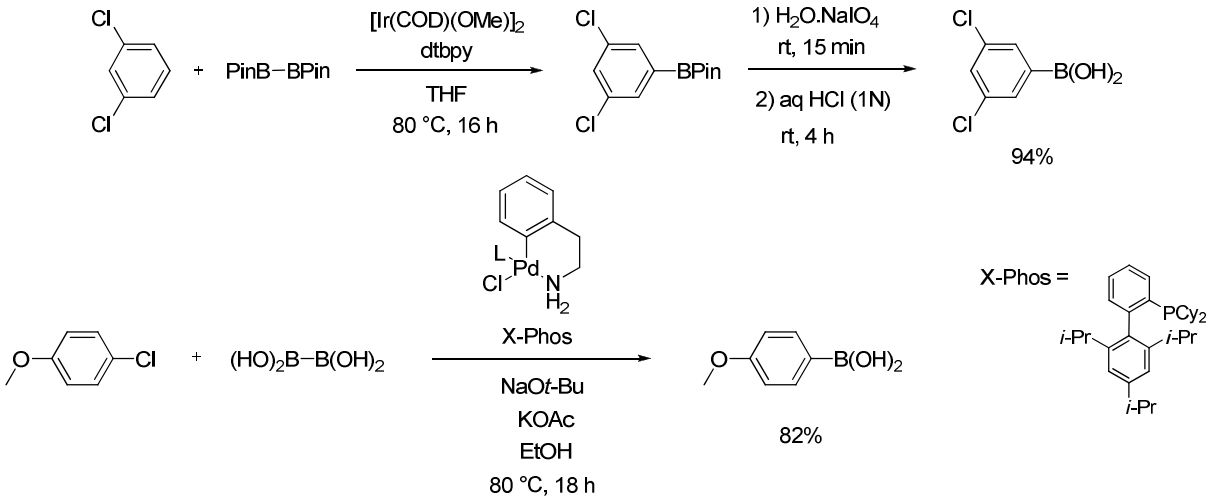
Acyclic and unhindered cyclic boronic esters are easily hydrolysed by water. However, hindered cyclic boronic esters are more difficult to hydrolyse and require acidic or oxidative conditions (Scheme 1.7).[13] The hydrolysis can also be achieved by *trans*-boro-esterification.[13a,14]



Scheme 1.7. Examples of hydrolysis of boronic esters.

1.1.1.2.6. One-pot metal-catalysed synthesis of arylboronic acids

Hartwig *et al.* have developed a method to synthesise arylboronic acids from arenes *via* a one-pot iridium-catalysed borylation followed by hydrolysis (Scheme 1.8).[15] Recently, Molander *et al.* have achieved the first direct synthesis of boronic acids *via* palladium-catalysed cross-coupling of aryl chlorides with tetrahydroxydiboron $B_2(OH)_4$.[16]



Scheme 1.8. One-pot syntheses of arylboronic acids.

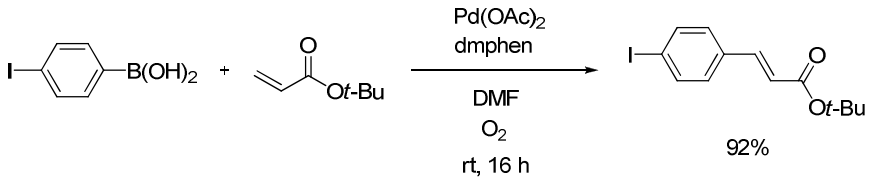
Many different methods have been devised in order to synthesise boronic acid derivatives. Because of this development, boron chemistry has experienced a dramatic surge in interest and applications; thus a wide range of boronic acids are now commercially available.

1.1.1.3. Applications in organic synthesis

Boronic acids are useful synthons in organic synthesis and participate in many reactions as reagents, catalysts or protecting groups. They are mainly known for the Suzuki-Miyaura reaction (which will be described later on) but have several other applications.

1.1.1.3.1. Boron Heck-type coupling with alkenes

This palladium-catalysed reaction is a cross coupling between aryl or alkenylboronic acids and olefins (Scheme 1.9). It involves a catalytic cycle where Pd(II) is the active catalyst which is transformed to Pd(0) and needs the presence of a oxidant such as acetic acid,[17] $Cu(OAc)_2$[18] or simply oxygen,[19] to be reoxidised to Pd(II) for the reaction to continue.

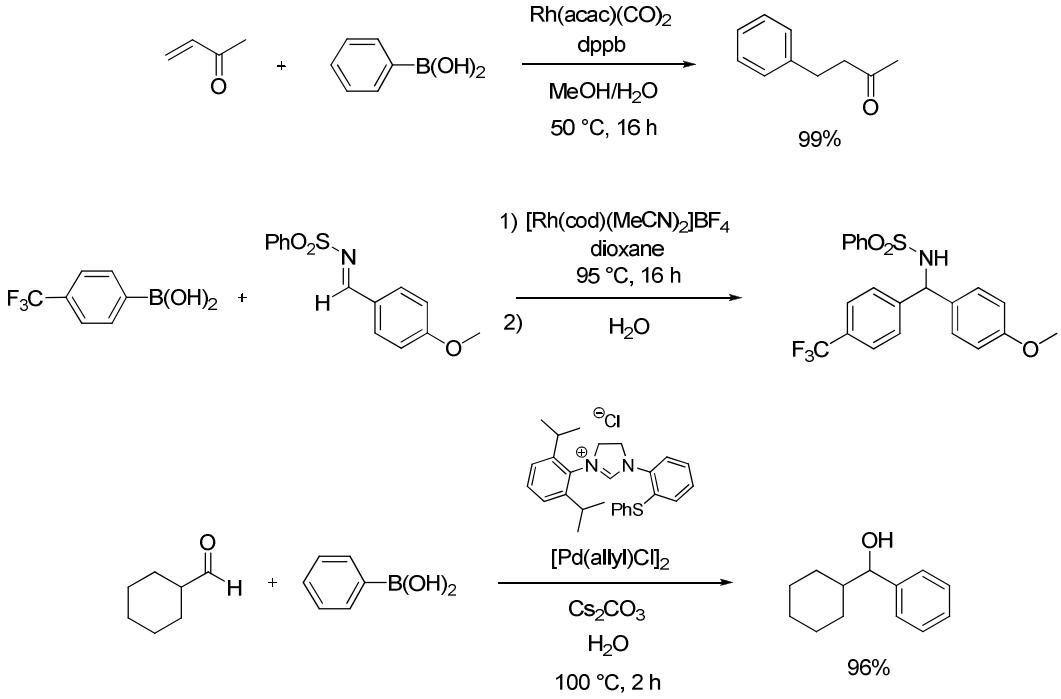


Scheme 1.9. Example of a boron Heck-type reaction.

This reaction is also achievable with rhodium and ruthenium catalysis.[20]

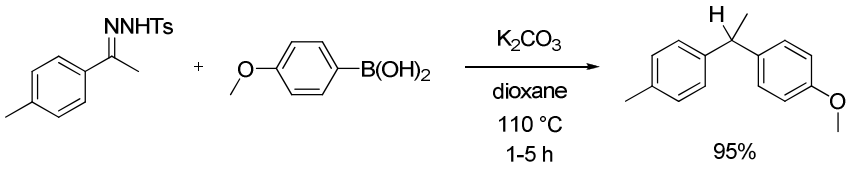
1.1.1.3.2. Addition on carbonyls, alkenes, alkynes, imines and iminiums

Boronic acid derivatives are very effective reagents for carbon-carbon bond forming reactions (Scheme 1.10). When catalysed by rhodium they can add to α,β-unsaturated ketones,[21] aldehydes,[22] imines,[23] etc. They can also add to aldehydes *via* palladium catalysis.[24]



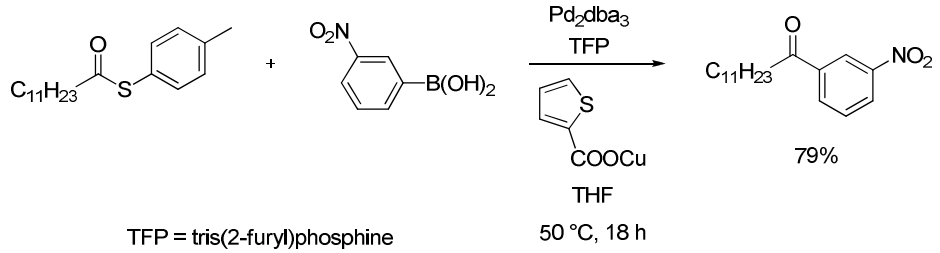
Scheme 1.10. Examples of boronic acid addition reactions.

The addition of boronic acids to hydrazones (Scheme 1.11) can be achieved by a metal-free carbon–carbon bond-forming reductive coupling.[25]



Scheme 1.11. Metal-free addition of a boronic acid to a tosylhydrazone.

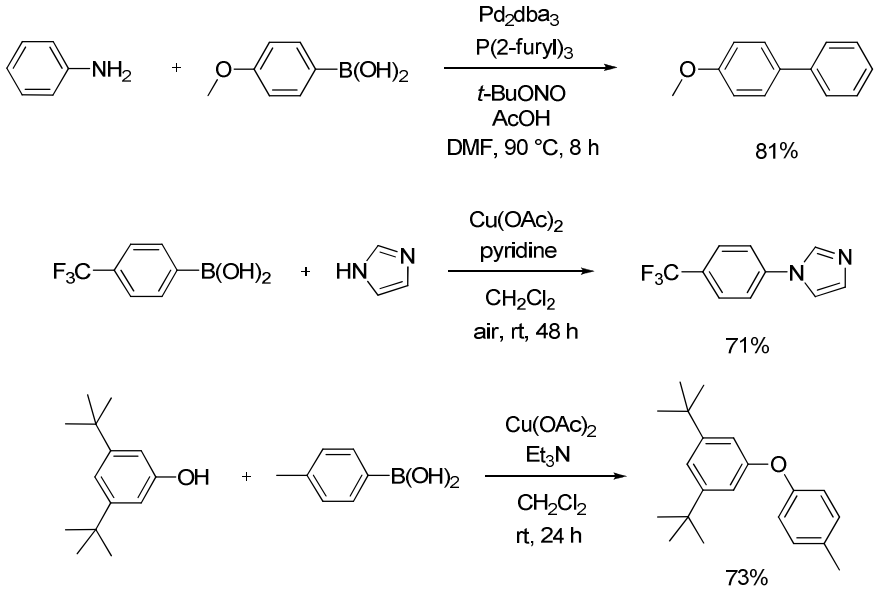
Liebeskind and Srogl discovered a reaction which allows the synthesis of ketones from the coupling of a boronic acid and a thioester *via* a carbon-carbon bond formation (Scheme 1.12). This reaction is catalysed by palladium and requires the presence of a copper derivative as co-catalyst.[26]



Scheme 1.12. Liebeskind-Srogl coupling reaction.

1.1.1.3.3. Coupling reactions

Arylboronic acids do not only couple with aryl halides or triflates. Wang *et al.* achieved a base-free, one-pot diazotization/cross-coupling of anilines with arylboronic acids (Scheme 1.13) for carbon-carbon bond formation.[27] Chan, Evans and Lam have developed a copper-catalysed coupling between arylboronic acids and heteroatom-containing derivatives (Scheme 1.13) in order to form carbon-heteroatom bonds.[28]



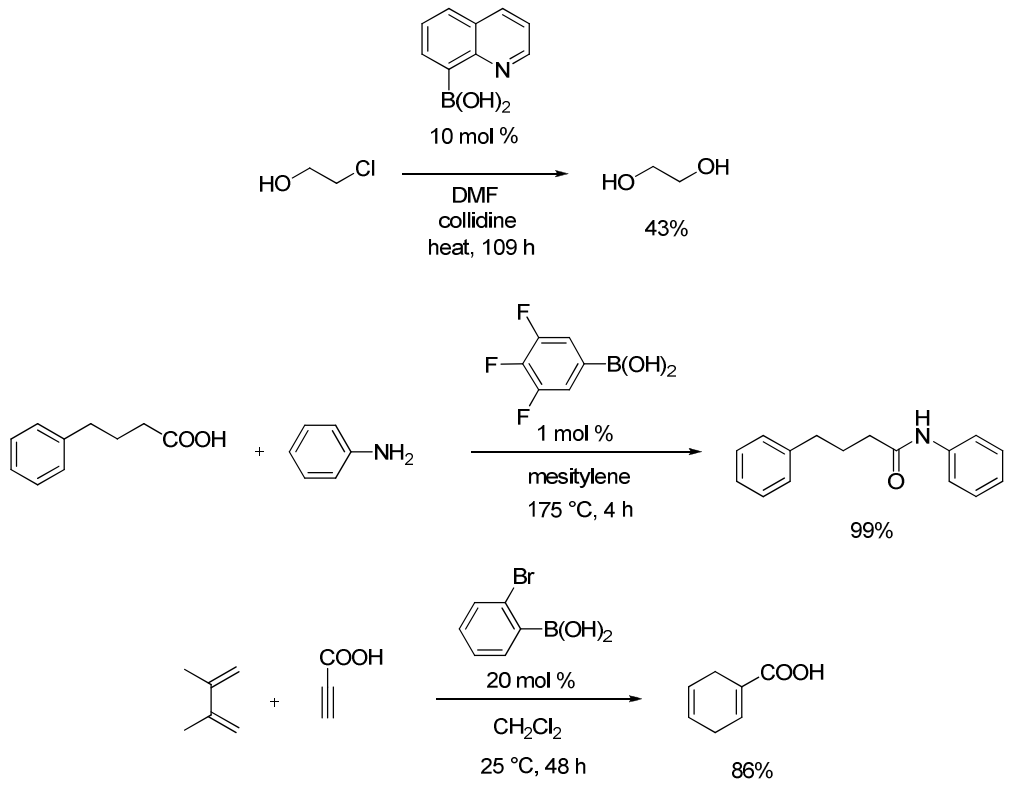
Scheme 1.13. Coupling reactions with boronic acids.

1.1.1.3.4. Oxidative replacement of boron

The boronic acid moiety can be transformed into an alcohol by oxidation,[29a] into a nitro group by nitration,[29b] into a cyano group by iridium-catalysed cyanation[29c] or to a halide by halogenation reactions.[29a]

1.1.1.3.5. Boronic acids as catalysts

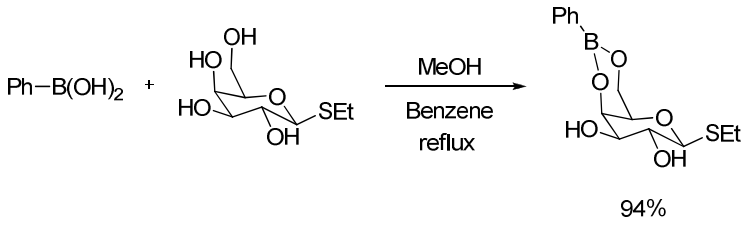
Because they contain an empty p-orbital, boronic acids act as Lewis acids and can act as catalyst in some reactions (Scheme 1.14). 8-Quinolineboronic acid was found to be a good catalyst in the hydrolysis of chloroalkenes[30] and arylboronic acids were found to be able to catalyse the amidation of carboxylic acid with amines.[31] Boronic acids are also known for their ability to catalyse the Diels-Alder reaction.[32]



Scheme 1.14. Examples of reactions catalysed by boronic acids.

1.1.1.3.6. Boronic acids as protecting groups for diols and diamines

Boronic acids are well known for the protection of 1,2-diols (Scheme 1.15), mainly in the field of carbohydrates.[33]

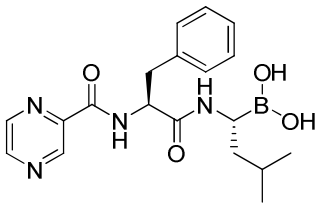


Scheme 1.15. Use of a boronic acid as protecting group.

1.1.1.4. Boronic acids in medicinal chemistry

Phenylboronic acid has been known for many years for its antimicrobial properties.[34]
In medicinal chemistry, boronic acids are considered to be bioisoteres of carboxylic acids and they were found to have many applications such as carbohydrate recognition,[35] protease enzyme inhibition,[36] etc.[37]

Velcade (PS-341; marketed by Millennium Pharmaceuticals; Figure 1.3) was the first boronic acid-containing marketed drug to be used in human health therapy. It is a proteasome inhibitor used for treating relapsed multiple myeloma (a bone marrow cancer) and mantle cell lymphoma.[38] Here, the boronic acid acts as a "serine trap" towards the proteasome serine protease.



Bortezomib (Velcade)

Figure 1.3. Example of a drug containing a boronic acid moiety.

Tubulin is a heterodimeric protein which plays a key role in cellular division. Targeting the microtubule system of eukaryotic cells represents an attractive strategy for the development of anticancer agents. A *cis*-isomer of the boronic acid analogue of combretastatin A-4 (Figure 1.4) was identified as a potent inhibitor of colchicine by binding to β-tubulin and it also inhibited tubulin polymerisation.[39] A boronic acid chalcone analogue of combretastatin A-4 (Figure 1.4) was found to be a potent inhibitor of human cancer in cell proliferation and angiogenesis.[40]

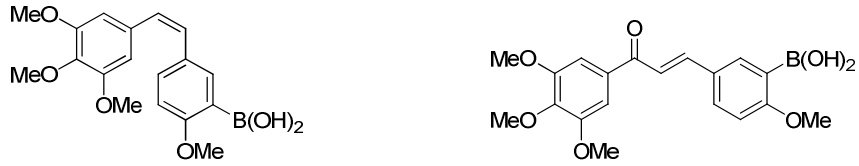


Figure 1.4. Examples of boronic acid analogues of combretastatin A-4.

The boronic acid analogue of estrone sulphate (Figure 1.5) was found to be a good competitive steroid sulphatase (STS) inhibitor.[41] STS is considered to be a potential target for the development of therapeutics for the treatment of steroid-dependent cancers (e.g. estrogen-dependent breast cancer).

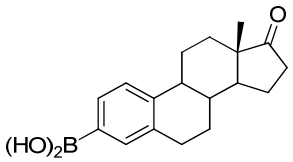


Figure 1.5. Example of boronic acid analogue of estrone sulphate.

Boron-conjugated 4-anilinoquinazolines (Figure 1.6) act as long acting inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase, which is vital for cell proliferation.[42]

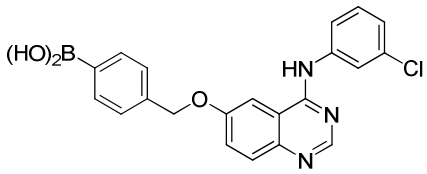


Figure 1.6. Example of a boron-conjugated 4-anilinoquinazoline.

A number of boronic acid derivatives (Figure 1.7) have been found to be potent inhibitors of fatty acid amide hydrolase (FAAH) which a potential target for therapeutic agents in the treatment of various medical conditions including inflammation and pain.[43]

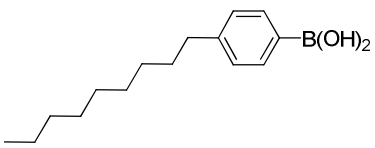


Figure 1.7. Example of an inhibitor of fatty acid amide hydrolase.

1.1.2. Boronic esters

1.1.2.1. Introduction

Boronic esters (Figure 1.8) are boronic acids in which the two hydroxyl group have been replaced by two alkoxy or aryloxy groups. They can be cyclic or acyclic.

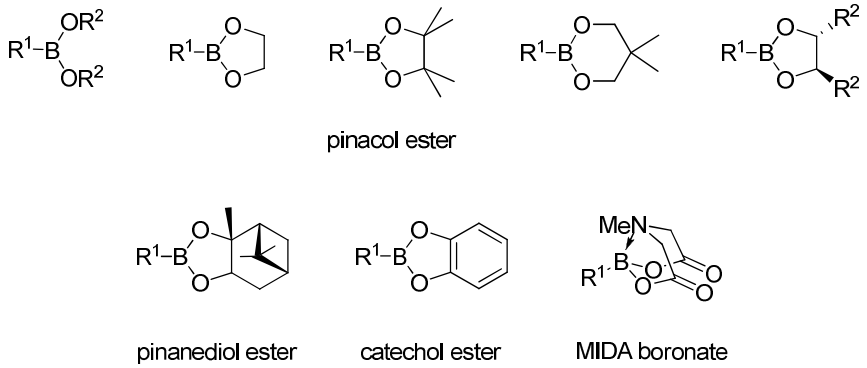
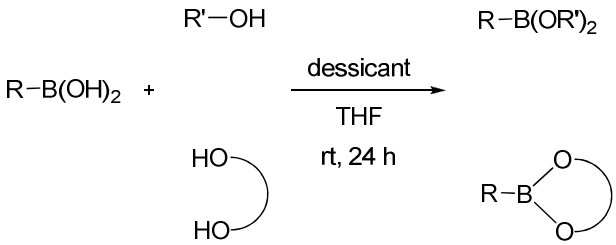


Figure 1.8. Examples of boronic esters.

1.1.2.2. Synthesis of boronic esters

1.1.2.2.1. Esterification

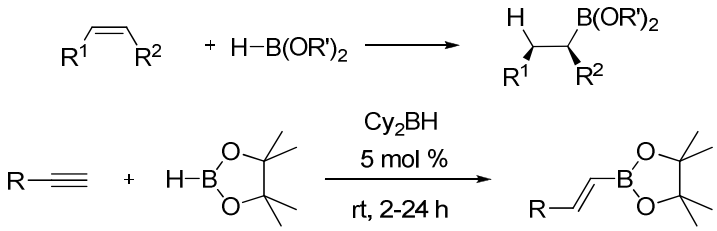
Boronic esters can be easily obtained from the reaction of a boronic acid with an alcohol or a diol (Scheme 1.16) in the presence of a dessicant (e.g. molecular sieves or magnesium sulphate).[44]



Scheme 1.16. Synthesis of boronic esters from boronic acids.

1.1.2.2.2. Hydroboration

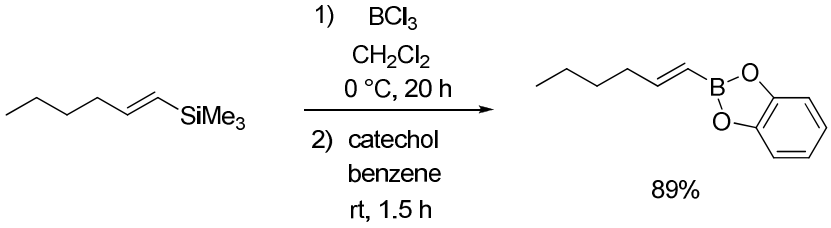
By choosing the appropriate hydroborane (Scheme 1.17) this method is ideal for the preparation of alkyl and alkenylboronic esters.[11,45]



Scheme 1.17. Synthesis of boronic esters *via* the hydroboration reaction.

1.1.2.2.3. Transmetallation of organosilanes

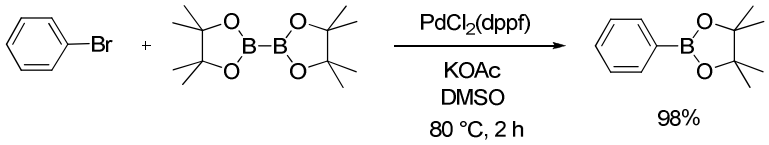
As for boronic acids, boronic esters can be obtained by a transmetallation reaction[46] (Scheme 1.18).



Scheme 1.18. Example of the synthesis of a boronic ester *via* transmetallation reaction.

1.1.2.2.4. Metal-catalysed coupling of aryl halides or triflates with diboron reagents

This coupling reaction between an aryl halide or triflate with a diboron reagent is catalysed by a transition metal, generally palladium (Scheme 1.19). This reaction allows the direct formation of boronic ester derivatives from aryl halides. Miyaura *et al.* first reported this reaction with aryl bromides and iodines and bis(pinacolato)diboron. They found that the best conditions for this coupling were [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium(II) as catalyst and potassium acetate as base in DMSO at 80 °C.[47]

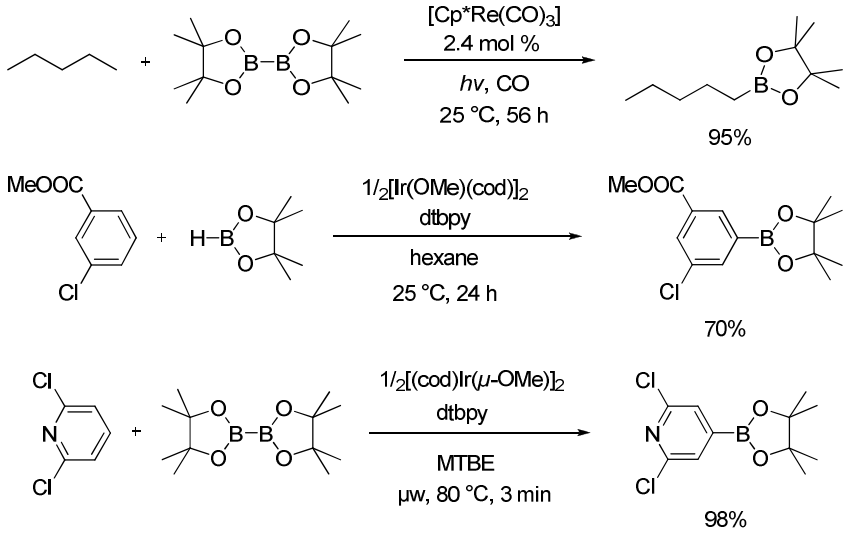


Scheme 1.19. Palladium-catalysed coupling of bromobenzene with bis(pinacolato)diboron.

This technique is very useful because many functional groups are tolerated. Miyaura and others extended this reaction to aryl triflates, boranes, new palladium and copper catalysts and ligands.[48]

1.1.2.2.5. Boronylation by C-H activation

The first boronylation of alkanes *via* a C-H activation photochemical process with boron containing transition-metal complexes (tungsten) was reported by Hartwig *et al*. in 1997.[49] However, this reaction was using the metal complex in stoichiometric quantities. A few years later, others managed to turn it into a catalytic reaction (Scheme 1.20) by using iridium, rhenium or rhodium complexes and borane or diboron compounds.[50] This reaction was then developed for the boronylation of aromatic and hereroaromatic compounds using iridium catalysts.[51]



Scheme 1.20. Transition metal-catalysed boronylation reaction by C-H activation.

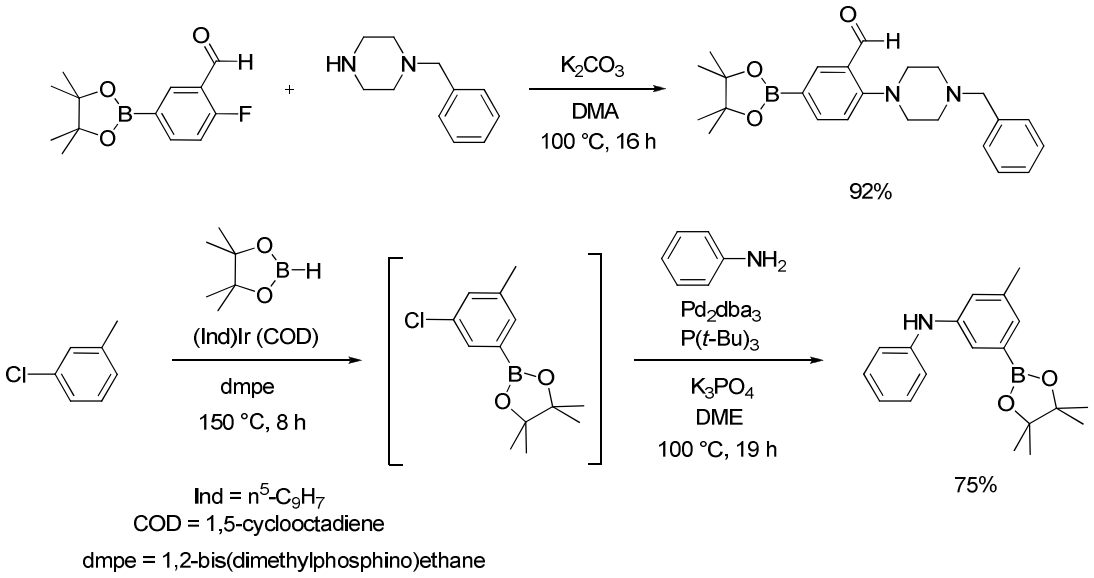
1.1.2.3. Applications

Boronic ester derivatives are widely known for their involvement in transition metal-catalysed coupling reactions (e.g. SM coupling), as for boronic acids. However, they are also very useful compared to boronic acids, because they are easy to handle, have good stability during the purification process and can act as a protecting group for the boronic acid. This is why many chemists used them as a second functionality point during syntheses. A lot of reactions have been performed with alkylboronic esters[12,52] but this section will focus on arylboronic acid pinacol esters.

Boronic acid pinacol esters are one of the most widely used boronic esters and its aryl derivatives allow the synthesis of very interesting aryl and polyaryl compounds. Here, some examples of reactions of arylboronic acid pinacol ester derivatives leading to highly functionalised arylboronates are presented.

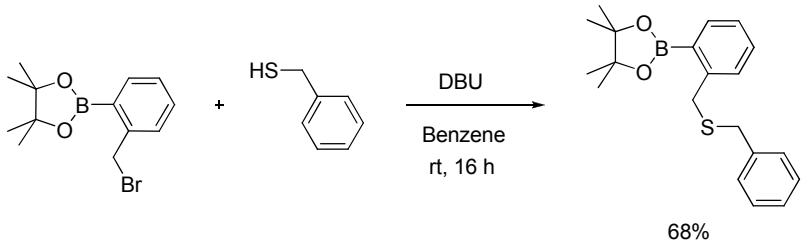
1.1.2.3.1. Nucleophilic substitutions

Trisubstituted arylboronates were synthesised *via* the aromatic nucleophilic substitution reaction of amines and phenols on 4-fluoro-3-formylbenzeneboronic acid pinacol ester (Scheme 1.21) in which the presence of *ortho* and *para* electron-withdrawing substituents facilitated the reaction.[53] They were also prepared *via* a one-pot borylation/amination of chloroaryls developed by Smith III *et al.*[54]



Scheme 1.21. Amination reactions on arylboronates.

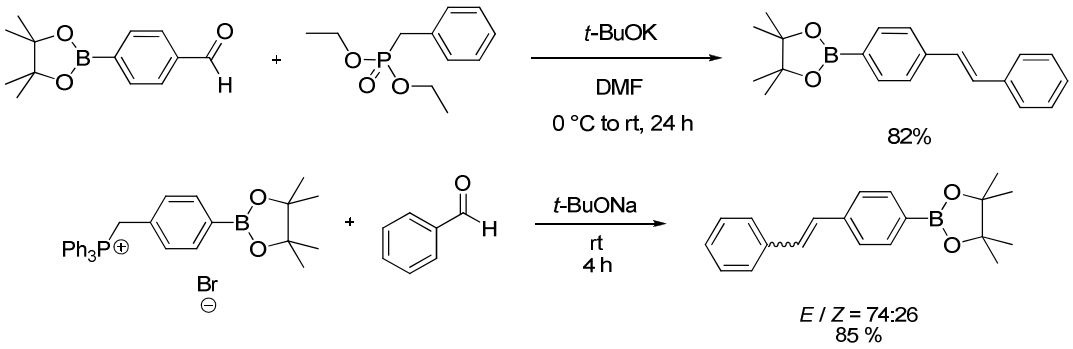
(Bromomethyl)phenylboronic acid pinacol esters have proven to be suitable precursors for S_N2 reactions (Scheme 1.22) with *N*-, *S*- and *O*-nucleophiles. This reaction was also achieved under microwave irradiation (which will be developed in Chapter 2).[55]



Scheme 1.22. S_N2 reaction on a 2-(bromomethyl)phenylboronic acid pinacol ester.

1.1.2.3.2. Wittig reactions

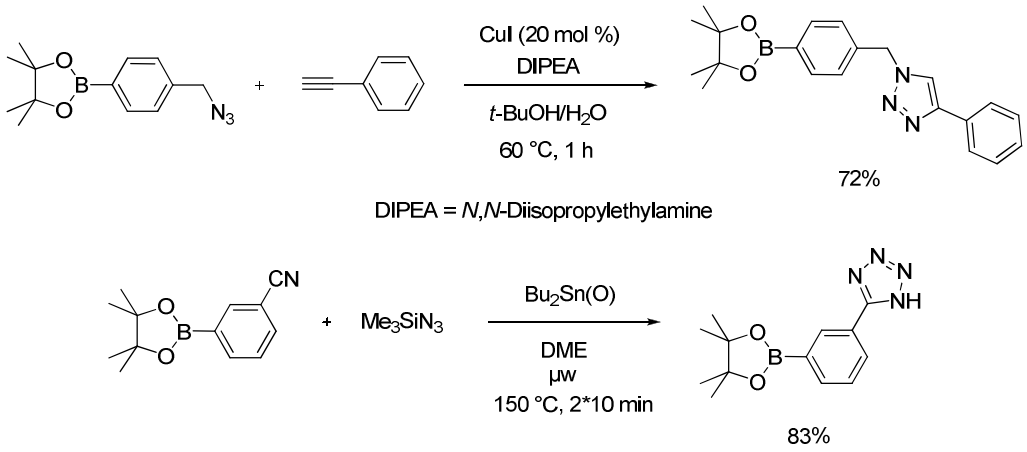
Aryl boronates have also been used to synthesise stilbene boronates (Scheme 1.23). They can play the role of either the carbonyl[56] or the phosphorus[57] containing partner.



Scheme 1.23. Wittig reaction on aryl boronates.

1.1.2.3.3. Triazole and tetrazole aryl boronate synthesis

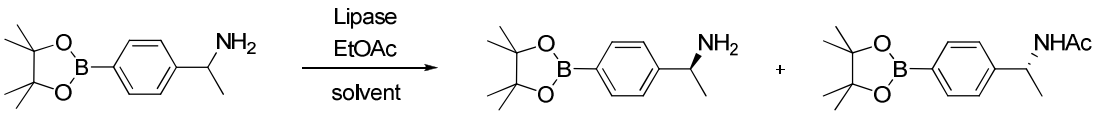
Frost *et al.* used click chemistry on a 4-(azidomethyl)phenylboronic acid pinacol ester for the synthesis of triazole boronates (Scheme 1.24).[58] Schulz *et al.* developed a microwave-assisted method for the preparation of aryltetrazoleboronic acid pinacol esters.[59]



Scheme 1.24. Triazole and tetrazole aryl boronates synthesis.

1.1.2.3.4. Asymmetric synthesis

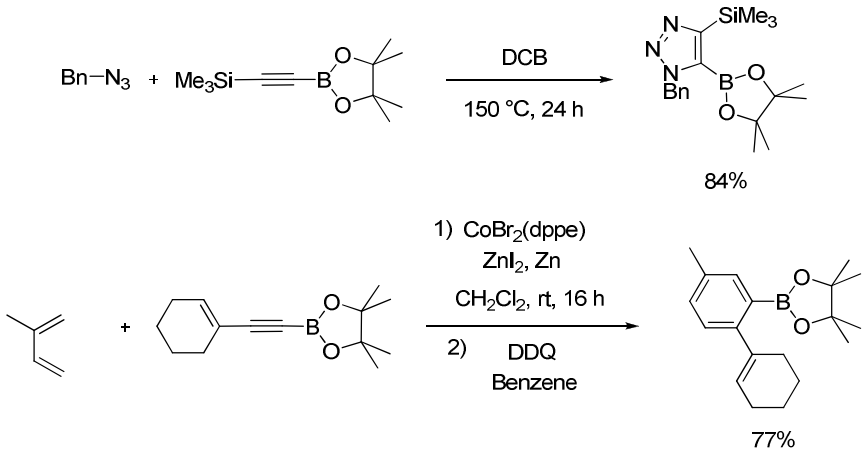
Optically active boron-containing chiral amines were synthesised from 1-(4-(phenylboronic acid pinacol ester)ethanamine *via* an lipase-mediated amide coupling reaction (Scheme 1.25).[60]



Scheme 1.25. Synthesis of optically active boron-containing chiral amines.

1.1.2.3.5. Synthesis of the aryl or heterocyclic moiety

The synthesis of highly functionalised arylboronic acid pinacol esters (Scheme 1.26) can also be achieved by the construction of the aryl moiety from highly functionalised precursors.[61]



Scheme 1.26. Examples of syntheses of highly functionalised arylboronic acid pinacol esters.

These types of reactions are very useful because they are part of diversity oriented synthesis of biphenyls.

1.1.2.4. MIDA boronates

MIDA (*N*-methyliminodiacetic acid) boronates (Figure 1.9) are one of the most recent types of boronic esters. Their first preparation was reported in 1986.[62] Unlike other boronic esters, the MIDA group on boronates completely deactivates the boron atom and makes it unreactive under anhydrous conditions.[63] The only way for the boron to recover its activity is *via* the hydrolysis of the MIDA boronate to the corresponding boronic acid.

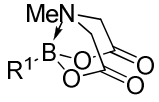
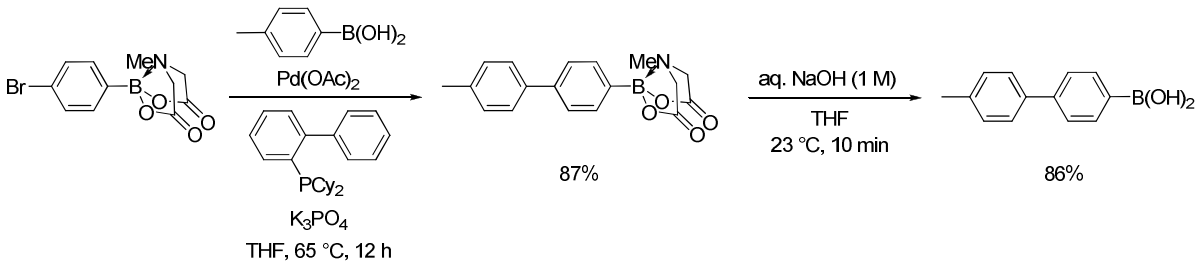


Figure 1.9. MIDA boronate.

The hydrolysis of MIDA boronates occurs under very mild conditions such as aqueous sodium hydroxide, THF, 10 min or even aqueous sodium bicarbonate, methanol, 6 h.[63] These properties make the MIDA group a very versatile building block for orthogonal synthesis (Scheme 1.27), since its synthesis and hydrolysis are very easy to achieve.

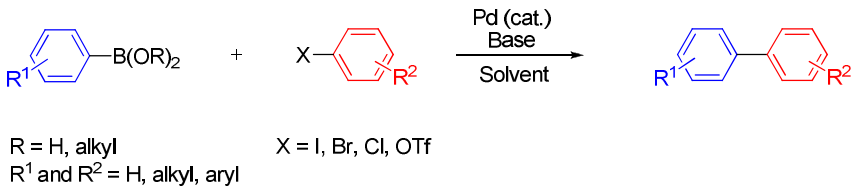


Scheme 1.27. SM coupling of a bromophenyl MIDA boronate and hydrolysis of the MIDA group.

This type of chemistry can be applied in the orthogonal synthesis of complex molecules,[64] polyene natural products[65] or peptide building blocks[66] and in olefin cross-metathesis reactions.[67] Some one-pot hydrolysis/coupling reactions of MIDA boronate derivatives have been developed in aqueous media.[68]

1.2. Suzuki-Miyaura coupling reaction

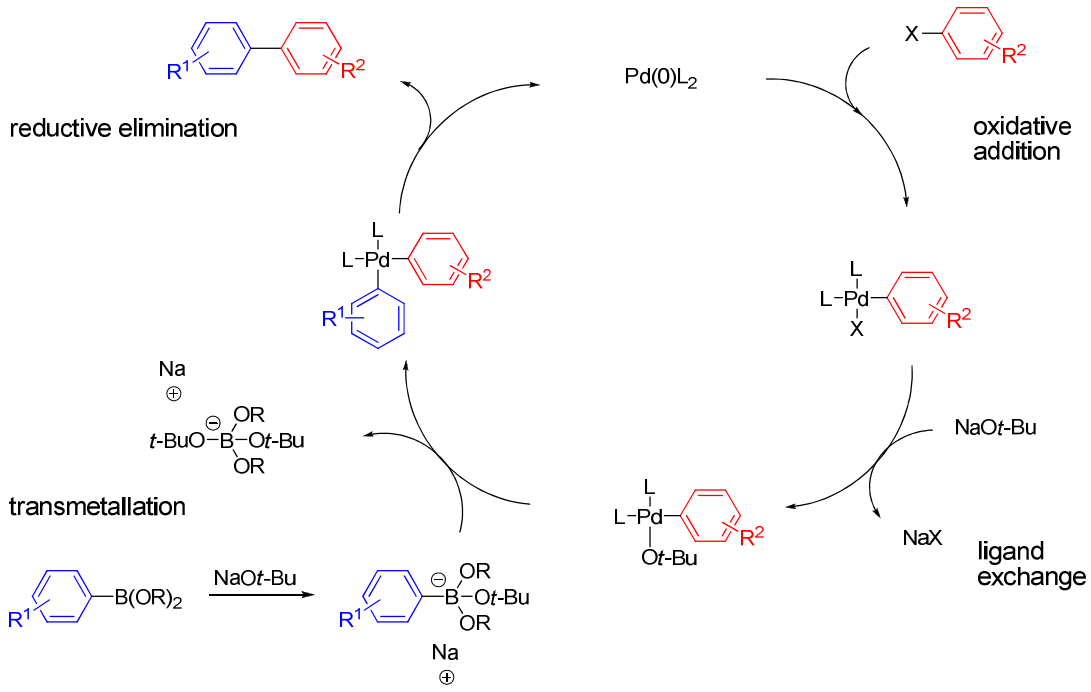
The Suzuki-Miyaura (SM) coupling reaction is a well-known reaction for carbon-carbon bond formation. It is also one of the most important and efficient strategies for the construction of symmetrical and unsymmetrical biaryl compounds. This reaction involves the coupling of organoboron compounds and organic halides or triflates, in the presence of a base and a catalytic amount of palladium complex (Scheme 1.28).[69]



Scheme 1.28. Suzuki-Miyaura coupling reaction.

Many chemists have investigated the various parameters involved in the SM coupling C-C bond forming process and have employed a vast array of conditions (different palladium complexes, bases, ligands, solvents, temperatures…), many of which are substrate specific.[69e]

The mechanism of the SM coupling consists of a catalytic cycle (Scheme 1.29) where the catalytic entity starts as palladium(0).[70]



Scheme 1.29. Mechanism of the Suzuki-Miyaura coupling.

The aryl halide adds onto palladium, which oxidises the palladium from the oxidation state (0) to the oxidation state (II) (oxidative addition). This entity undergoes a ligand exchange *via* the participation of the base. The base also plays the role of increasing the carbanion character of the organoborane which facilitates the transfer of the aryl group from the boron to the palladium complexes in the transmetallation step.[69a] Finally, the biaryl moiety is formed by reductive elimination (palladium(II) reverts to palladium(0)).

1.3. Biphenyls

1.3.1. Introduction

Biphenyls are organic compounds made of two phenyl groups linked together by a carbon-carbon bond (Figure 1.10).

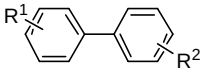


Figure 1.10. Representation of a biphenyl molecule.

Biphenyl compounds have many applications (Figure 1.11, 1.12) such as herbicides,[71] fungicides,[72] chiral ligands in catalysis,[73] liquid crystals[74] or materials (organic conductors, organic electric wires, hosts, etc.).[75]

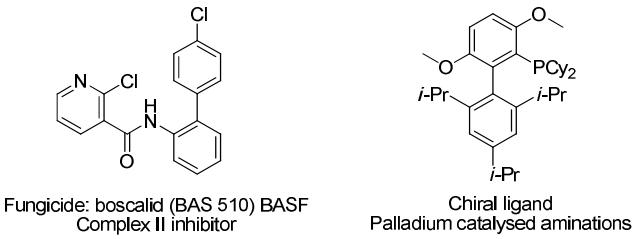
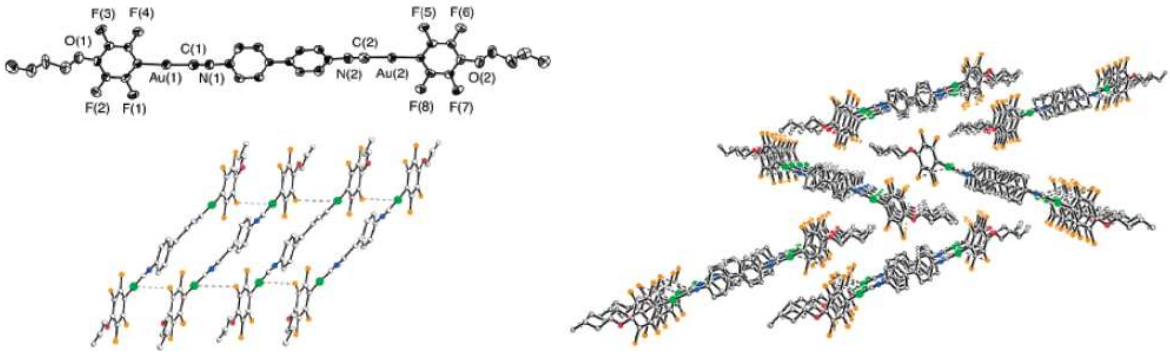


Figure 1.11. Examples of useful biphenyl compounds.



([μ-(4,4'-CN-C_6H_4-C_6H_4-NC)-{Au($C_6F_4OC_4H_9$)}$_2$] dinuclear gold(I) isocyanide complex) [74b]

Figure 1.12. Example of a liquid crystalline biphenyl compound.

If one or both of the phenyl rings are replaced by a heteroaromatic cycle (Figure 1.13), the compound is called a biaryl.

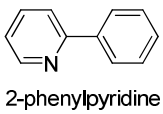


Figure 1.13. Example of a biaryl compound.

1.3.2. Biphenyls in medicinal chemistry

The biphenyl nucleus is found in many natural and synthetic products that display a wide range of biological activity.[76] This explains why the biphenyl scaffold is widely encountered in medicinal chemistry as a privileged scaffold, notably in a variety of inhibitors of enzymes, transporter proteins and GPCR ligands (Figure 1.14).[77,78]

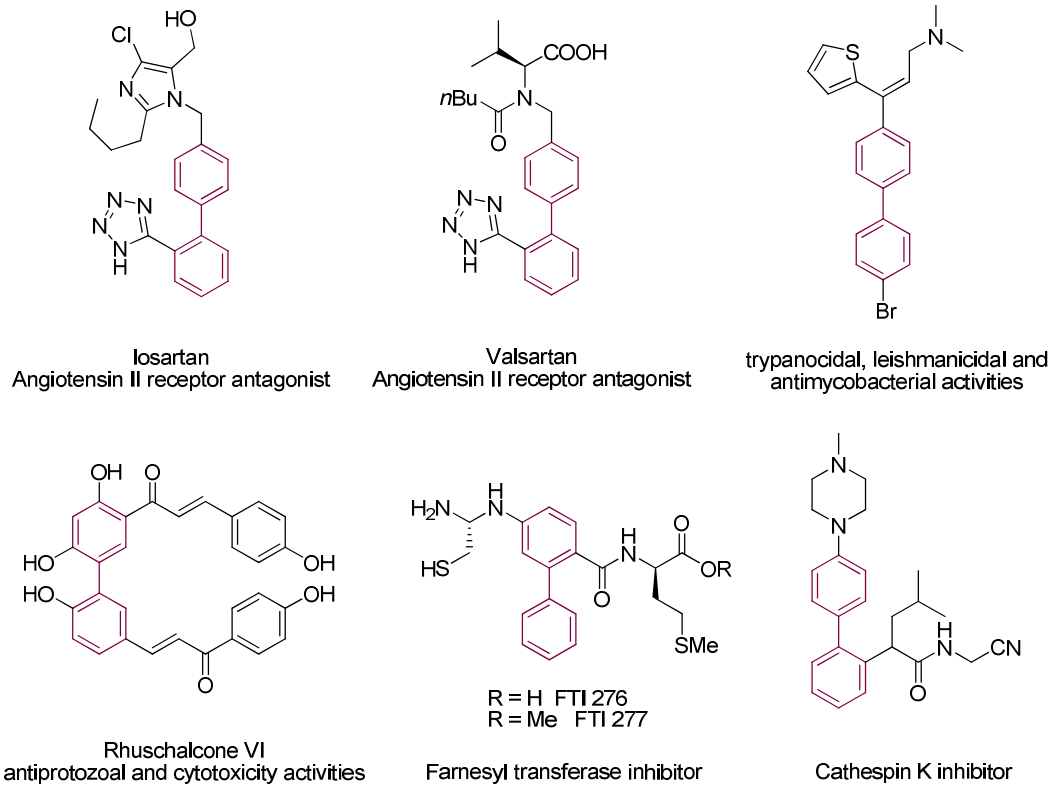


Figure 1.14. Examples of important biologically active biphenyls.

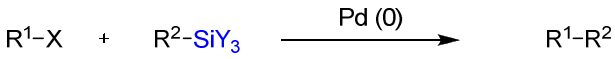
1.3.3. Synthesis of biphenyls/biaryls

The formation of the carbon-carbon bond is one of the most important synthetic steps in chemistry. Biphenyl derivatives are mainly synthesised *via* cross-coupling reactions but few other pathways have been developed for their preparation.

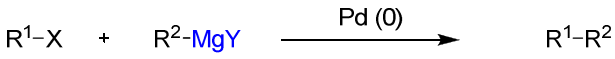
1.3.3.1. Cross-coupling reactions

The considerable potential of transition metal-catalysed reactions has been extensively demonstrated in organic synthesis. There are several main cross-coupling reactions which allow the synthesis of biaryls. They consist of a palladium-catalysed coupling of an aromatic organometallic derivative with an aryl halide and are named after the chemists who discovered them. Some of them can also be applied to alkynes, alkenes and alkanes. The Hiyama, Kumada, Negishi, Stille and Suzuki-Miyaura cross-coupling reactions (Scheme 1.30), implying the used of organosilicon, organomagnesium, organozinc, organotin and organoboron reagents, respectively, are widely documented in the literature.[69,79]

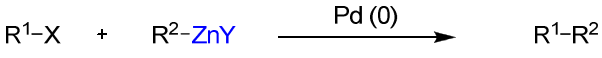
Hiyama Coupling:



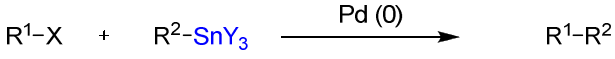
Kumada Coupling:



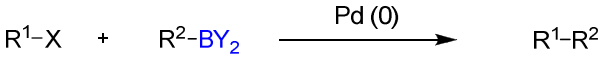
Negishi Coupling:



Stille Coupling:



Suzuki-Miyaura Coupling:



Scheme 1.30. Cross-coupling reactions.

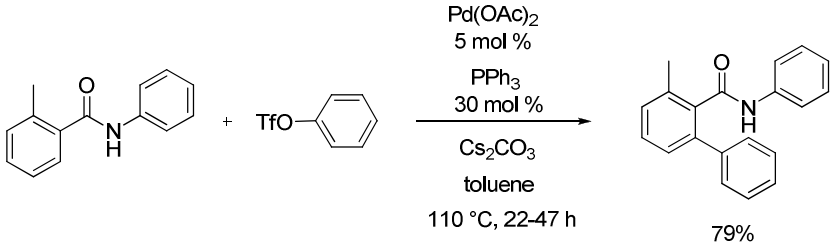
The Nobel Prize in Chemistry 2010 was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki "for palladium-catalysed cross-couplings in organic synthesis".

1.3.3.2. C-H activation

The C-H activation reaction is a catalyst controlled reaction which leads to the functionalisation of carbon-hydrogen bonds.[80] This carbon-carbon or carbon-heteroatom formation technique has become an important and challenging tool in total synthesis.[81] It is an atom economical process in organic chemistry and also a very useful method for the synthesis of biaryls.

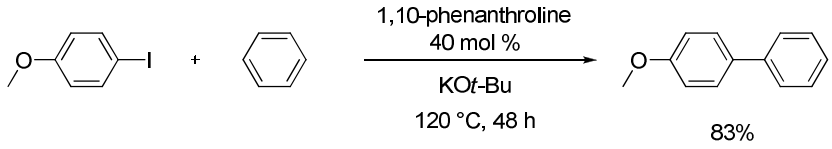
An impressive functionalisation of an aryl C-H bond was performed by ruthenium-catalysed *ortho* alkylation of acetophenones with terminal alkenes.[82] The presence of the carbonyl group facilitates the *ortho* C-H activation process because it makes a complex with the catalyst.

This method was then utilised for the synthesis of biaryls (Scheme 1.31) using rhodium,[83] palladium[84] and ruthenium[85] based-catalysts.



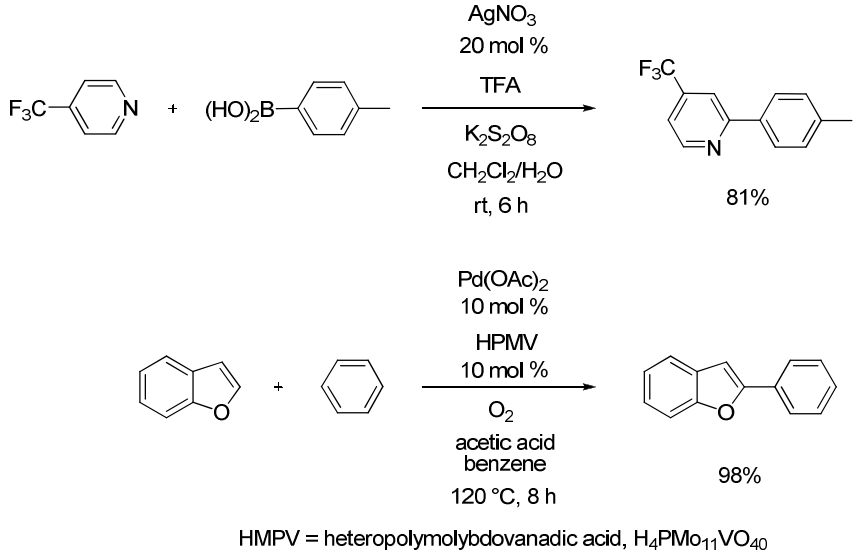
Scheme 1.31. Biaryl synthesis *via ortho* C-H activation.

The palladium coupling of aryl derivatives with aryl halide *via* C-H activation is widely document in the literature.[86] This coupling has been developed using other metals such as rhodium[87] or without a transition metal (Scheme 1.32).[88]



Scheme 1.32. C-H activation reaction catalysed by a non-metallic complex.

The silver-catalysed C-H activation reaction of arylboronic acids with aromatic heterocycles (Scheme 1.33) yields the biaryl product in very good yields within a few hours.[89] DeBoef *et al.* developed a palladium-catalysed aryl-aryl coupling without the use of organometallic or aryl halide derivatives.[90]



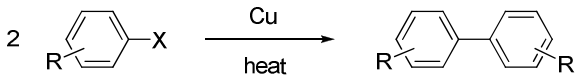
Scheme 1.33. C-H activation reactions.

1.3.3.3. Other reactions

There are a few other ways to synthesise biaryl compounds.

Ullmann reaction

The Ullman reaction (Scheme 1.34) is the synthesis of symmetric biaryls from the coupling of aryl halides in the presence of copper.[91]

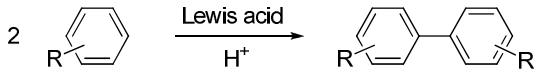


Scheme 1.34. Ullmann reaction.

The homocoupling of aryl halides can also be achieved by iron catalysis.[92]

Scholl reaction

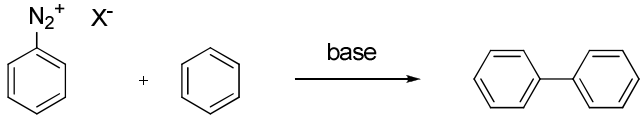
The Scholl reaction (Scheme 1.35) is a coupling reaction between two arene compounds with the presence of a Lewis acid and a protic acid.[93]



Scheme 1.35. Scholl reaction.

Gomberg-Bachmann reaction

The Gomberg-Bachmann reaction (Scheme 1.36) is an aryl-aryl coupling reaction *via* a diazonium salt.[94]



Scheme 1.36. Gomberg-Bachmann reaction.

1.4. Microwave-Assisted Organic Synthesis (MAOS)

Microwaves move at the speed of light and are composed of oscillating electric and magnetic fields (Figure 1.15) with wavelengths between 300 MHz and 300 GHz (1 cm to 1 m). Materials react to the applied electromagnetic fields in a variety of ways including displacements of both free and bound electrons by electric fields and the orientation of atomic moments by magnetic fields.[95] The microwave dielectric heating effect uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions.[96] The microwave heating effect depends on the frequency as well as the power applied. In chemistry, microwaves generate heat much faster than conventional heat using a hotplate.

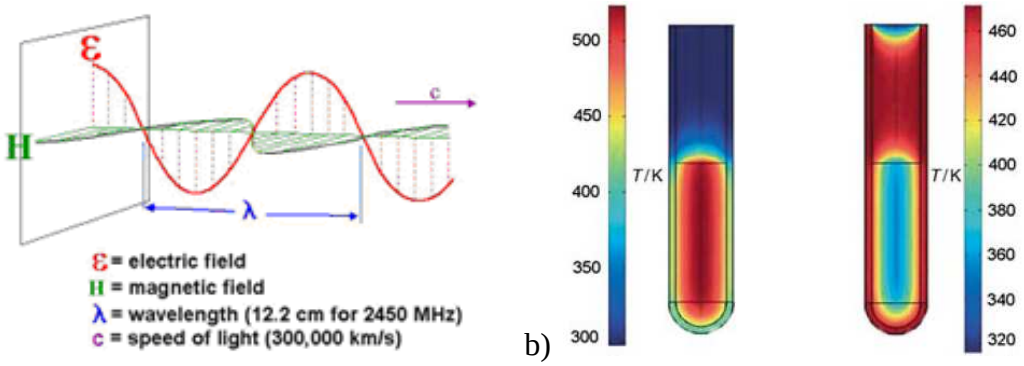


Figure 1.15. a) Electromagnetic field illustration of a microwave. b) Infrared image of a microwave heated solvent (left) compared with a thermal method (right) showing the uniform heating achieved with microwaves.[97g]

Over the last 15 years, microwave-assisted reactions have been shown to improve the yields and decrease the reaction times of many types of reactions[97] including SM couplings.[2,98]

Microwave heating depends on the material irradiated (e.g. the solvent) and its dielectric properties. The loss tangent (tan $\delta = \varepsilon'' / \varepsilon'$) determines the ability of a specific substance to convert electromagnetic energy to heat at a given frequency and temperature. ε'', the dielectric loss, indicates the efficiency with which electromagnetic radiation is converted into heat and ε', the dielectric constant, describes the polarisability of molecules in the electric field (Table 1.1).

Table 1.1. Loss tangents (tan δ) of different solvents.

Solvent	tan δ
Ethanol	0.941
Methanol	0.659
Acetic acid	0.174
Water	0.123
Acetonitrile	0.062
THF	0.047
Toluene	0.040

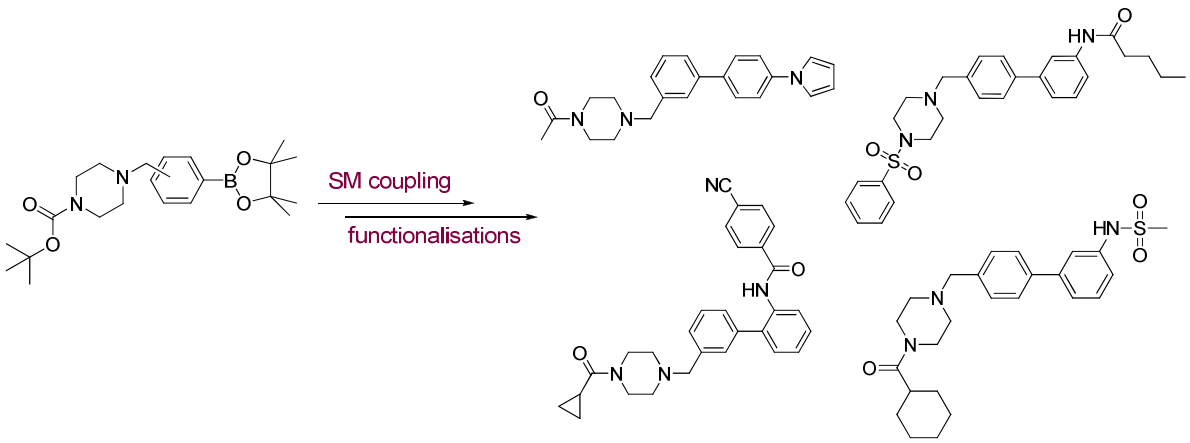
A reaction medium with a high tan δ is required for an efficient absorption and rapid heating. Some common solvents without a permanent dipole moment, such as carbon tetrachloride, benzene or dioxane, are more or less microwave transparent.[97m]

1.5. Summary of the work carried out in this thesis

In Chapter 2, a microwave-mediated S_N2 reaction of (bromomethyl)phenyl boronic acid pinacol esters with *N*-, *S*- and *O*-nucleophiles was achieved in order to synthesise a library of arylboronates. The latter were coupled with aryl bromides in a SM coupling and provided a library of substituted methylbiaryls (Scheme 1.37).

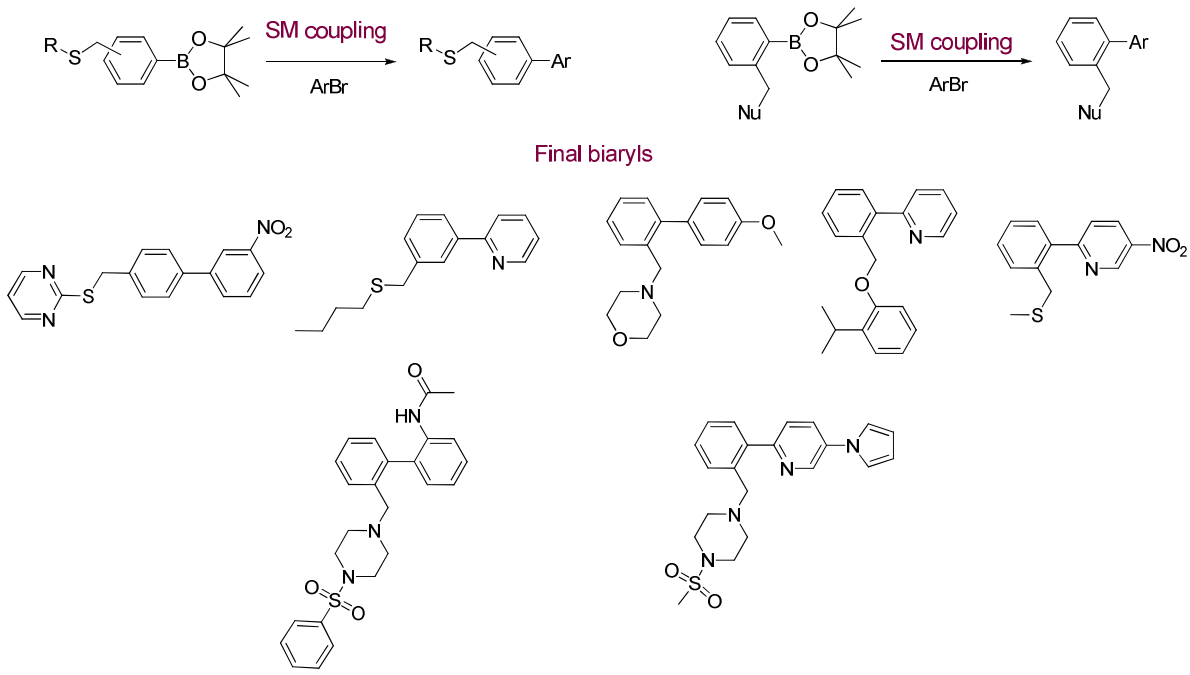
Scheme 1.37. S_N2 reactions followed by SM couplings.

Chapter 3 describes the synthesis of a library of highly functionalised (piperazin-1-ylmethyl)biaryls from *p*- and *m*-(Boc-piperazin-1-ylmethyl)phenylboronic esters *via* microwave-mediated SM coupling followed by protecting group removal, hydrogenation and functionalisation steps (Scheme 1.38).



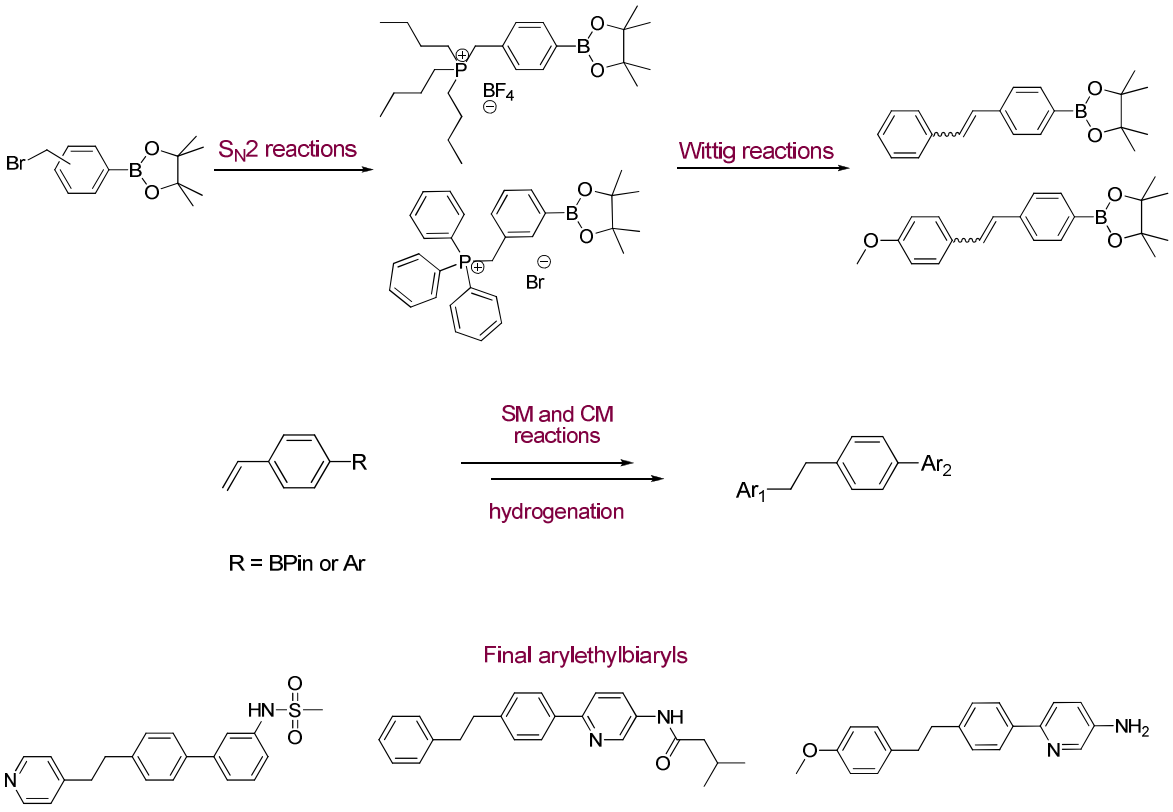
Scheme 1.38. (Piperazin-1-ylmethyl)biaryl library.

The optimisation of the conditions for the SM coupling of *S*- and *o*-substituted methylphenylboronic esters, which were previously found to be cumbersome, was achieved leading to interesting sulphur-containing and *o*-substituted biaryls and an *o*-(piperazin-1-ylmethyl)biaryl library, as described in Chapter 4 (Scheme 1.39).



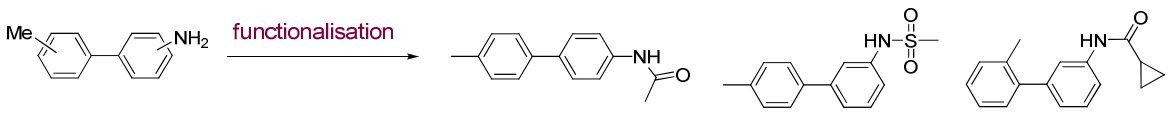
Scheme 1.39. SM coupling of *S*- and *o*-substituted methylphenylboronic esters.

In Chapter 5, phosphines were used as nucleophiles in the microwave-mediated S_N2 reaction on (bromomethyl)phenylboronic acid pinacol esters leading to phosphonium aryl boronates which reacted with aldehydes in Wittig reactions to form alkenylaryl boronates. The latter were also obtained *via* the cross-metathesis reaction of 4-vinylphenylboronic acid pinacol esters. The alkenylaryl boronates obtained were reduced and coupled in SM coupling reactions leading to the synthesis of an arylethylbiaryl library. The latter was also synthesised from 4-vinylphenylboronic acid, which was first coupled in a SM reaction followed by a CM reaction and the resulting arylethenylbiaryls were hydrogenated (Scheme 1.40).



Scheme 1.40. Biphenyl synthesis *via* Wittig, CM and SM reactions.

Chapter 6 describes the synthesis and solid state study of methybiphenylamides with interesting solid state features (Scheme 1.41).



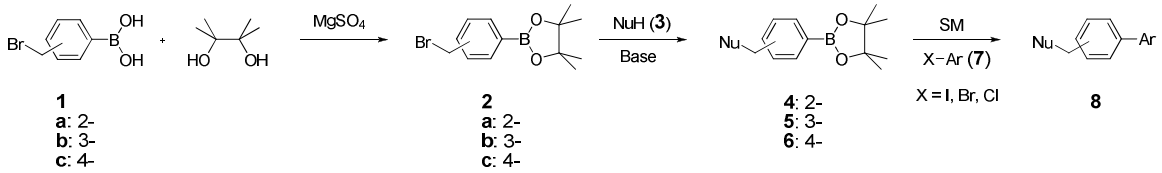
Scheme 1.41. Biphenylamide derivatives.

Chapter 2: Synthesis of a substituted-methylbiaryl library

2.1. Introduction

An arylboronic acid is a key partner in the SM coupling reaction, leading to the synthesis of biphenyl compounds. However, preparing and purifying elaborated arylboronic acids is sometimes difficult due to the high polarity of the acid functionality (e.g. streaking on a silica gel column). A boronic acid pinacol ester has been chosen for the multi-step biphenyl syntheses outlined hereafter because of its stability, its facile synthesis from the boronic acid and its reactivity in subsequent SM couplings.

o-, *m*- and *p*-(bromomethyl)phenylboronic acids (**1**) (Scheme 2.1) have been selected as starting materials because their corresponding pinacol esters (**2**) are easy to synthesise in quantitative yields from pinacol, in the presence of a dessicant e.g. molecular sieves or anhydrous magnesium sulphate ($MgSO_4$), easier to handle and purify by chromatography or crystallisation and also because several functionalisations can be carried out in parallel by displacement of the bromide group by a simple S_N2 reactions[55,99] followed by a SM coupling reaction leading to an interesting biaryl library (Scheme 2.1).

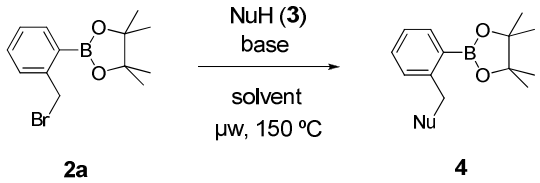


Scheme 2.1. Synthesis of substituted-methylbiaryls.

Once the pinacol ester has been synthesised, several nucleophilic reagents, such as amines, thiols, phenols and alcohols, have been tested on **2** in a S_N2 reaction. Nucleophilic displacement chemistry leading to amino and thioether derivatives has already been performed on **2a** under thermal conditions (oil bath) in acetonitrile with sodium carbonate as a base or using toluene/DBU respectively, giving good results within a few hours.[99a] Alkylation of amines can also be achieved under microwave irradiation[100] in order to enhance this chemistry and make it amenable to parallel synthesis.

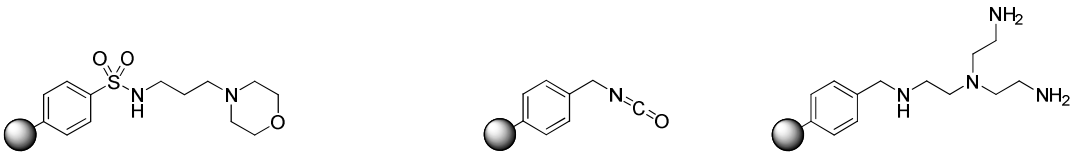
2.2. Optimisation of the microwave-mediated S_N2 reaction

The optimisation process (Scheme 2.2) has been achieved on the bromide displacement by a nitrogen nucleophile.



Scheme 2.2. Bromide displacement by a nitrogen nucleophile on compound **2a**.

The S_N2 reactions were performed in THF or water under microwave irradiation at 150 °C (Scheme 2.2). Different bases were used, such as PS-NMM (polystyrene supported *N*-methylmorpholine; Figure 2.1), potassium carbonate or the nucleophile itself. The use of a supported base can be explained by the facile work up, which is a simple filtration to remove the salts formed.[101] When the reaction is not quantitative, excess starting materials can be removed by using scavengers (Figure 2.1) (in this case PS-Isocyanate for nucleophiles and PS-Trisamine for electrophiles).[102]

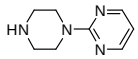
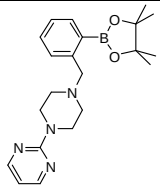
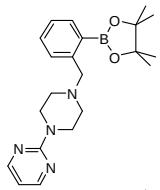
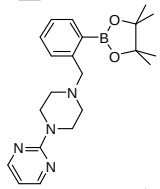
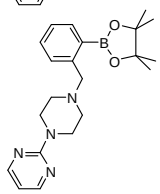
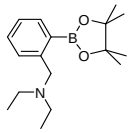
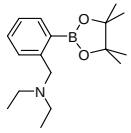
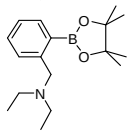


PS-NMM PS-Isocyanate PS-Trisamine

Figure 2.1. Supported reagents.

Supported reagents are expensive. Hence, other bases have been tested as an alternative (Table 2.1).

Table 2.1. Optimisation of S_N2 reactions on **2a** with amines.

Entry	**3**	Base	Solvent	Time (min)	Products **4**		Yield (%)
1	 **3a**	PS-NMM	THF	15		**4a**	> 99
2	**3a**	K_2CO_3	water	15		**4a**	_ [a]
3	**3a**	**3a**	THF	20		**4a**	31
4	**3a**	K_2CO_3	THF	30		**4a**	_ [b]
5	 **3b**	PS-NMM	THF	25		**4b**	63
6	**3b**	K_2CO_3	THF	30		**4b**	_ [c]
7	**3b**	**3a**	THF	20		**4b**	_ [d]

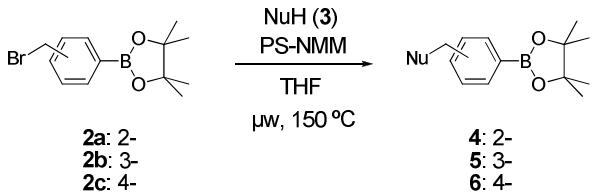
[a] Mixture of the expected product and its boronic acid (by ^{1}H NMR and MS). [b] Starting materials. [c] Starting materials mainly and traces of expected compound. [d] Complex mixture.

The above reactions were carried out using the same molar equivalents of **2a**, nucleophile and base. A number of important observations can be gleaned from Table 2.1. It was observed that when PS-NMM is used as base, good to excellent results are obtained (Table 2.1, entries 1 and 5). The expected product is obtained in quantitative yield after only 15 minutes of irradiation in the microwave (Table 1, entry 1). When potassium carbonate is used as a base, in THF, the reaction is not successful (Table 1, entries 4 and 6).

In water, with potassium carbonate as a base, the expected compound was obtained but as a mixture with the substituted boronic acid (Table 1, entry 2). The observed yields are low when the amine plays a dual role of nucleophile and base (Table 1, entries 3 and 7). Hence, the best results are obtained when using **2**, with one molar equivalent of nucleophile and one molar equivalent of a supported base, PS-NMM, in THF at 150 ºC under microwave irradiation. These conditions have been adopted for all the other S_N2 reactions of *o*-, *m*- and *p*-**2** using amines as nucleophiles.

2.3. Microwave-mediated S_N2 reactions employing the optimised conditions

S_N2 reactions on **2a-c** using amine, thiols, phenols and alcohols as nucleophiles and PS-NMM as base were achieved under microwave irradiation at 150 °C (Scheme 2.3).



Scheme 2.3. S_N2 reaction on compounds **2** with *N*-nucleophiles.

2.3.1. Bromide displacement by nitrogen nucleophiles

These reactions were achieved using the optimised conditions using amines as nucleophiles (Figure 2.2). When required, supported scavengers, PS-trisamine and PS-isocyanate, were used to remove unreacted bromide or amine, respectively, and in general, yields of product were good to excellent (Table 2.2).

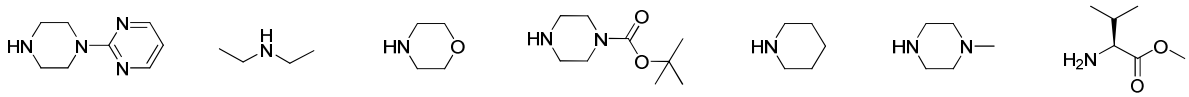


Figure 2.2. *N*-Nucleophiles.

Table 2.2. *N*-substituted Arylboronates **4**, **5** and **6**.

Entry	**3**	Time (min)	Product (**4**-**6**)	Isolated yield (%)
1	**3a**	15	**4a**	> 99
2	**3b**	15	**4b**	63
3	**3c**	15	**4c**	> 99
4	**3d**	15	**4d**	> 99
5	**3a**	15	**5a**	> 99
6	**3b**	15	**5b**	> 99
7	**3c**	15	**5c**	98
8	**3d**	15	**5d**	75
9	**3e**	30	**5e**	> 99
10	**3a**	30	**6a**	93
11	**3b**	15	**6b**	> 99
12	**3c**	40	**6c**	99
13	**3d**	45	**6d**	95
14	**3f**	35	**6e**	> 99
15[a]	**3g**	120	**6f**	72

[a] 2 equivalents of (*L*)-Val(OMe), 140 ºC.

In most cases, the reaction times were 15 min but in some cases, slightly longer reaction times were needed in order to obtain the expected product in good yields. Cooled reaction mixtures were assessed by TLC after 15 or 30 min reaction time, and if incomplete, the reaction was extended an additional 15-30 min. A protected valine analogue was successfully able to react to yield a precursor to valsartan (*vide supra*) (Table 2.2, entry 15). The reaction of other primary amines, including benzylamine as well as tautomerizable heterocycles such as imidazoles, often led to a mixture of products, presumed to result from mono- or disubstitution reactions, and these were not investigated further in the present study. Next, we focused our attention to thiols as nucleophiles.

2.3.2. Bromide displacement by sulphur nucleophiles

Having demonstrated that amines react readily with **2** in S_N2 reactions, related reactions were attempted with thiols (Figure 2.3), which are expected to be better nucleophiles than amines, in order to synthesise *S*-substituted arylboronates (Figure 2.4).

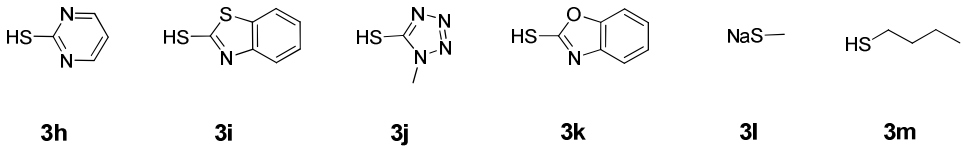
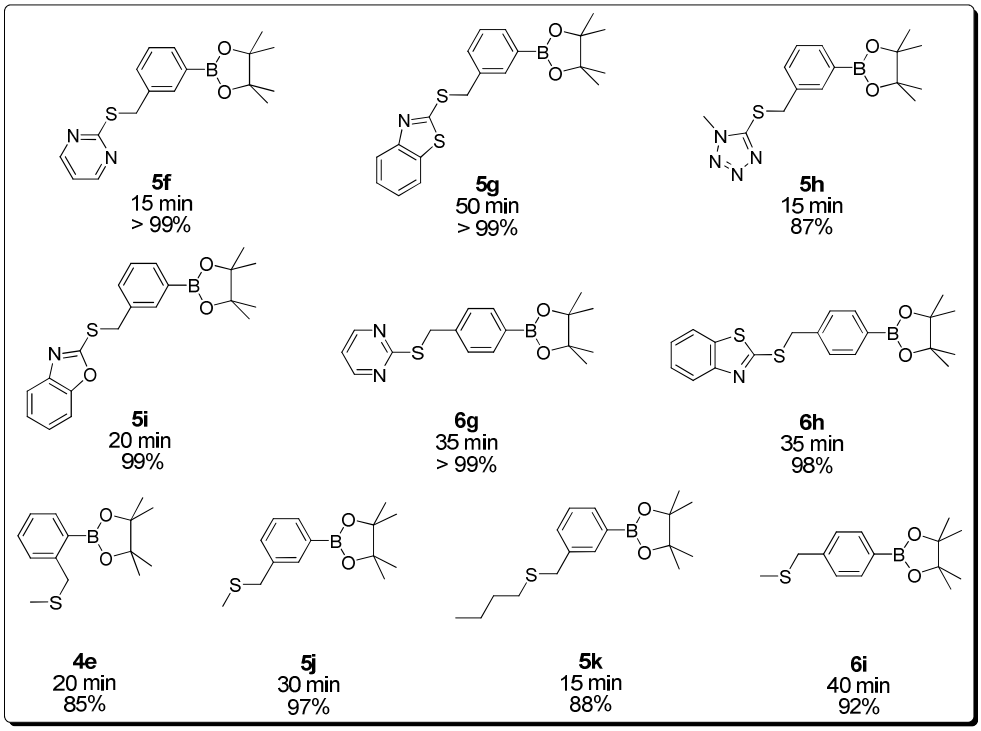


Figure 2.3. *S*-Nucleophiles.



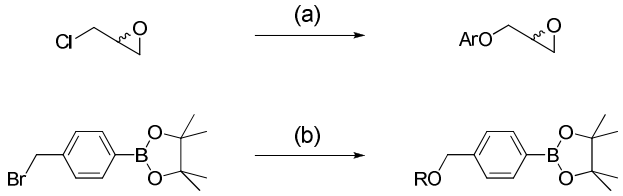
Reaction times and percentage yields given.

Figure 2.4. *S*-boronate library.

Hence, heteroaromatic thiols such as mercaptopyrimidine afforded the thioethers **5f** and **6g** in excellent yields using the standard conditions (Scheme 2.3). Aliphatic thiols were found to be unreactive when employing a supported base. However, when treated with sodium hydride prior to the microwave-mediated reaction, an excellent yield of thioether **5k** was recorded (Figure 2.4). Sodium thiomethoxide proved to be an effective nucleophile in the synthesis of **4e**, **5j** and **6i**.

2.2.3. Bromide displacement by oxygen nucleophiles

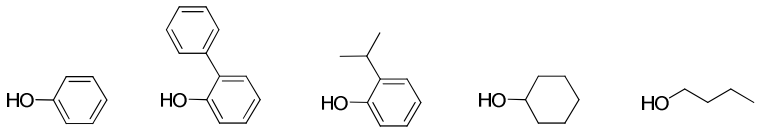
Phenol and alcohol derivatives were chosen as *O*-nucleophiles for related S_N2 displacements. The previous conditions employed (PS-NMM as base, THF, 150 ºC, microwave irradiation) were unsuccessful. Hence, a modified literature method was used to synthesise the ether-containing boronates (Scheme 2.4).[103]



Conditions: (a) ArOH (1 equiv.), RCl (1.5 equiv.), TBAB (0.1 equiv.), NaOH (1 equiv.), K_2CO_3 (4 equiv.), microwave irradiation (power 60 W), 110 °C, 5 min, 81% yield. (b) ROH, *n*BuNOH, THF (37-73% yield) or K_2CO_3, acetone, 50 °C (25-64% yield).

Scheme 2.4. Examples of S_N2 reactions using *O*-nucleophiles from the literature.

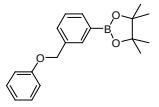
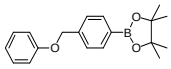
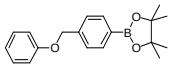
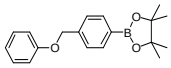
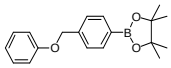
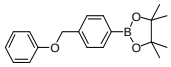
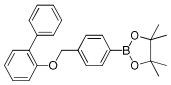
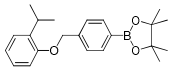
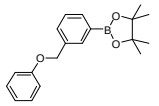
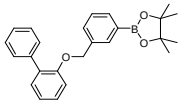
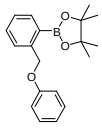
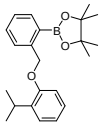
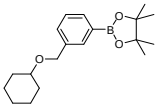
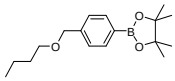
Phenols and alcohols (Figure 2.5) were chosen as *O*-Nucleophiles for the S_N2 reaction on **2** (Table 2.3).



3n **3o** **3p** **3q** **3r**

Figure 2.5. *O*-Nucleophiles.

Table 2.3. S_N2 reactions on compounds **2** with phenol and alcohol derivatives.

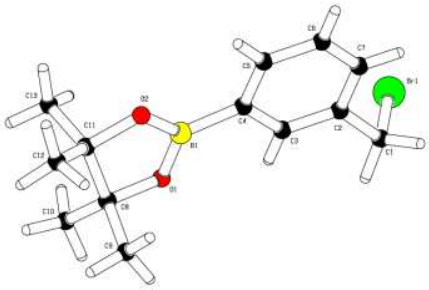
Entry	**3**	Temperature (ºC)	Time (min)	Base	Solvent	Product (**4**-**6**)		Yield (%)
1	**3n**	150	45	PS-NMM	THF		**5l**	–
2	**3n**	150	25	NaH	THF		**6j**	49[a]
3	**3n**	150	40	Na_2CO_3	THF		**6j**	–
4	**3n**	150	5	Na_2CO_3	–		**6j**	–
5	**3n**	120	5	K_2CO_3 NaOH TBAB	–		**6j**	> 99[b]
6	**3n**	120	5	K_2CO_3 NaOH TBAB	–		**6j**	91
7	**3o**	120	5	K_2CO_3 NaOH TBAB	–		**6k**	21
8	**3p**	120	5	K_2CO_3 NaOH TBAB	–		**6l**	24[a]
9	**3n**	110	5	K_2CO_3 NaOH TBAB	–		**5l**	42
10	**3o**	110	5	K_2CO_3 NaOH TBAB	–		**5m**	20[c]
11	**3n**	110	5	K_2CO_3 NaOH TBAB	–		**4f**	46
12	**3p**	110	5	K_2CO_3 NaOH TBAB	–		**4g**	44
13	**3q**	150	15	NaH	THF		**5n**	–[d]
14	**3r**	150	15	NaH	THF		**6m**	48

[a] Yield determined by ^{1}H NMR. [b] Use of excess bromide **2c**. [c] Corresponding boronic acid observed. [d] Complex mixture.

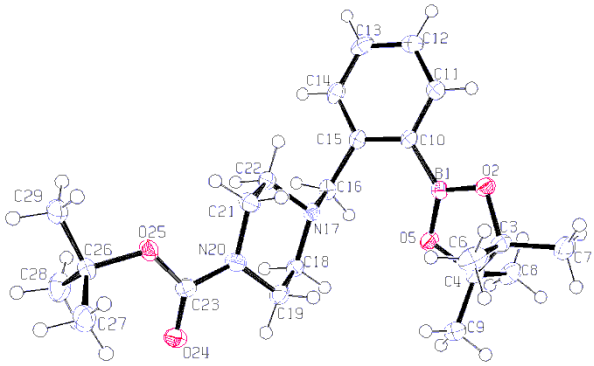
Sodium hydride was effective as base, although a combination of potassium carbonate, sodium hydroxide, and tetrabutylammonium bromide gave moderate to good yields (e.g. > 99% for **6j** and 46% yield for **4f**, Table 2.3, entries 5 and 11 respectively). Limited success was achieved with an aliphatic alcohol as nucleophile **6m**.

2.3. X-Ray diffraction analysis of boronic ester derivatives

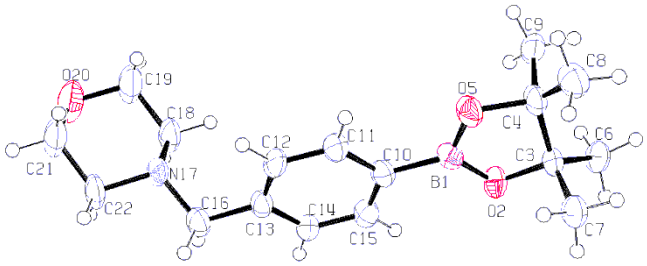
To investigate the structures of the arylboronates in the solid state, X-ray structure determinations on compounds **2b**, **5h**, **6g**, **4d**, and **6c** were carried out and are shown in Figure 2.6.



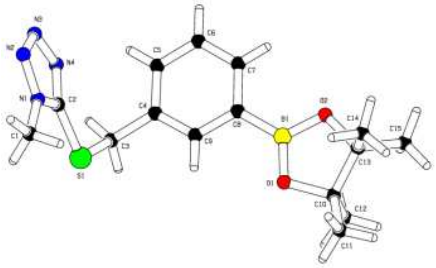
2b



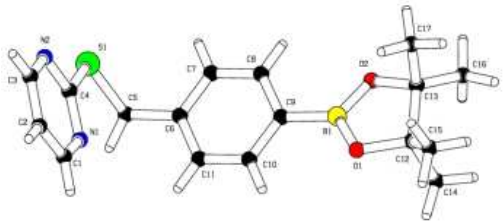
4d



6c



5h



6g

Figure 2.6. Crystal structures of **2b**, **4d**, **6c**, **5h** and **6g**.

The geometry of the boronate rings in all five molecules is very similar. The rings are twisted in every case, with the angle between the least-squares planes drawn through atoms B1, O2, and O3 and those drawn through atoms O2, C3 and C4 ranging from 21.4° to 24.5°.

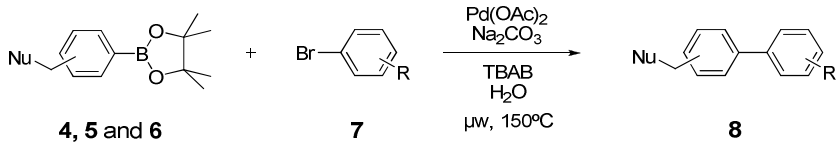
In three out of five cases, **2b**, **5h**, and **6c**, the least-squares plane drawn through atoms B1, O2, O3, and C10 is almost parallel to the plane of the phenyl ring C10-C15, with the angle between the least-squares planes ranging from 4.2° to 5.0°. This angle is larger in structures **4d** and **6g**: 21.3° and 16.3°, respectively. Structure **4d** has two substituents of the phenyl ring that are in ortho positions, and it is thought that the steric hindrance caused by this configuration is the reason for the twisting of the plane of the phenyl ring away from the B1, O2, O3, C10 plane. Structure **6g** is the only one of the five structures in which a π-π stacking interaction is formed, with the distance between the least-squares planes drawn through the two pyrimidine rings (C18, C20-C22, N19, N23) involved being 3.6 Å.

2.5. Suzuki-Miyaura cross-coupling reaction

After being functionalised by S_N2 reactions, some selected members of the arylboronate library were subjected to SM couplings under microwave conditions in order to obtain a biaryl library.

2.5.1. SM cross-coupling reaction catalysed by $Pd(OAc)_2$

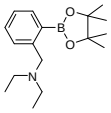
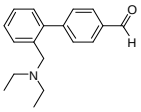
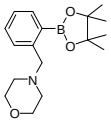
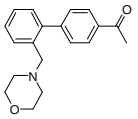
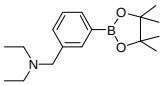
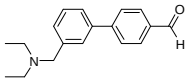
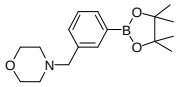
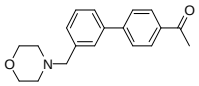
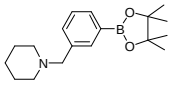
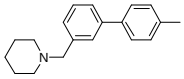
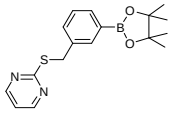
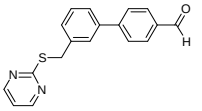
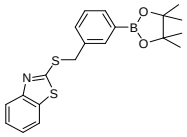
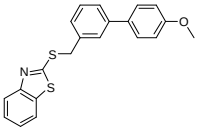
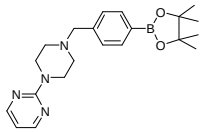
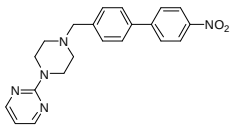
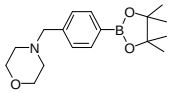
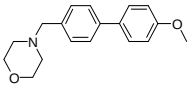
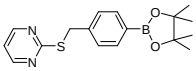
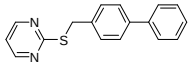
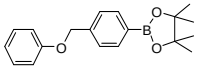
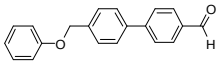
The conditions which have been adopted for these C-C bond forming reactions were those of Leadbeater *et al.*,[98b,104] which avoid organic solvents, employing water instead (cheap, readily available, non-toxic and non-flammable) and use palladium(II) acetate as precatalyst without an auxiliary ligand (Scheme 2.5). These conditions, in our hands, were used without any significant optimisation and they appeal due to their relevance to the twelve principles of green chemistry[105] with the use of catalytic conditions, atom economy and benign solvent.



Scheme 2.5. SM coupling catalysed by $Pd(OAc)_2$.

A range of aryl bromides (Figure 2.7) was chosen to participate as partner in the SM coupling reaction (Table 2.4).

Table 2.4. SM coupling reaction on compounds **4**, **5** and **6** catalysed by $Pd(OAc)_2$.

Entry	**4-6**		**7**	Time (min)	Product		Yield (%)
1		**4b**	**7a**	20		**8a**	–[a]
2		**4c**	**7b**	10		**8b**	–[b]
3		**5b**	**7a**	20		**8c**	72
4		**5c**	**7b**	10		**8d**	98
5		**5e**	**7h**	20		**8e**	37
6		**5f**	**7a**	20		**8f**	–[c]
7		**5g**	**7i**	10		**8g**	–[c]
8		**6a**	**7c**	10		**8h**	56
9		**6c**	**7i**	20		**8i**	49
10		**6g**	**7g**	20		**8j**	–[c]
11		**6j**	**7a**	10		**8k**	38

Conditions: Aryl halide (1.1 equiv), $Pd(OAc)_2$ (1 mol. %), Na_2CO_3 (3 equiv), TBAB (1 equiv) water (2 mL per 1 mmol of boronic ester), 150 °C, microwave irradiation (power max 300 W).
[a] Expected product, 4-bromobenzaldehyde and protodeborylation product observed. [b] Expected product and protodeborylation product observed. [c] Protodeborylation product and starting materials observed.

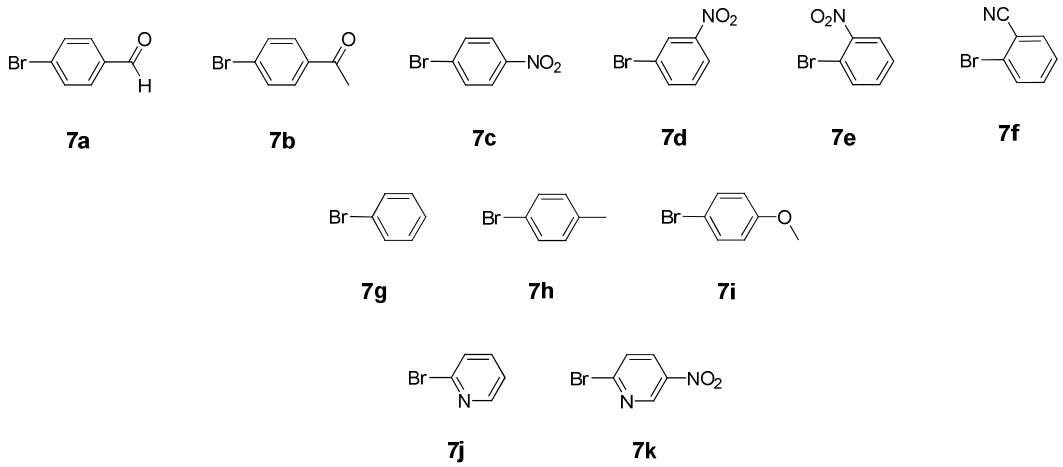


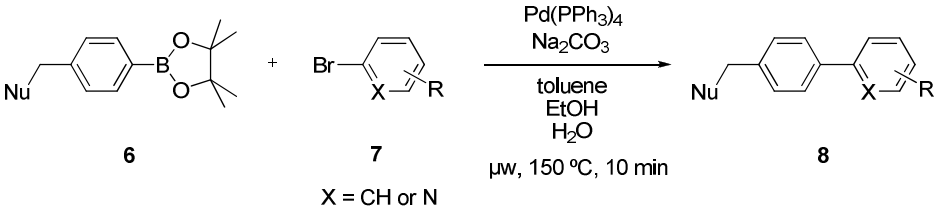
Figure 2.7. Aryl bromides **7**.

Good to excellent yields were obtained for the coupling of *N*-substituted *meta*- and *para*-ArBPin derivatives. Excellent yields were observed for aryl halide coupling partners substituted with electron withdrawing groups (e.g. 98% yield obtained for **8d**, Table 2.4, entry 4), as opposed to moderate yields for aryl halides substituted with electron rich groups (e.g. 37% yield obtained for **8e**, Table 2.4, entry 5).[106] An O-substituted compound gave a moderate yield of 38% of the expected biphenyl **8k** (Table 2.4, entry 11).

These coupling conditions do not appear to be appropriate for either *S*-substituted or *ortho*-substituted arylboronic acid pinacol ester coupling partners. In these two cases, protodeborylation products and/or starting materials were observed (Table 2.4, entries 1, 2, 6, 7 and 10). This issue will be further discussed in Chapter 4.

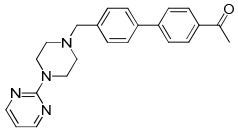
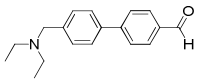
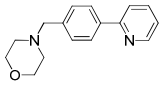
2.5.2. SM cross coupling reaction catalysed by $Pd(PPh_3)_4$

Tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) is a very efficient precatalyst for the SM cross-coupling process[107] and was effective in the presence of sodium carbonate as base, a toluene/ethanol/water solvent system,[108] under microwave conditions[109] to afford, *N*-substituted methylbiaryl derivatives (Scheme 2.6; Table 2.5).



Scheme 2.6. SM coupling reaction catalysed by $Pd(PPh_3)_4$ on compounds **6**.

Table 2.5. SM coupling reaction on compounds **6** catalysed by $Pd(PPh_3)_4$.

Entry[a]	**6**	**7**	Product (**8**)	Yield (%)
1	**6a**	**7b**	 **8l**	71
2	**6b**	**7a**	 **8m**	73
3	**6c**	**7j**	 **8n**	86

[a] Conditions: Aryl bromide (1.1 equiv.), $Pd(PPh_3)_4$ (3 mol. %), Na_2CO_3 (3 equiv.), toluene/ethanol/water 1:1:1, microwave irradiation (power max 300 W), 150 ºC, 10 min.

N-Substituted methylbiaryl derivatives were obtained in good yields.

2.5.3. Synthesis of precursors to valsartan

Finally, we investigated the coupling reaction in the synthesis of precursors to valsartan (Figure 2.8).

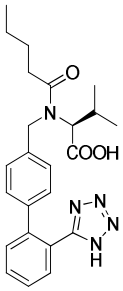
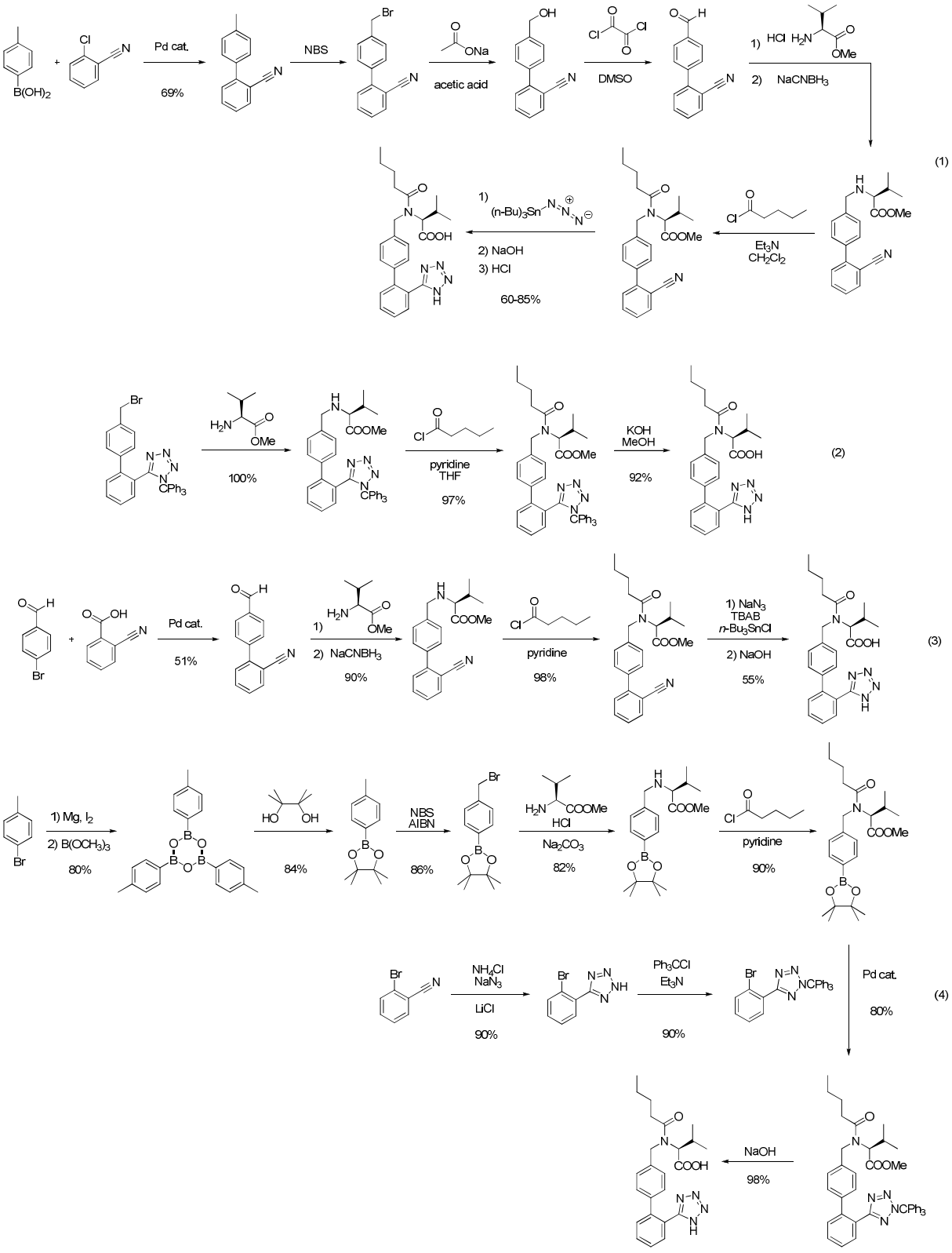


Figure 2.8. Valsartan.

Valsartan (CGP48933, (S)-*N*-Valeryl-*N*-{[2'-(*1H*-tetrazol-5-yl-)biphenyl-4-yl]methyl)-valine), is a non-peptide angiotensin II receptor antagonist disclosed by Ciba in 1994 (an antihypertensive).[110] Angiotensin II is a hormone involved in regulating blood pressure and fluid balance.[111] Many different synthetic pathways have been published towards valsartan (Scheme 2.7).[112]



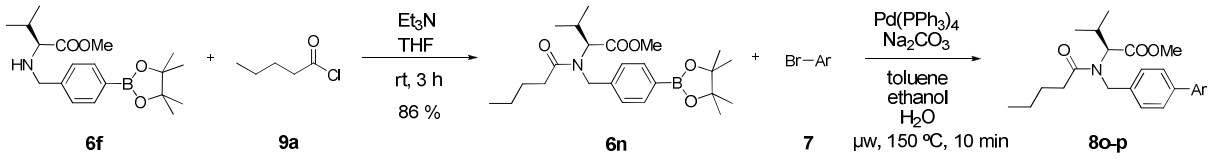
Scheme 2.7. Examples of reported synthetic pathways to valsartan.

The biphenyl moiety can be synthesised *via* a SM coupling (Scheme 2.7, (1) and (4)) or a decarboxylative biaryl coupling (Scheme 2.7, (3)). The amide part is generally inserted via reductive amination or S_N2 reaction to form the amine then coupled with valeroyl chloride to obtain the amide.

The tetrazole unit can be incorporated at the beginning of the synthesis, in a linear synthesis (Scheme 2.7, (2)) and in a convergent synthesis (Scheme 2.7, (4)), or at the very end of the synthesis (Scheme 2.7, (1) and (3)).

None of these syntheses were microwave-mediated so the chemistry previously developed can bring novelty and maybe better yields in the synthesis of this well-known drug.

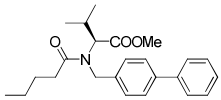
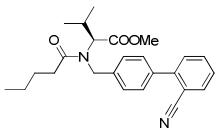
Compound **6f** (Scheme 2.8), previously synthesised *via* a microwave-mediated S_N2 reaction, is one of the numerous precursor in the synthesis of valsartan. **6f** was reacted with valeroyl chloride in CH_2Cl_2 with triethylamine to form the amide derivative **6n** which can then be coupled in a microwave-mediated SM reaction with an aryl halide to form the biphenyl motif leading to a precursor to valsartan (Scheme 2.8).



Scheme 2.8. Preparation of the derivative **6n** and its SM coupling.

The compound **6n** was obtained in good yield after a reaction time of 3 h and was then coupled in a SM reaction with bromobenzene (**7g**) and 2-bromobenzonitrile (**7f**) (Table 2.6).

Table 2.6. SM coupling of **6n**.

Entry	7	Product (8)		Yield (%)[a]
1	**7g**		**8o**	89
2	**7f**		**8p**	55

Conditions: Aryl bromide (1.1 equiv.), $Pd(PPh_3)_4$ (3 mol. %), Na_2CO_3 (3 equiv.), toluene/ethanol/water 1:1:1, microwave irradiation (power max 300 W), 150 °C, 10 min.

[a] Isolated yield.

The known compound **6n**, synthesised from **6f**, was coupled with both bromobenzene **7g** and 2-bromobenzonitrile **7f** in acceptable yields (Table 2.6). The biphenyl derivative **8p** is a known intermediate in the synthesis of valsartan. The ^{1}H NMR spectra of the compounds **6f**, **6n** and **8o**-**p** showed the presence of rotamers as noted in the literature.[112d] For **6n**, increasing the temperature (and changing the solvent to DMSO-d_6) led to coalescence (see Experimental Procedures). A previous synthesis of **8p** employed a reductive amination of 2-cyano-4'-formylbiphenyl, formed *via* a decarboxylative coupling, with a protected valine derivative followed by treatment with valeroyl chloride, in an overall yield of around 45% (Scheme 2.7 (3)). In this study, **8p** was synthesised *via* a S_N2 reaction, followed by an amide coupling and a SM reaction with an overall yield of 34% which is similar to the previously reported literature value.[112c,d] Analogue **6n** has been shown to undergo direct SM couplings with phenyltetrazole halides under thermal conditions. Attempts using protected and unprotected phenyltetrazole chlorides or bromides under microwave conditions gave unsatisfactory yields.

2.6. Conclusion

A library of *N*- and *S*-substituted arylboronates can be synthesised using MAOS coupled with supported reagents to ease work-up. *O*-Substituted analogues were formed under solventless conditions. SM coupling reactions of the arylboronates with aryl bromides led to an interesting library of biphenyls. Precursors of a well-known drug were synthesised using this MAOS chemistry. Further studies were aimed at expanding the scope of the SM coupling reaction involving the arylboronate library as coupling partners, especially in regard to the use of thioether or *ortho*-substituted ArBPin.

2.7. Experimental conditions and analytical methods

Reactions

To perform the different reactions, general reaction conditions were followed:
Anhydrous solvents were purchased from Aldrich or Fisher and used without being distilled. Sensitive product such as catalysts, bases and phosphines were purchased from Aldrich, Alfa Aesar, Novabiochem, Fisher and Strem. These were used without any further purification and were stored in a refridgerator at 4 °C. For anhydrous and inert reactions, the glassware needed was dried in an oven and several vacuum-nitrogen cycles were performed beforehand.

Microwave reactions were performed in a CEM Discover unit.

The TLC studies were performed using commercial glass or aluminium silica gel plates (60 Å, F_{254}). The mobile phase used was generally a solvent mixture, e.g. hexane/ethyl acetate and the visualisation was undertaken under UV light.

The purifications by chromatography on silica gel columns were carried out on an ISCO purification unit, Combi Flash RF 75 PSI, with Redisep flash silica gel columns (60 Å, 230-400 mesh, grade 9385). The mobile phase used was a generally a solvent mixture in variable proportions according to the product to separate.

Analyses

Purities of compounds were assessed by inspection of their ^{1}H and ^{13}C NMR spectra, high resolution mass specta and elemental analysis. Crystal structures were determined by X-ray crystallographic analyses.

NMR Spectroscopy

The samples were prepared in deuterated solvents, chloroform ($CDCl_3$) or DMSO-d_6 and analysed usinf a Jeol EX 270 MHz (^{1}H) and 75 MHz (^{13}C) or ECP 400 MHz (^{1}H) and 100 MHz (^{13}C) FT NMR Spectrometer, incorporating a Tuneable H-5/270 probe. The notations used are: δ: chemical shift (ppm), s: singlet; d: doublet; dd: doublet of doublet; t: triplet; q: quartet; m: multiplet; *J*: coupling constant (Hz).

Mass Spectrometry

The mass spectrometry was performed with a Finnigan AQA Thermo Quest spectrometer using an Agilent Technology auto sampler. Electro Spray Ionisation, positive ion, 20 V; detector: 650 V; probe temperature: 150 °C; gas: nitrogen; MeOH/water 7:3 with 0.1 % acid formic, flow: 200 $\mu L.min^{-1}$; injection: 10 μL; 1.20 $s.scan^{-1}$. The notation used is: m/z: mass-to-charge ratio.

The HRMS (high resolution mass spectrometry) was performed by the mass spectrometry service in Swansea, University of Wales.

The LC-MS analyses were performed with an Agilent 1100 fitted with a Waters XSelect C18 column.

Elemental Analyses

The elemental analyses, CHN, were performed on a CE Instruments apparatus Flash EA 1112 Series. The samples were weighted in tin capsules.

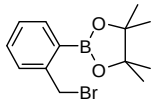
X-ray crystallography

X-ray analyses were carried out at the National Crystallography Services in Southampton, University of Southampton and Newcastle upon Tyne, Newcastle University (EPSRC units).

2.8. Experimental procedures and data

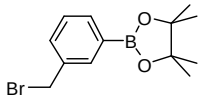
General procedure for the synthesis of (bromomethyl)phenylboronic acid pinacol esters 2:

2-(2-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2a**



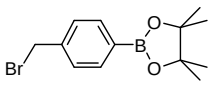
2-(Bromomethyl)phenylboronic acid (16.50 mmol, 3.55 g), pinacol (18.6 mmol, 2.20 g) and a spatula tip of magnesium sulphate were combined in anhydrous THF (50 mL) and left to stir at room temperature for 1 h. The mixture was filtered and concentrated under reduced pressure to afford 4.9 g of the expected product as a beige solid in > 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (d, 1H, *J* = 7.0 Hz), 7.36-7.41 (m, 2H), 7.23-7.30 (m, 1H), 4.91 (s, 2H), 1.36 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 144.2, 136.4, 131.3 (2C), 130.1, 127.6, 83.9 (2C), 33.9, 24.8 (4C). Elemental analysis CH (%) found C: 52.7, H: 6.3, calcd for $C_{13}H_{18}O_2BBr$ C: 52.6, H: 6.1.

2-(3-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2b**



White solid, 3.7 g, > 99% yield (12.40 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.81 (s, 1H), 7.72 (d, 1H, *J* = 7.3 Hz), 7.48 (d, 1H, *J* = 7.7 Hz), 7.34 (dd, 1H, *J* = 7.3 Hz), 4.49 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.1, 135.2, 134.8 (2C), 132.0, 128.3, 84.0 (2C), 33.5, 24.9 (4C). Elemental analysis CH (%) found C: 52.8, H: 6.1, calcd for $C_{13}H_{18}O_2BBr$ C: 52.6, H. 6.1.

2-(4-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2c**

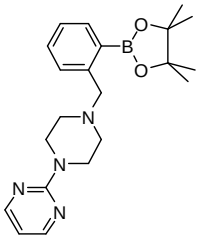


Beige solid, 5.2 g, > 99% yield (17.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, *J* = 8.1 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 4.47 (s, 2H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm):

140.6, 135.1 (2C), 128.3 (2C), 125.7, 83.9 (2C), 33.3, 24.8 (4C). Elemental analysis CH (%) found C: 52.4, H: 6.3, calcd for $C_{13}H_{18}O_2BBr$ C: 52.6, H. 6.1.

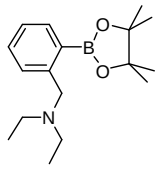
General procedure for the synthesis of 4, 5 and 6 using *N*- and aromatic *S*-nucleophiles:

2-(4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazin-1-yl) pyrimidine **4a**



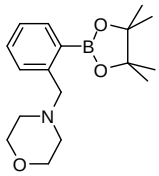
2a (0.50 mmol, 149 mg), **3a** (0.70 mmol, 0.1 mL), PS-NMM (0.75 mmol, 2.28 $mmolg^{-1}$, 329 mg) and THF (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 20 min. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to afford 229 mg of a yellow oil, which contained starting materials, observed by TLC and ^{1}H NMR analysis. The oil was treated with PS-trisamine (0.10 mmol, 3.34 $mmol.g^{-1}$, 30 mg) and PS-Isocyanate (0.20 mmol, 1.58 $mmol.g^{-1}$, 127 mg) in THF under microwave irradiation at 150 ºC for 5 minutes, cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to give 210 mg of the pure expected product as a beige solid in > 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22 (d, 2H, *J* = 4.8 Hz), 7.65 (d, 1H, *J* = 7.3 Hz), 7.20-7.35 (m, 3H), 6.40 (dd, 1H, *J* = 4.8 Hz), 3.68 (m, 6H), 2.42 (m, 4H), 1.28 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.7 (2C), 135.1, 130.9, 130.0, 129.3, 128.8, 126.5, 125.5, 109.7, 83.4 (2C), 62.1, 52.8 (2C), 43.5 (2C), 25.1 (4C). HRMS-ES (m/z) found 381.2462, calcd for $[C_{21}H_{29}O_2N_4B + H]^+$ = 381.2456. Elementary analysis CHN (%) found C: 66.0, H: 7.7, N: 14.3, calcd for $C_{21}H_{29}O_2N_4B$ C: 66.3, H: 7.7, N: 14.7.

N-Ethyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)ethanamine **4b**



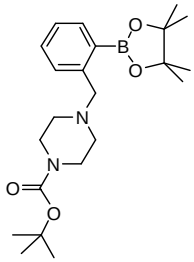
Yellow oil, 90 mg, 63 % yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.53 (d, 2H, *J* = 7.0 Hz), 7.30-7.10 (m, 2H), 3.66 (m, 2H), 3.56 (q, 4H, *J* = 7.0 Hz), 1.27 (s, 12H), 0.96 (t, 6H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 133.7, 129.3, 127.2 (2C), 126.3 (2C), 82.6 (2C), 57.7, 46.0 (2C), 25.3 (4C), 10.5 (2C). HRMS-ES (m/z) found 290.2282, calcd for $[C_{17}H_{28}O_2NB + H]^+$ 290.2286.

4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine **4c**



Yellow oil, 306 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (d, 1H, *J* = 7.0 Hz), 7.40-7.20 (m, 3H), 3.69 (m, 6H), 2.45 (m, 4 H), 1.35 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.2 (2C), 130.1, 129.7, 128.8, 126.6, 83.5 (2C), 66.8 (2C), 62.3, 53.3 (2C), 24.9 (4C). HRMS-ES (m/z) found 304.2080, calcd for $[C_{17}H_{26}O_3NB + H]^+$ 304.2079.

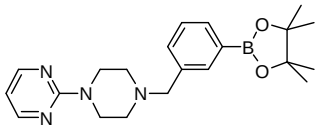
tert-Butyl 4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine-1-carboxylate **4d**



Yellow solid, 408 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (d, 1H, *J* = 7.0Hz), 7.40-7.20 (m, 3H), 3.69 (s, 2H), 3.36 (m, 4H), 2.37 (m, 4H), 1.42 (s, 9H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 135.3, 130.3, 129.8, 129.0, 128.7, 119.3, 83.5 (2C), 79.6, 61.5 (2C), 52.5, 43.5 (2C), 28.4 (3C), 24.9 (4C). HRMS-ES (m/z) found

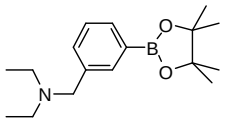
403.2762, calcd for $[C_{22}H_{35}O_4N_2B + H]^+$ 403.2763. Elemental analysis CHN (%) found C: 63.7, H: 8.7, N: 6.7, calcd for $C_{22}H_{35}O_4N_2B.0.19\ CH_2Cl_2$ C: 63.7, H: 8.5, N: 6.7.

2-(4-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazin-1-yl)pyrimidine **5a**



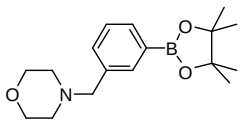
White solid, 320 mg, > 99% yield (0.84 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (d, 2H, *J* = 4.8 Hz), 7.70 (d + s, 2H), 7.48 (d, 1H, *J* = 7.3 Hz), 7.33 (dd, 1H, *J* = 7.7 Hz), 6.44 (dd, 1H, *J* = 4.8 Hz), 3.81 (m, 4H), 3.54 (s, 2H), 2.49 (m, 4H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.7, 157.7 (2C), 141.1, 135.6 (2C), 133.7, 132.3, 127.8, 109.7, 83.8 (2C), 63.0 (2C), 52.9, 43.6 (2C), 24.9 (4C). HRMS-ES (m/z) found 381.2459, calcd for $[C_{21}H_{29}O_2N_4B + H]^+$ 381.2456. Elemental analysis CHN (%) found C: 65.9, H: 7.6, N: 14.3, calcd for $C_{21}H_{29}O_2N_4B.0.035\ CH_2Cl_2$ C: 65.9, H: 7.7, N: 14.6.

N-Ethyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)ethanamine **5b**



Yellow oil, 290 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.66 (d + s, 2H), 7.55 (d, 1H, *J* = 7.7 Hz), 7.30 (dd, 1H, *J* = 7.3 Hz), 3.65 (s, 2H), 2.59 (q, 4H, *J* = 7.3 Hz), 1.28 (s, 12H), 1.08 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.6 (2C), 134.0, 132.6, 128.0 (2C), 83.8 (2C), 57.0, 46.5 (2C), 24.8 (4C), 10.9 (2C). HRMS-ES (m/z) found 290.2283, calcd for $[C_{17}H_{28}O_2NB + H]^+$ 290.2286.

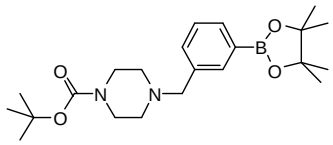
4-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine **5c**



Pale yellow oil, 296 mg, 98% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.69 (m, 2H), 7.46 (d, 1H, *J* = 7.34 Hz), 7.32 (dd, 1H, *J* = 7.7 Hz), 3.70 (m, 4H), 3.50 (s, 2H), 2.44 (m, 4H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.7 (2C), 133.8, 132.3, 127.8 (2C), 83.8

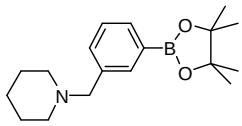
(2C), 66.9 (2C), 63.3, 53.5 (2C), 24.9 (4C). HRMS-ES (m/z) found 304.2083, calcd for $[C_{17}H_{26}O_3NB + H]^+$ 304.2079.

tert-Butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine-1-carboxylate **5d**



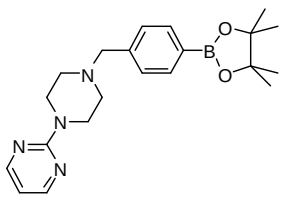
Beige solid, 301 mg, 75% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.64 (d + s, 2H), 7.38 (d, 1H, *J* = 7.7 Hz), 7.26 (dd, 1H, *J* = 7.7 Hz), 3.44 (s, 2H), 3.35 (m, 4H), 2.31 (m, 4H), 1.38 (s, 9H), 1.28 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.3, 134.6, 133.1 (2C), 131.2, 129.7, 125.2, 81.3 (2C), 77.0, 60.5 (2C), 50.4, 41.2 (2C), 25.9 (3C), 22.4 (4C). HRMS-ES (m/z) found 403.2763, calcd for $[C_{22}H_{35}O_4N_2B + H]^+$ 403.2763.

1-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine **5e**



Yellow semi-solid, 335 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (d, 1H, *J* = 7.3 Hz), 7.64 (s + d, 2H), 7.36 (dd, 1H, J_1 = 7.7 Hz), 3.71 (s, 2H), 2.59 (m, 4H), 1.74 (m, 4H), 1.50 (m, 2H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 136.3 (2C), 134.6, 133.3, 128.1 (2C), 83.9 (2C), 62.7, 53.7 (2C), 24.9 (4C), 23.4 (2C), 22.5. HRMS-ES (m/z) found 301.2319, calcd for $[C_{18}H_{28}O_2N^{10}B + H]^+$ 301.2322.

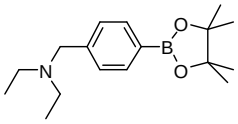
2-(4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazin-1-yl)pyrimidine **6a**



Beige solid, 352 mg, 93% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (d, 2H, *J* = 4.8 Hz), 7.78 (d, 2H, *J* = 7.7 Hz), 7.38 (d, 2H, *J* = 7.7 Hz), 6.46 (dd, 1H, *J* = 4.8 Hz), 3.87 (m, 4H), 3.64 (m, 2H), 2.56 (m, 4H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.5, 157.9

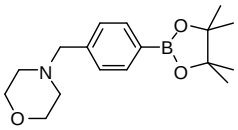
(2C), 135.5, 134.9 (2C), 133.0, 129.0 (2C), 109.9, 83.8 (2C), 62.9, 52.7 (2C), 43.4 (2C), 24.9 (4C). HRMS-ES (m/z) found 381.2460, calcd for $[C_{21}H_{29}O_2N_4B + H]^+$ 381.2456. Elemental analysis CH (%) found C: 62.7, H: 7.4, calcd for $C_{21}H_{29}O_2N_4B.0.35\ CH_2Cl_2$ C: 62.5, H: 7.3.

N-Ethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)ethanamine **6b**



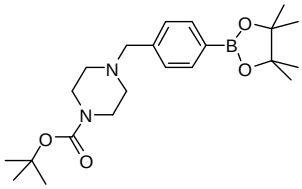
Beige solid, 288 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (d, 2H, *J* = 7.7 Hz), 7.48 (m, 2H), 3.90 (m, 2H), 2.80 (m, 4H), 1.32 (s, 12H), 1.25 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.5, 135.2, 134.8, 132.1, 129.4, 128.5, 83.9 (2C), 56.5, 46.5 (2C), 24.6 (4C), 10.2 (2C). HRMS-ES (m/z) found 290.2287, calcd for $[C_{17}H_{28}O_2NB + H]^+$ 290.2286. Elemental analysis CH (%) found C: 60.8, H: 8.6, calcd for $C_{17}H_{28}O_2NB.0.45\ CHCl_3$ C: 61.1, H: 8.4.

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine **6c**



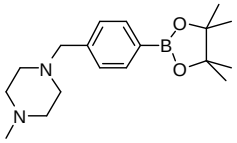
Beige solid, 299 mg, 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (d, 2H, *J* = 8.1 Hz), 7.32 (d, 2H, *J* = 7.7 Hz), 3.69 (m, 4H), 3.51 (s, 2H), 2.43 (m, 4H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 134.8 (3C), 128.6 (3C), 83.7 (2C), 66.9 (2C), 63.4, 53.6 (2C), 24.8 (4C). HRMS-ES (m/z) found 304.2076 m/z, calcd for $[C_{17}H_{26}O_3NB + H]^+$ 304.2079. Elemental analysis CHN (%) found C: 66.1, H: 8.4, N: 4.4, calcd for $C_{17}H_{26}O_3NB.0.09\ CH_2Cl_2$ C: 66.0, H: 8.5, N: 4.5.

tert-Butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine-1-carboxylate **6d**



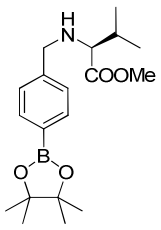
Beige solid, 380 mg, 95% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (d, 2H, *J* = 8.1 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 3.53 (s, 2H), 3.42 (m, 4H), 2.38 (m, 4H), 1.43 (s, 9H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.7, 134.8 (3C), 128.6 (3C), 83.7 (2C), 79.6, 63.0 (2C), 52.8, 43.6 (2C), 28.4 (3C), 24.8 (4C). HRMS-ES (m/z) found 403.2763, calcd for $[C_{22}H_{35}O_4N_2B + H]^+$ 403.2763. Elemental analysis CHN (%) found C: 63.5, H: 8.5, N: 6.7, calcd for $C_{22}H_{35}O_4N_2B.0.2\ CH_2Cl_2$ C: 63.6; H: 8.5; N: 6.7.

1-Methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine **6e**



Beige solid, 353 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (d, 2H, *J* = 8.1 Hz), 7.29 (d, 2H, *J* = 7.7 Hz), 3.57 (s, 2H), 2.70-2.90 (m, 8H), 2.56 (s, 3H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 134.9 (3C), 128.5 (3C), 83.8 (2C), 62.3, 54.3 (2C), 50.8 (2C), 44.5, 24.6 (4C). HRMS-ES (m/z) found 317.2402, calcd for $[C_{18}H_{29}O_2N_2B + H]^+$ 317.2395.

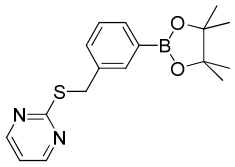
(*S*)-Methyl 3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylamino)-butanoate **6f**



2c (0.89 mmol, 264 mg), *L*-valinemethyl ester (1.79 mmol, 234 mg), PS-NMM (1.00 mmol, 250 mg) and THF (3 mL) were mixed in a microwave vial and stirred under microwave

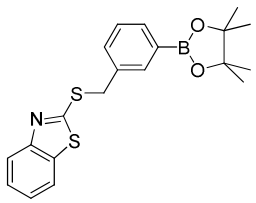
irradiation at 130 °C for 2 h. The mixture was cooled to room temperature, filtered and concentrated to give 417 mg of a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc from 0% to 20% of EtOAc, to give 222 mg of the expected product as a pale yellow oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, *J* = 7.7 Hz), 7.35 (d, 2H, *J* = 8.1 Hz), 3.86 (d, 1H, *J* = 13.2 Hz), 3.72 (s, 3H), 3.58 (d, 1H, *J* = 13.2 Hz), 2.99 (d, 1H, *J* = 6.2 Hz), 1.90 (m, 1H), 1.80 (m, 1H), 1.34 (s, 12H), 0.93 (2d, 6H, *J* = 7.0 Hz).). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.8, 143.3, 134.8 (3C), 127.6 (2C), 83.7 (2C), 66.4, 52.5, 51.4, 31.7, 24.8 (4C), 19.3, 18.6. HRMS-ES (m/z) found 347.2378, calcd for $[C_{19}H_{30}O_4NB + H]^+$ 347.2377.

2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)pyrimidine **5f**



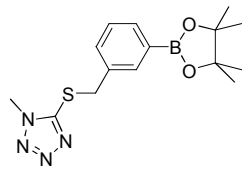
Yellow oil, 165 mg, > 99% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.50 (d, 2H, *J* = 5.1 Hz), 7.85 (s, 1H), 7.67 (d, 1H, *J* = 7.3 Hz), 7.55 (d, 1H, *J* = 7.7 Hz), 7.29 (dd, 1H, *J* = 7.4 Hz), 6.94 (dd, 1H, *J* = 4.8 Hz), 4.41 (s, 2H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.2 (3C), 136.6, 135.5, 133.6 (2C), 132.0, 127.9, 116.5, 83.8 (2C), 35.2, 24.9 (4C). HRMS-ES (m/z) found 329.1495, calcd for $[C_{17}H_{21}O_2N_2BS + H]^+$ 329.1490.

2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)benzo[d]thiazole **5g**



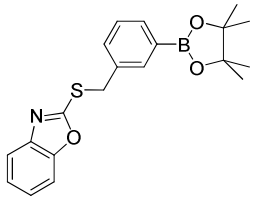
Yellow oil, 307 mg, > 99% yield (0.80 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.88 (s + d, 2H), 7.71 (dd, 2H, J_1 = 6.6 Hz, J_2 = 7.7 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.40 (m, 1H), 7.26-7.35 (m, 2H), 4.59 (s, 2H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.5, 135.3, 134.1 (2C), 132.0 (2C), 128.1, 126.0 (2C), 124.2 (2C), 121.5, 121.0, 83.9 (2C), 37.7, 24.9 (4C). HRMS-ES (m/z) found 384.1258, calcd for $[C_{20}H_{22}O_2NBS_2 + H]^+$ 384.1258. Elemental analysis CHN (%) found C: 61.8, H: 5.6, N: 3.5, calcd for $C_{20}H_{22}O_2NBS_2$.0.08 CH_2Cl_2 C: 61.8, H: 5.7, N: 3.6.

1-Methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)-1*H*-tetrazole **5h**



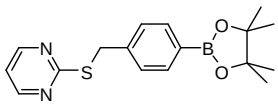
Beige solid, 290 mg, 87% yield (0.90 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (s, 1H), 7.72 (d, 1H, J = 7.3 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz), 7.30 (dd, 1H, J = 7.3 Hz), 4.52 (s, 2H), 3.79 (s, 3H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.2 (2C), 134.8, 134.6, 131.9, 128.3 (2C), 84.0 (2C), 37.8, 33.3, 24.8 (4C). HRMS-ES (m/z) found 333.1551, calcd for $[C_{15}H_{21}O_2N_4BS + H]^+$ 333.1551. Elemental analysis CHN (%) found C: 53.9, H: 6.3, N: 17.1, calcd for $C_{15}H_{21}O_2N_4BS$ C: 54.2, H: 6.4, N: 16.9.

2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)benzo[d]oxazole **5i**



Beige solid, 362 mg, 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.86 (s, 1H), 7.72 (d, 1H, J = 7.3 Hz), 7.60 (m, 1H), 7.56 (d, 1H, J = 7.3 Hz), 7.43 (m, 1H), 7.33 (dd, 1H, J = 7.3 Hz), 7.24 (2dd, 2H, J_1 = 1.5 Hz, J_2 = 7.3 Hz), 4.56 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 164.5, 151.8 (2C), 141.9, 135.4, 135.0, 134.3, 132.0, 128.2, 124.3, 123.9, 118.5, 109.9, 83.9 (2C), 36.5, 24.9 (4C). HRMS-ES (m/z) found 367.1522, calcd for $[C_{10}H_{22}O_3N^{10}BS + H]^+$ 367.1523. Elemental analysis CHN (%) found C: 63.8, H: 6.0, N: 3.8, calcd for $C_{10}H_{22}O_3NBS.0.15\ CH_2Cl_2$ C: 63.7, H: 5.9, N: 3.7.

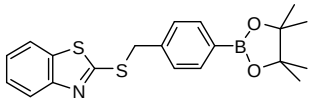
2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)pyrimidine **6g**



Beige solid, 334 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.49 (d, 2H, J = 4.8 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.1 Hz), 6.94 (dd, 1H, J = 5.1 Hz), 4.40 (s, 2H), 1.31 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.9, 157.2 (2C), 140.7, 135.2, 134.9

(2C), 128.4 (2C), 116.6, 83.7 (2C), 35.3, 24.8 (4C). HRMS-ES (m/z) found 329.1488, calcd for $[C_{17}H_{21}O_2N_2BS + H]^+$ 329.1490. Elemental analysis CHN (%) found C: 62.2, H: 6.4, N: 8.3, calcd for $C_{17}H_{21}O_2N_2BS$ C: 62.2, H: 6.5, N: 8.5.

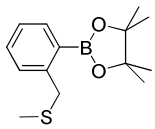
2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylthio)benzo[d]thiazole **6h**



Yellow oil, 379 mg, 98% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.89 (d, 1H, *J* = 8.1 Hz), 7.74 (m, 3H), 7.45 (d, 2H, *J* = 8.1 Hz), 7.39 (d, 1H, *J* = 7.0 Hz), 7.28 (m, 1H), 4.60 (s, 2H), 1.31 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 139.1, 135.1 (4C), 128.4 (4C), 126.1, 124.4, 121.4, 121.0, 83.8 (2C), 37.9, 24.8 (4C). HRMS-ES (m/z) found 384.1262, calcd for $[C_{20}H_{22}O_2NBS_2 + H]^+$ 384.1258.

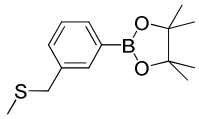
General procedure for the synthesis of 4, 5 and 6 using sodium thiomethoxide as nucleophile:

4,4,5,5-Tetramethyl-2-(2-(methylthiomethyl)phenyl)-1,3,2-dioxaborolane **4e**



2a (1.00 mmol, 297 mg), **3l** (1.00 mmol, 70 mg) and THF (3 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 20 minutes. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 225 mg of the expected product as a pale yellow oil in 85% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 1H, *J* = 7.3 Hz), 7.34 (dd, 1H, *J* = 8.4 Hz), 7.18-7.30 (m, 2H), 3.97 (s, 2H), 1.93 (s, 3H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 145.3, 136.1, 130.5, 129.4, 126.1, 83.6 (2C), 37.4, 24.9 (4C), 14.7.

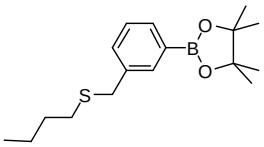
4,4,5,5-Tetramethyl-2-(3-(methylthiomethyl)phenyl)-1,3,2-dioxaborolane **5j**



Yellow oil, 258 mg, 97% yield (1.01 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 7.69 (d, 1H, *J* = 8.3 Hz), 7.43 (d, 1H, *J* = 7.4 Hz), 7.33 (dd, 1H, *J* = 7.4 Hz), 3.68 (s, 2H), 1.99 (s, 3H), 1.39 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.6, 135.2, 133.4, 131.8 (2C), 127.9, 83.8 (2C), 38.2, 24.9 (4C), 14.9.

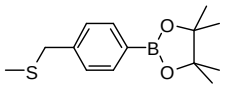
General procedure for the synthesis of 4, 5 and 6 using alkylthiols or alcohols nucleophiles:

2-(3-(Butylthiomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **5k**



3m (1.00 mmol, 107 µL, 0.842 g.mL^{-1}), sodium hydride (1.00 mmol, 40 mg) and THF (2 mL) were mixed in a microwave vial and stirred at room temperature for 15 minutes then a solution of **2b** (1.00 mmol, 297 mg) in THF (2 mL) was added. The mixture was stirred under microwave irradiation at 150 ºC for 15 minutes. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 270 mg of the expected product as a pale yellow liquid in 88% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.65 (d, 1H, *J* = 7.3 Hz), 7.42 (d, 1H, *J* = 7.7 Hz), 7.30 (dd, 1H, *J* = 7.3 Hz), 3.69 (s, 2H), 2.39 (t, 2H, *J* = 7.3 Hz), 1.53 (m, 2H), 1.36 (m, 5H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.9, 135.1 (2C), 133.3, 131.7, 127.9, 83.8 (2C), 36.2, 31.3, 31.1, 24.9 (4C), 22.0, 13.6.

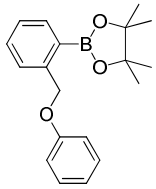
4,4,5,5-Tetramethyl-2-(4-(methylthiomethyl)phenyl)-1,3,2-dioxaborolane **6i**



Beige solid, 243 mg, 92% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (d, 2H, *J* = 8.1 Hz), 7.29 (d, 2H, *J* = 8.1 Hz), 3.66 (s, 2H), 1.95 (s, 3H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 141.5 (2C), 134.9 (2C), 128.2 (2C), 83.8 (2C), 38.3, 24.8 (4C), 14.8. Elemental analysis CH (%) found C: 63.4, H: 7.9, calcd for $C_{14}H_{21}O_2BS$ C: 63.7, H: 8.0.

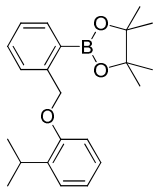
General procedure for the synthesis of 4, 5 and 6 using phenols nucleophiles:

4,4,5,5-Tetramethyl-2-(2-(phenoxymethyl)phenyl)-1,3,2-dioxaborolane **4f**



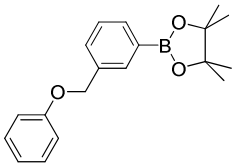
2a (1.00 mmol, 298 mg), phenol **3n** (1.03 mmol, 97 mg), sodium hydroxide (1.13 mmol, 45 mg), potassium carbonate (4.00 mmol, 552 mg) and tetrabutylammonium bromide (0.10 mmol, 32 mg) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 110 ºC for 5 minutes. The mixture was cooled to room temperature, diluted with EtOAc and water, extracted with EtOAc, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 269 mg of a brown oil. The crude product was purified by chromatography on silica gel, hexane/EtOAc 9:1, to give 144 mg of the expected product as a yellow oil in 46% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (d, 1H, *J* = 7.3 Hz), 7.53 (d, 1H, *J* = 7.7 Hz), 7.44 (dd, 1H, J_1 = 1.5 Hz, J_2 = 7.3 Hz), 7.34-7.23 (m, 3H), 6.97 (d, 2H, *J* = 8.8 Hz), 6.91 (d, 1H, *J* = 7.3 Hz), 5.34 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.1, 143.4, 136.4, 135.9, 131.1, 129.3 (2C), 127.4, 127.0, 120.5, 114.8 (2C), 83.7 (2C), 69.4, 24.8 (4C).

2-(2-((2-Isopropylphenoxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **4g**



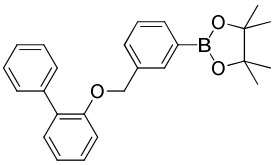
Yellow oil, 119 mg, 34% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (dd, 1H, J_1 = 1.1 Hz and J_2 = 7.3 Hz), 7.58 (d, 1H, J = 7.7 Hz), 7.45 (dd, 1H, J_1 = 1.5 Hz and J_2 = 7.7 Hz), 7.28 (dd, 1H, J = 7.3 Hz), 7.22 (d, 1H, J = 7.7 Hz), 7.12 (dd, 1H, J_1 = 1.8 Hz and J_2 = 7.7 Hz), 6.91 (m, 2H), 5.37 (s, 2H), 3.42 (sept, 1H, J = 7.0 Hz), 1.30 (s, 12H), 1.22 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.2, 144.2, 137.2, 135.9 (2C), 131.2, 126.6 (2C), 126.4, 125.9, 120.5, 111.8, 83.7 (2C), 69.4, 26.8, 24.9 (4C), 22.7 (2C).

4,4,5,5-Tetramethyl-2-(3-(phenoxymethyl)phenyl)-1,3,2-dioxaborolane **5l**



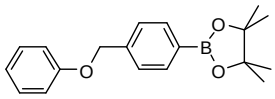
Yellow solid, 107 mg, 32% yield (1.01 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (s, 1H), 7.76 (d, 1H, J = 7.3 Hz), 7.54 (d, 1H, J = 7.7 Hz), 7.38 (dd, 1H, J = 7.3 Hz), 7.24-7.30 (m, 2H), 6.91-6.98 (m, 3H), 5.04 (s, 2H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.9, 136.3, 134.4, 133.9, 131.9, 130.5, 129.4 (2C), 128.0, 120.9, 114.9 (2C), 83.9 (2C), 70.0, 24.9 (4C). Elemental analysis CH (%) found C: 72.1, H: 7.4, calcd for $C_{19}H_{23}O_3B.0.09\ CH_2Cl_2$ C: 72.1, H: 7.4.

2-(3-((Biphenyl-2-yloxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **5m**



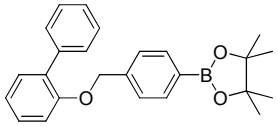
Yellow oil, 70 mg, 20% yield calculated by ^{1}H NMR (mixture with its boronic acid derivative) (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.30-7.50 (m, 8H), 7.20-7.30 (m), 6.95-7.00 (m, 4H), 5.15 (s, 2H), 4.54 (s, 0.5H), 1.33 (s, 5H).

4,4,5,5-Tetramethyl-2-(4-(phenoxymethyl)phenyl)-1,3,2-dioxaborolane **6j**



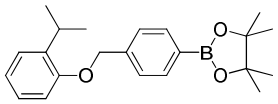
Yellow semi-solid oil, 284 mg, 91% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (d, 2H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 7.7 Hz), 7.18-7.30 (m, 1H), 6.80-6.96 (m, 4H), 5.08 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.7, 140.3, 135.0 (2C), 129.9, 129.5 (2C), 126.4 (2C), 121.0, 114.9 (2C), 183.8 (2C), 69.8, 24.9 (4C).

2-(4-((Biphenyl-2-yloxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **6k**



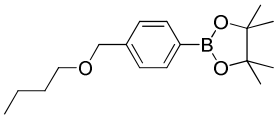
Yellow oil, 82 mg, 21% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (d, 2H, *J* = 8.1 Hz), 7.56 (d, 2H, *J* = 8.1 Hz), 7.42-7.21 (m, 7H), 7.06-6.96 (m, 2H), 5.08 (s, 2H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 155.5, 140.4, 138.5, 134.9 (2C), 131.0, 129.6 (2C), 128.5, 128.4, 127.9 (3C), 126.9, 125.9 (2C), 121.3, 113.2, 83.8 (2C), 70.3, 24.8 (4C).

2-(4-((2-Isopropylphenoxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **6l**



Yellow solid, 169 mg, 24% yield calculated by ^{1}H NMR (mixture 1:1 with **3p**) (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.82 (d, 2H, *J* = 8.1 Hz), 7.43 (d, 2H, *J* = 8.1 Hz), 7.20 (m, 2H), 7.15-7.00 (m, 2H), 6.80-6.95 (m, 3H), 6.72 (d, 1H, *J* = 7.3 Hz), 5.08 (s, 2H), 4.64 (s, 1H), 3.39 (q, 1H, *J* = 7.0 Hz), 3.20 (q, 1H, *J* = 7.0 Hz), 1.33 (s, 12H), 1.20 (2d, 6H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 155.9, 140.7, 137.4, 135.0 (2C), 128.5, 126.5, 126.3 (2C), 126.1, 120.9, 111.7, 83.8 (2C), 69.9, 26.9, 24.9 (4C), 22.6 (2C). Elemental analysis CH (%) found C: 75.7, H: 8.3, calcd for $C_{22}H_{29}O_3B$ C: 75.0, H: 8.3.

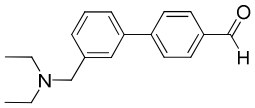
2-(4-(Butoxymethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **6m**



The crude product was purified by chromatography on silica gel, CH_2Cl_2, to give 139 mg of the pure expected product as a colourless oil in 48% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 2H, *J* = 8.1 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 4.50 (s, 2H), 3.43 (t, 2H, *J* = 6.6 Hz), 1.60 (m, 2H), 1.35 (m, 2H), 1.32 (s, 12H), 0.89 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 142.0, 134.8 (3C), 126.7 (2C), 83.7 (2C), 72.7, 70.2, 31.8, 24.9 (4C), 19.4, 13.9.

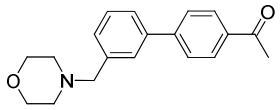
General procedure for the SM coupling reaction catalysed by $Pd(OAc)_2$:

3'-((Diethylamino)methyl)biphenyl-4-carbaldehyde **8c**



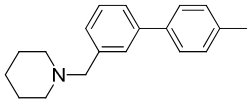
4b (0.56 mmol, 161 mg), **7b** (0.56 mmol, 104 mg), palladium(II) acetate (0.01 mmol, 1 mg), sodium carbonate (1.12 mmol, 119 mg), tetrabutylammonium bromide (0.56 mmol, 181 mg) and water (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 20 minutes (2 times 10 min). The mixture was cooled and diluted with EtOAc and water. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 132 of a yellow oil which was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 108 mg of the pure expected product as a yellow oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 10.04 (s, 1H), 7.93 (d, 2H, *J* = 8.8 Hz), 7.75 (d, 2H, *J* = 8.4 Hz), 7.61 (s, 1H), 7.49 (dd, 1H, J_1 = 1.8 Hz, J_2 = 6.6 Hz), 7.40 (m, 2H), 3.62 (s, 2H), 2.54 (q, 4H, *J* = 7.0 Hz), 1.04 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 192.0, 147.4, 141.3, 139.6, 135.1, 130.2 (2C), 129.0, 128.8, 127.7 (3C), 125.8, 57.5, 46.8 (2C), 11.8 (2C). HRMS-ES (m/z) found 268.1701, calcd for $[C_{18}H_{21}ON + H]^+$ 268.1696.

1-(3'-(Morpholinomethyl)biphenyl-4-yl)ethanone **8d**



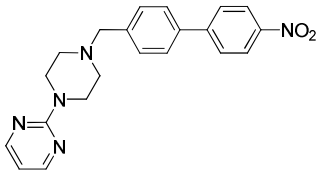
The crude product was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 150 mg of the pure expected product as a yellow oil in 98% yield (0.52 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.02 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.58 (s, 1H), 7.51 (dd, 1H, *J* = 7.3 Hz), 7.41 (dd, 1H, *J* = 7.7 Hz), 7.35 (d, 1H, *J* = 7.3 Hz), 3.71 (m, 4H), 3.56 (s, 2H), 2.62 (s, 3H), 2.47 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 197.7, 145.7, 139.9, 138.7, 135.9, 129.1, 128.9 (3C), 128.0, 127.3 (2C), 126.1, 67.0 (2C), 63.4, 53.7 (2C), 26.7. HRMS-ES (m/z) found 296.1644, calcd for $[C_{19}H_{21}O_2N + H]^+$ 296.1645.

1-((4'-Methylbiphenyl-3-yl)methyl)piperidine **8e**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 7:3-1:1, to give 53 mg of the pure expected product as a yellow oil in 37% yield (0.54 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.47-7.52 (s + d, 3H, J_d = 8.1 Hz), 7.44 (d, 1H, *J* = 7.7 Hz), 7.34 (dd, 1H, *J* = 7.7 Hz), 7.26 (d, 1H), 7.23 (d, 2H), 3.52 (s, 2H), 2.38 (m, 7H), 1.56 (m, 4H), 1.42 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.9, 139.0, 138.4, 136.9, 129.4 (2C), 128.5, 127.9, 127.8, 127.0 (2C), 125.5, 63.9, 54.9 (2C), 26.0 (2C), 24.4, 21.1. HRMS-ES (m/z) found 266.1907, calcd for $[C_{19}H_{23}N + H]^+$ 266.1903.

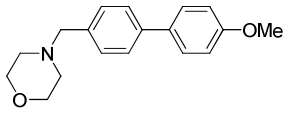
2-(4-((4'-Nitrobiphenyl-4-yl)methyl)piperazin-1-yl)pyrimidine **8h**



Brown solid, 105 mg, 56% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (2d, 4H), 7.73 (d, 2H, *J* = 8.8 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 6.46 (dd, 1H, *J* = 4.8 Hz), 3.83 (m, 4H), 3.59 (s, 2H), 2.52 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.7, 157.7 (2C), 147.4, 147.0, 139.2 (2C), 129.8 (2C), 127.6 (2C), 127.3 (2C), 124.1 (2C), 109.8,

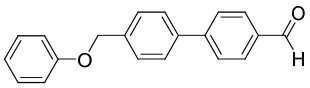
62.6, 53.0 (2C), 43.6 (2C). HRMS-ES (m/z) found 376.1770, calcd for $[C_{21}H_{21}O_2N_5 + H]^+$ 376.1768. Elemental analysis CH (%) found C: 65.2, H: 5.7, calcd for $C_{21}H_{21}O_2N_5$.0.17 CH_2Cl_2 C: 65.2, H: 5.5.

4-((4'-Methoxybiphenyl-4-yl)methyl)morpholine **8i**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 1:1, to give 77 mg of an off white solid (mixture expected product and boronic pinacol ester 9:1; calculated yield by ^{1}H NMR 49%) (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.50 (d, 2H, *J* = 8.8 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 7.35 (d, 2H, *J* = 8.1 Hz), 6.95 (d, 2H, *J* = 8.8 Hz), 3.83 (s, 3H), 3.69 (m, 4H), 3.51 (s, 2H), 2.44 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.1, 136.1, 134.7, 133.4, 129.6 (2C), 128.2 (2C), 126.5 (2C), 114.2 (2C), 67.0, 63.4, 63.1, 55.3, 53.6, 24.8. MS-ES (m/z) found 284.2, calcd for $[C_{18}H_{21}O_2N + H]^+$ 284.4.

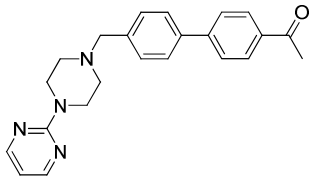
4'-(Phenoxymethyl)biphenyl-4-carbaldehyde **8k**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 8:2-6:4, to give 30 mg of the pure expected product as an off white solid in 38% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.04 (s, 1H), 7.94 (d, 2H, *J* = 8.4 Hz), 7.74 (d, 2H, *J* = 8.1 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 2H, *J* = 8.1 Hz), 7.28 (m, 3H), 6.98 (d, 2H, *J* = 8.8 Hz), 5.11 (s, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.8, 158.7, 146.8, 139.4, 137.6, 135.3, 130.3 (2C), 129.6 (2C), 128.1 (2C), 127.7 (2C), 127.6 (2C), 121.1, 114.9 (2C), 69.5. Elemental analysis CH (%) found C: 82.8, H: 5.7, calcd for $C_{20}H_{16}O_2$.0.07 EtOAc C: 82.7, H: 5.7.

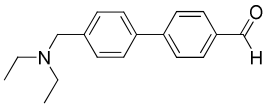
General procedure for the SM coupling reaction catalysed by $Pd(PPh_3)_4$:

1-[4'-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-biphenyl-4-yl]-ethanone **8l**



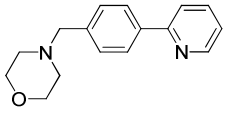
6a (0.30 mmol, 115 mg), **7b** (0.35 mmol, 70 mg), tetrakis(triphenylphosphine)palladium(0) (0.01 mmol, 12 mg), sodium carbonate (0.90 mmol, 95 mg), toluene (1 mL), ethanol (1 mL) and water (1 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 10 min then cooled to room temperature, diluted with EtOAc and water and extracted with EtOAc. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a crude product, which was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 1:1, to give 79 mg of the pure expected product as a white solid in 71% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.31 (d, 2H, *J* = 4.8 Hz), 8.04 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.61 (d, 2H, *J* = 8.1 Hz), 7.46 (d, 2H, *J* = 8.4 Hz), 6.48 (dd, 1H, *J* = 4.8 Hz), 3.85 (m, 4H), 3.61 (s, 2H), 2.65 (s, 3H), 2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm):197.7, 161.7, 157.7 (2C), 145.5, 138.8, 138.2, 135.8, 129.8 (2C), 128.9 (2C), 127.2 (2C), 127.1 (2C), 109.8, 62.7, 53.0 (2C), 43.7 (2C), 26.6. HRMS-ES (m/z) found 373.2023, calcd for $[C_{23}H_{24}ON_4 + H]^+$ 373.2023. Elemental analysis CHN (%) found C: 73.6, H: 6.4, N: 14.2, calcd for $C_{23}H_{24}O_1N_4$.0.34 EtOAc C: 73.6, H: 6.7, N: 14.3.

4'-((Diethylamino)methyl)biphenyl-4-carbaldehyde **8m**



The crude product was purified by chromatography on silica gel, DCM/MeOH 95:5-9:1, to give 140 mg of the pure expected product as a yellow oil in 73% yield (0.72 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.05 (s, 1H), 7.95 (d, 2H, *J* = 8.3 Hz), 7.76 (d, 2H, *J* = 8.3 Hz), 7.59 (d, 2H, *J* = 8.3 Hz), 7.45 (d, 2H, *J* = 8.3 Hz), 3.62 (s, 2H), 2.56 (q, 4H, *J* = 7.3 Hz), 1.07 (t, 6H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 192.0, 147.1, 140.7, 138.0, 135.0, 130.3 (2C), 129.5 (2C), 127.5 (2C), 127.1 (2C), 57.2, 46.8 (2C), 11.8 (2C). HRMS-ES (m/z) found 268.1699, calcd for $[C_{18}H_{21}ON + H]^+$ 268.1696.

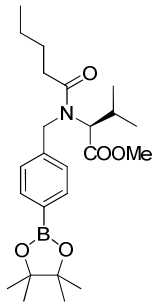
4-(4-Pyridin-2-yl-benzyl)-morpholine **8n**



The crude product was purified by chromatography on silica gel, DCM/MeOH 95:5-9:1, to give 70 mg of the pure expected product as an off white solid in 86% yield (0.32 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.69 (m, 1H), 7.95 (d, 2H, *J* = 8.3 Hz), 7.73 (m, 2H), 7.44 (d, 2H, *J* = 7.9 Hz), 7.20-7.25 (m, 1H), 3.73 (m, 4H), 3.56 (s, 2H), 2.48 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.2, 149.7, 138.7, 138.4, 136.7, 129.6 (2C), 126.8 (2C), 122.0, 120.4, 67.0 (2C), 63.1, 53.6 (2C). HRMS-ES (m/z) found 255.1491, calcd for $[C_{16}H_{18}ON_2 + H]^+$ 255.1492. Elemental analysis CHN (%) found C: 74.8, H: 7.1, N: 10.8, calcd for $C_{16}H_{18}O_1N_2$.0.04 CH_2Cl_2 C: 74.8, H: 7.1, N: 10.9.

General procedure for the amide coupling reaction:

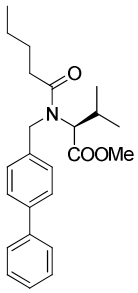
(*S*)-Methyl 3-methyl-2-(*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pentan-amido)butanoate **6n**



6f (2.06 mmol, 714 mg), **9a** (4.12 mmol, 0.995 g.mL^{-1}, 0.50 mL), triethylamine (2.10 mmol, 0.726 g.mL^{-1}, 0.31 mL) and THF (10 mL) were mixed and stirred at room temperature for 3 h. THF was removed under reduced pressure and the mixture was diluted with EtOAc, washed with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated to give 1.006 g of a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc from 0% to 20% of EtOAc to give 763 mg of the pure expected product as a yellow oil in 86% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 and 7.69 (2d, 2H, *J* = 8.1 Hz), 7.17 and 7.14 (2d, 2H, *J* = 8.1 Hz), 5.00 and 4.91 (2d, 1H, J_{d1} = 10.4 Hz, J_{d2} = 15.3 Hz), 4.63 (s, 1.5H), 4.32 (d, 0.25H, *J* = 15.4 Hz), 4.03 (d, 0.25H, *J* = 10.6 Hz), 3.44 and 3.37 (2s, 3H), 2.65-2.11 (m, 3H), 1.79-1.53 (m, 2H), 1.49-1.17 (m + s, 14H), 0.96 (d, 3H, *J* = 6.2 Hz), 0.88 (d, 3H, *J* = 7.0 Hz), 0.84 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR

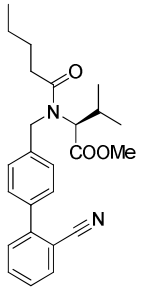
($CDCl_3$) δ (ppm): 174.7, 174.1, 171.0, 170.3, 141.3, 140.5, 135.1, 134.6 (2C), 126.8, 125.0 (2C), 83.8 (2C), 66.0, 61.6, 51.7, 51.6, 48.3, 45.8, 33.3, 27.8, 27.6, 27.4, 24.8 (4C), 22.4, 19.8, 18.7, 13.8. ^{1}H NMR (DMSO-d_6, 373 K) δ (ppm): 7.63 (d, 2H, *J* = 7.4 Hz), 7.19 (d, 2H, *J* = 7.5 Hz), 4.68 (d, 1H, *J* = 17.1 Hz), 4.53 (m, 2H), 3.44 (s, 3H), 2.50-2.18 (m + t, 3H, J_t = 7.3 Hz), 1.52 (m, 2H), 1.31 (m + s, 14H), 0.94 (d, 3H, *J* = 6.5 Hz), 0.89 (t, 3H, *J* = 7.3 Hz), 0.82 (d, 3H, *J* = 6.9 Hz). HRMS-ES (m/z) found 431.2947, calcd for $[C_{24}H_{38}O_5N^{10}B + H]^+$ 431.2952.

(*S*)-Methyl 2-(*N*-(biphenyl-4-ylmethyl)pentanamido)-3-methylbutanoate **8o**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 126 mg of the pure expected product as a pale yellow oil in 89% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.61-7.52 (m, 3H), 7.52-7.30 (m, 4H), 7.30-7.18 (m, 2H), 4.97 (2d, 1H, *J* = 10.3 Hz), 4.66 (s, 1.3H), 4.29 (d, 0.3H, *J* = 15.3 Hz), 4.05 (d, 0.3H, *J* = 10.9 Hz), 3.45 and 3.36 (2s, 3H), 2.67-2.20 (m, 3H), 1.82-1.54 (m, 2H), 1.50-1.20 (m, 2H), 0.99 (d, 3H, *J* = 6.5 Hz), 0.95-0.80 (d + t, 6H, J_d = 7.0 Hz, J_t = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.6, 171.2, 140.5, 140.2, 136.4, 128.8, 128.7, 128.1, 127.4, 127.3, 127.0 (2C), 126.8, 126.4, 65.9, 61.8, 51.6, 48.2, 45.4, 33.4, 27.9, 27.4, 22.5, 19.9, 18.8, 13.8. HRMS-ES (m/z) found 382.2375, calcd for $[C_{24}H_{31}O_3N_1 + H]^+$ 382.2377.

(*S*)-Methyl 2-(*N*-((2'-cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate **8p**



Yellow oil, 85 mg, 55% yield (0.38 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79-7.71 (m, 1H), 7.69-7.58 (m, 1H), 7.58-7.38 (m, 4H), 7.34-7.25 (m, 2H), 5.08 (d, 0.3H, *J* = 15.3 Hz), 4.98 (d, 0.6H, *J* = 10.3 Hz), 4.69 (s, 1H), 4.27 (d, 0.3H, *J* = 15.3 Hz), 4.06 (d, 0.3H, *J* = 10.9 Hz), 3.45 and 3.37 (2s, 3H), 2.70-2.20 (m, 3H), 1.85-1.53 (m, 2H), 1.52-1.20 (m, 2H), 0.99 (d, 3H, *J* = 6.5 Hz), 0.96-0.81 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.6, 171.1, 144.8, 138.8, 138.1, 137.2, 136.6, 133.8, 132.8, 130.0, 129.0, 128.5, 128.0, 127.7, 127.4, 126.3, 118.6, 111.3, 65.9, 61.7, 52.0, 51.7, 48.1, 45.3, 33.4, 27.9, 27.5, 22.5, 19.9, 18.7, 13.9. HRMS-ES (m/z) found 407.2337, calcd for $[C_{25}H_{30}O_3N_2 + H]^+$ 407.2329. The data are in accordance with the literature.[112d]

Chapter 3: Synthesis of a (piperazin-1-ylmethyl)biaryl library

3.1. Introduction

An arylboronate library was previously synthesised (compounds **4**, **5** and **6**) using microwave-mediated S_N2 reactions of (bromomethyl)phenylboronic acid pinacol esters **2** with a range of *N*-, *S*- and *O*-nucleophiles **3**. These underwent further reactions to afford a library of biaryls.[55b] In certain instances, Boc-piperazine (**3d**) was used as an *N*-nucleophile and the arylboronic esters obtained (**4d**, **5d** and **6d**) were found to be interesting and useful precursors for the synthesis of a wide range of highly functionalised biaryls, because the protecting group on the piperazine could be easily removed to liberate an amine, allowing further functionalisation prior to, or following, a Suzuki-Miyaura cross-coupling with a variety of aryl halides.

The incorporation of a piperazine motif into a molecule is interesting from a medicinal chemistry point of view since it produces analogues that have a lower lipophilicity and this enhances aqueous solubility.[113] Hence, piperazine is found in many drugs with a broad scope of actions such as antidepressants,[114] antihistamines,[115] antiretrovirals,[116] anti-Parkinson's,[117] antianginals[118] and antipsychotics[119] amongst others (Figure 3.1).[120,121,122]

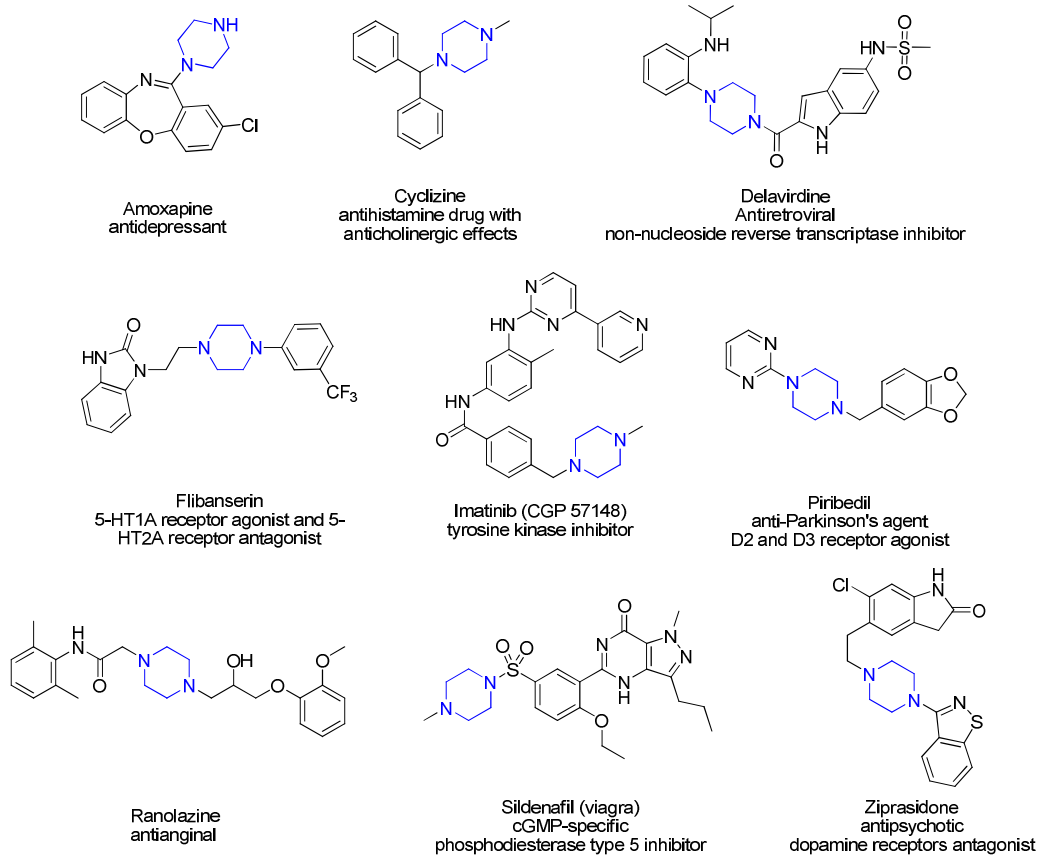
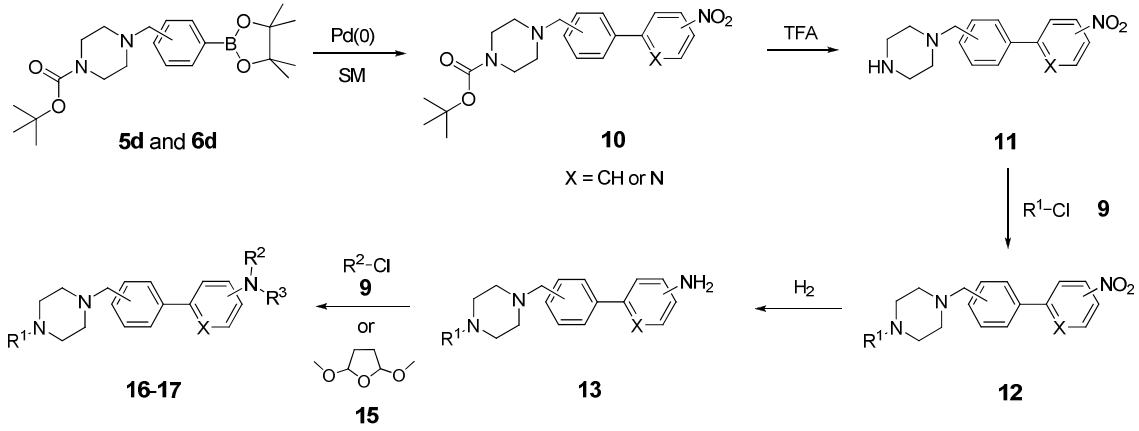


Figure 3.1. Examples of drugs containing the piperazine motif (in blue).

A Boc-protected (piperazin-1-ylmethyl)biaryl library has been synthesised from (Boc-piperazin-1-ylmethyl)phenylboronic acid pinacol esters **5d** and **6d** *via* a microwave-mediated Suzuki-Miyaura (SM) coupling with aryl bromides *viz.* 1-bromo-, 2-, 3- or 4-nitrobenzene or 2-bromo-5-nitropyridine. Judicial removal of the protecting group on the piperazine, or facile reduction of the nitro group on the biaryl system, enabled the manipulation of two points of functionality in order to diversify the scope of the resulting biaryl library (Scheme 3.1).



Scheme 3.1. Synthetic sequence to the (piperazin-1-ylmethy)biaryl library.

3.2. SM cross-coupling reaction

The SM coupling was achieved employing Leadbeater's conditions (previously used) with palladium(II) acetate as precatalyst and 1-bromo-, 2-, 3- and 4-nitrobenzene or 2-bromo-5-nitropyridine as aryl bromides **7** (Figure 3.2) under microwave irradiation (μw) on compounds **5d** and **6d** (Scheme 3.2).

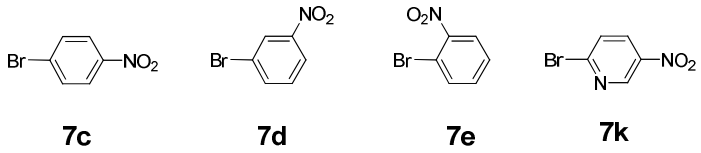
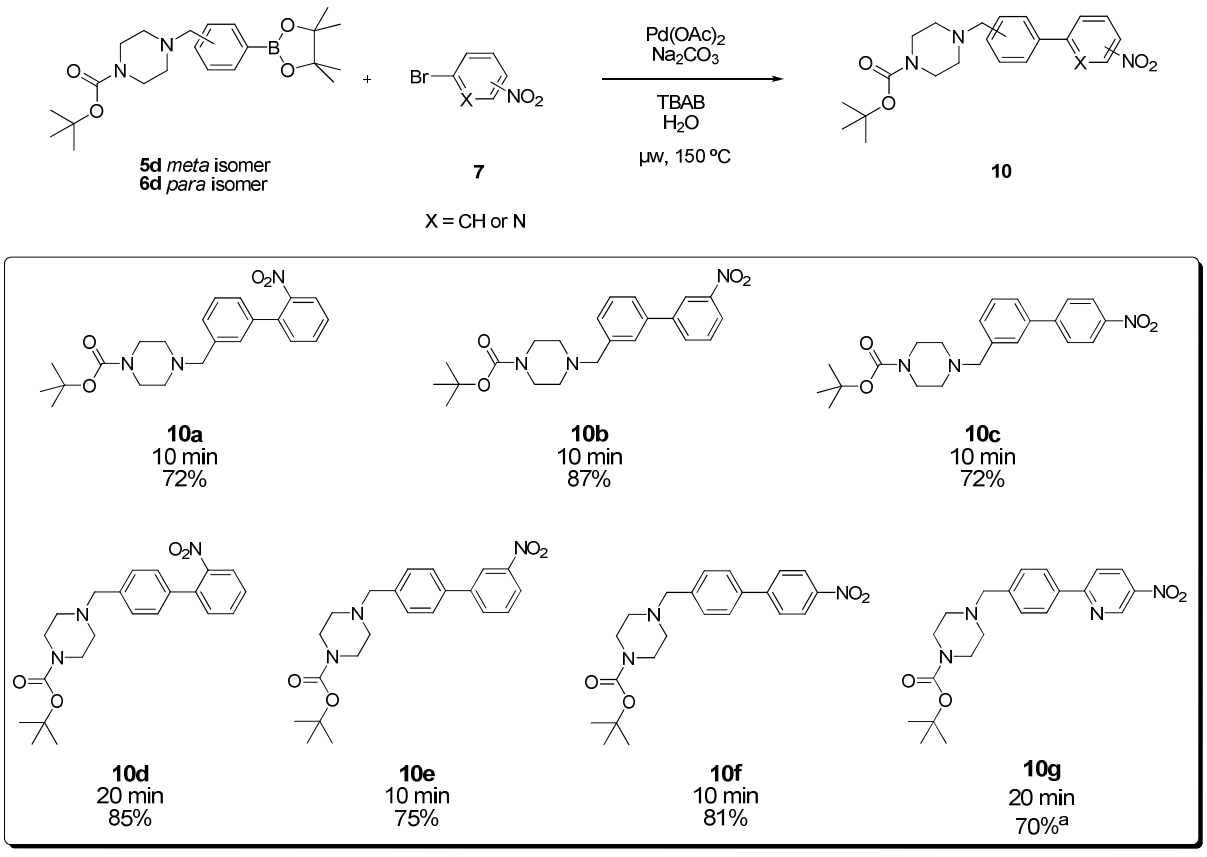


Figure 3.2. Aryl bromides **7** used in the SM coupling of **5d** and **6d**.



Reaction times and yields after purification by chromatography given.
[a] $Pd(PPh_3)_4$ used as precatalyst (3 mol %), Na_2CO_3 (3 equiv.) in toluene/EtOH/H_2O 1:1:1 (3 mL per mmol of boronate), 150 °C, microwave irradiation (maximum power 300 W).

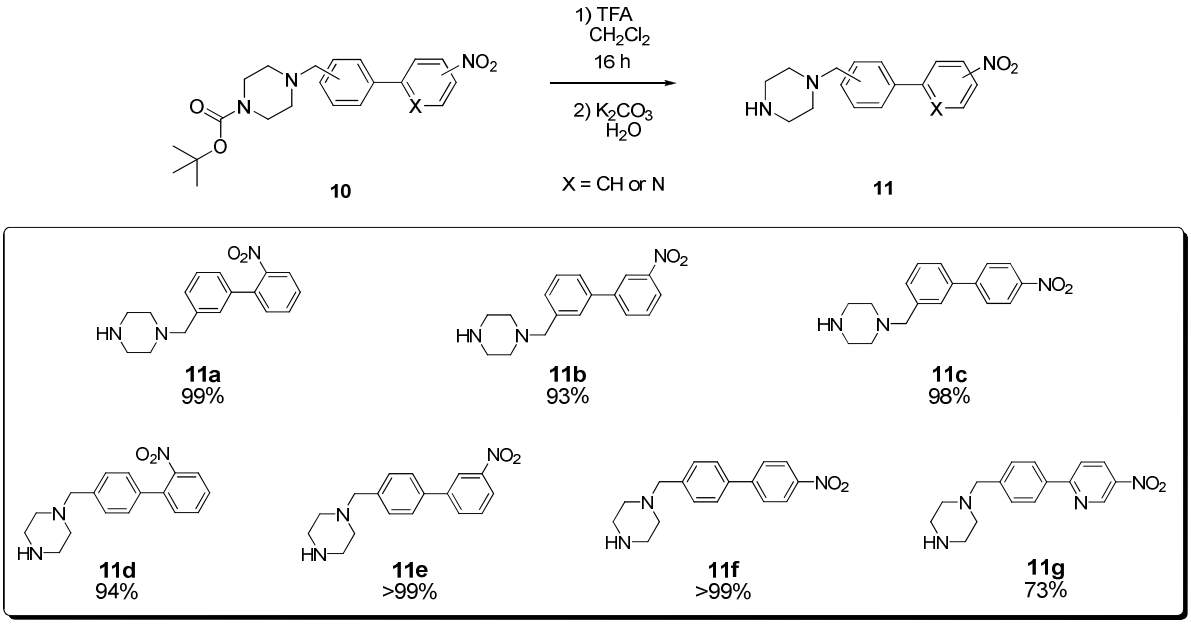
Scheme 3.2. SM reactions on compounds **5d** and **6d** and biaryls **10** library.

As found previously, the expected biaryls were obtained with good yields, within 10 to 20 minutes (Scheme 3.2).

Once the biphenyl unit had been synthesised, the functionalisation reactions could be initiated.

3.3. Cleavage of the Boc group

Boc group cleavage was achieved with trifluoroacetic acid (TFA) in dichloromethane at room temperature within 2 hours or overnight, followed by a basic work-up to liberate the free amine (Scheme 3.3).[123]



Reaction yield given without further purification.

Scheme 3.3. Cleavage of the Boc group in **10** and biaryls **11** library.

The pure deprotected amine was obtained after a basic wash in very good yields. Hence, no further purification was required.

3.4. Piperazine functionalisation

The piperazine motif in compounds **11** was functionalised by reaction with acid and sulphonyl chlorides **9** (Figure 3.2) (1.1 equiv.) in CH_2Cl_2 at room temperature in the presence of a supported base (PS-NMM) (Scheme 3.4).

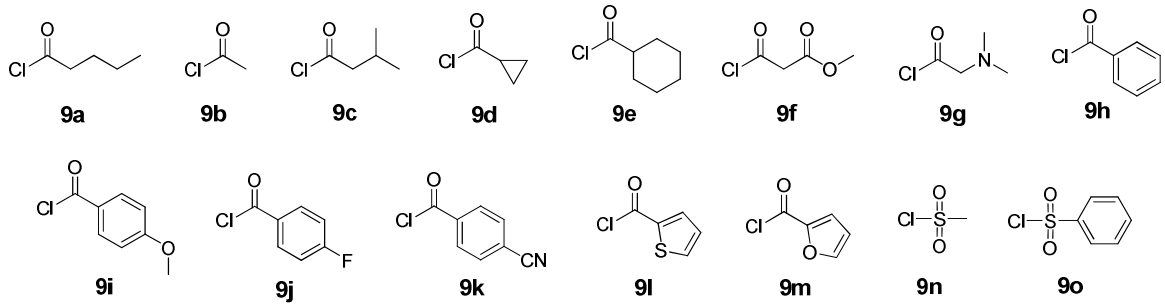
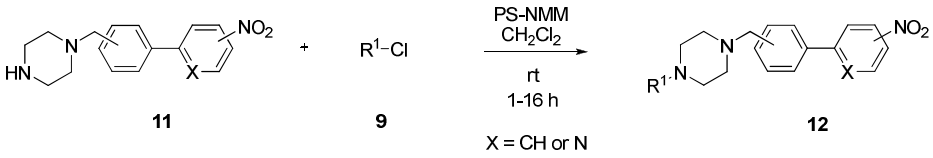
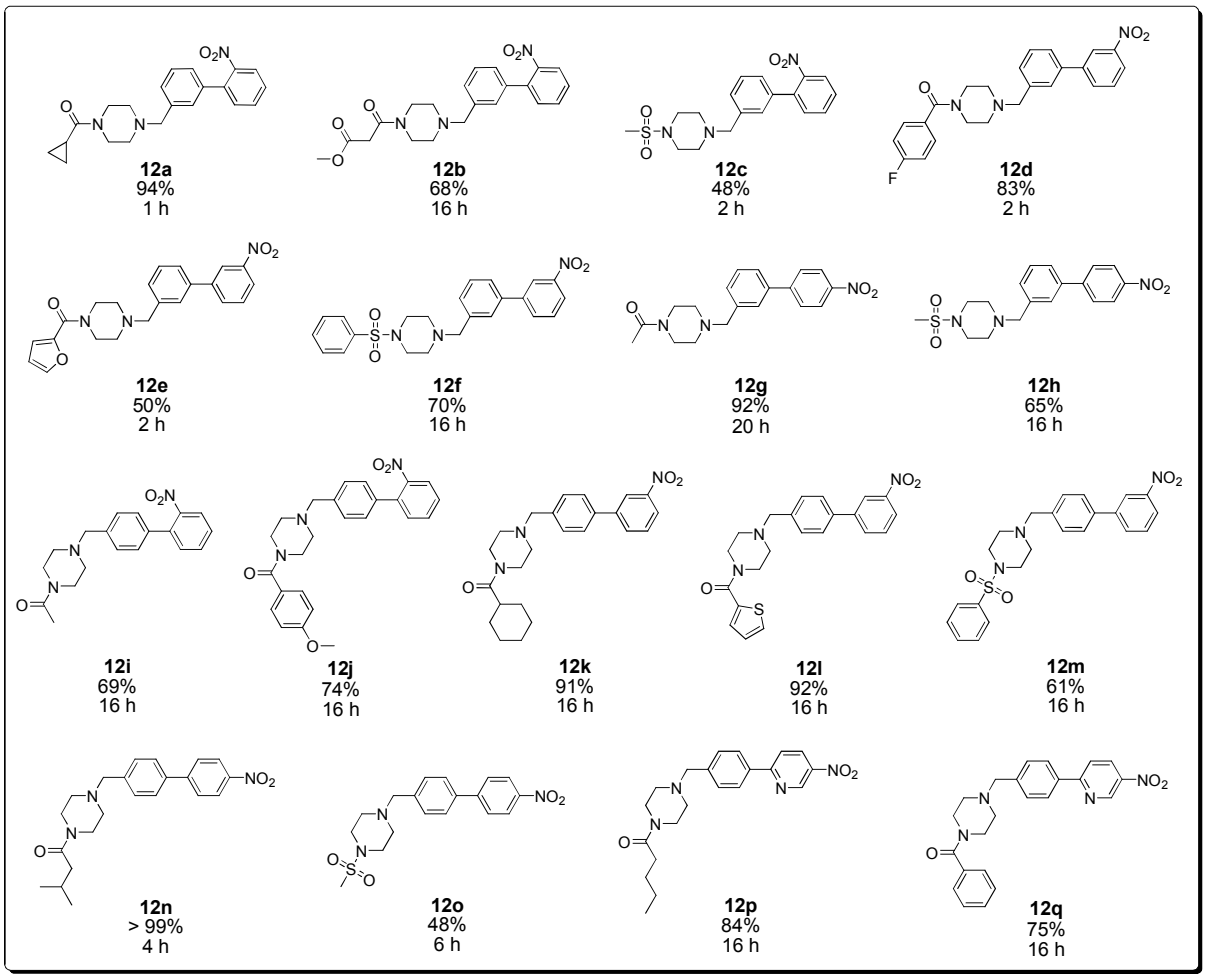


Figure 3.3. Acid and sulphonyl chlorides **9**.





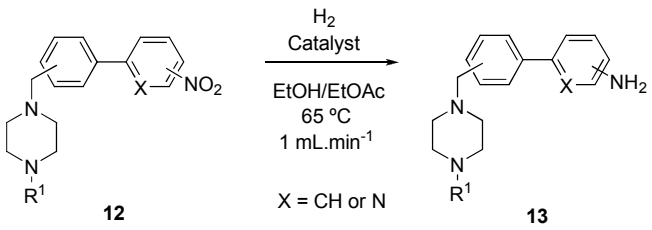
Reaction yields given after purification by chromatography.

Scheme 3.4. Functionalisation of compounds **11** to afford **12**.

The amidation reaction gave the expected products in good yields (e.g. **12a** in 94% yield) while the sulphonylation process afforded the expected products in moderate yields (e.g. **12c** in 48% yield). Most reactions with acid chlorides worked very well in a few hours (e.g. **12a** in 94% yield in 1 h, **12d** in 83% yield in 2 h and **12n** in > 99% yield in 4 h), whereas some required an overnight reaction to give the expected products in moderate yields (e.g. **12i** in 69% yield and **12m** in 61% yield).

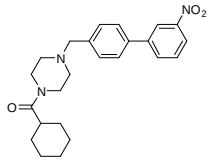
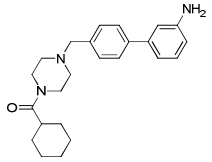
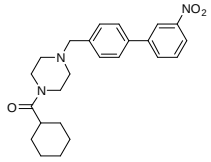
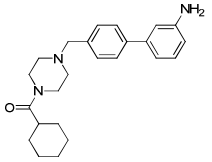
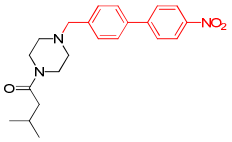
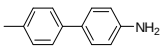
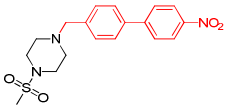
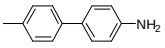
3.5. Nitro group reduction

The reduction of the nitro group in **12** was next intended in order to produce amines for further functionalisation reactions. Nitro group reduction reaction can be performed by thermal, microwave or flow chemistry (H-Cube)[124] routes. The latter option was found to be the most straightforward option since it generally obviated a purification or work-up step. The attempted reduction of nitro-biaryl derivatives was investigated in an H-Cube, in EtOH/EtOAc 1:1, at 65 °C, with a flow rate of 1 mL.min^{-1} and in full hydrogen mode, as outlined in Table 3.1 (Scheme 3.5).



Scheme 3.5. Nitro group reduction of **12**.

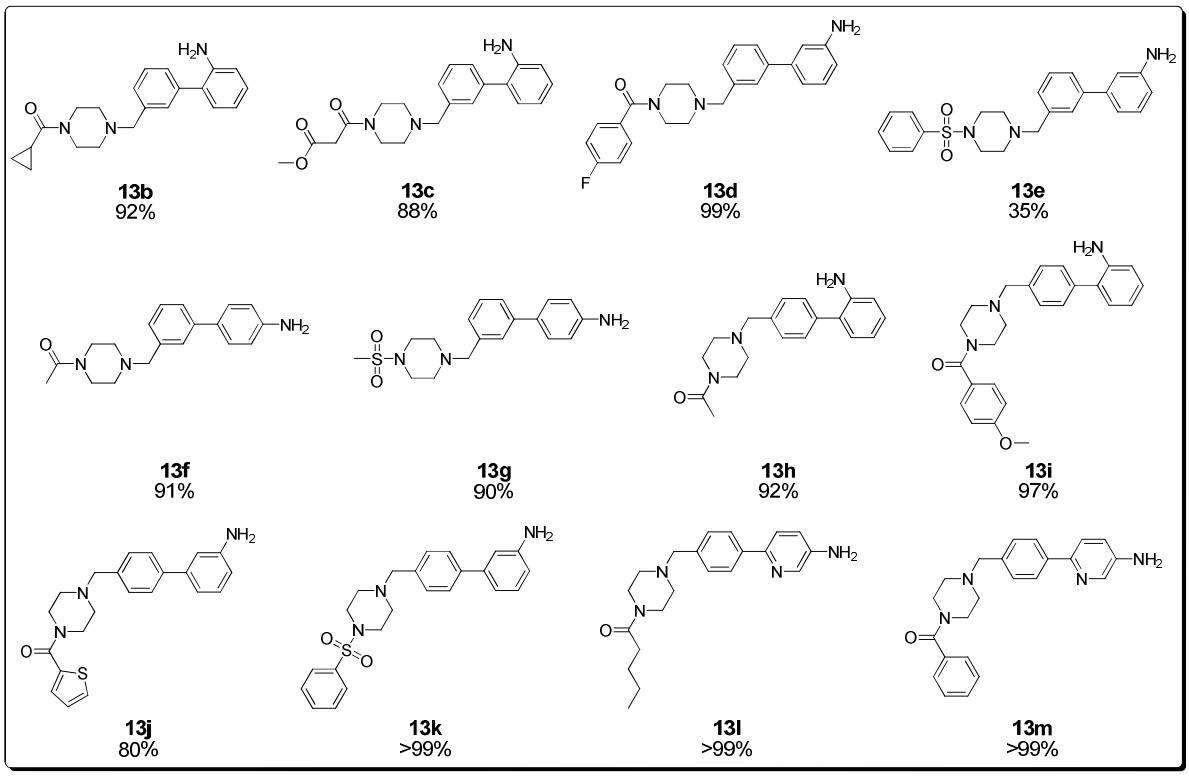
Table 3.1. Optimisation of the nitro group reduction of **12**.

Entry	**12**	Catalyst	**13**	Yield (%)
1	 **12k**	Raney Nickel	 **13a**	94
2	 **12k**	$SnCl_2.2H_2O$	 **13a**	67[a]
3	 **12n**	Pd/C	 **14a**	97
4	 **12o**	Pd/C	 **14a**	94

[a] Microwave irradiation (maximum power 300 W), EtOH, 130 ºC, 30 min.

When Raney Nickel was used as the catalyst, the expected product **13a** was obtained in very good yield (Table 3.1, entry 1). A microwave-mediated nitro reduction was attempted using tin chloride dihydrate (Table 3.1, entry 2), but gave an inferior yield and a more complicated work-up, compared with the former reduction.

However, unexpected hydrogenolysis of the benzylic-like unit in **12n** and **12o** led to the corresponding 4-tolylaniline **14a** when Pd/C and was used as catalyst (Table 3.1, entries 3 and 4). This is akin to a standard debenzylation reaction in organic synthesis.[123] Thereafter, the Raney Nickel/H-cube conditions were used to reduce the other (piperazin-1-ylmethyl)nitrobiaryl derivatives (Figure 3.4).



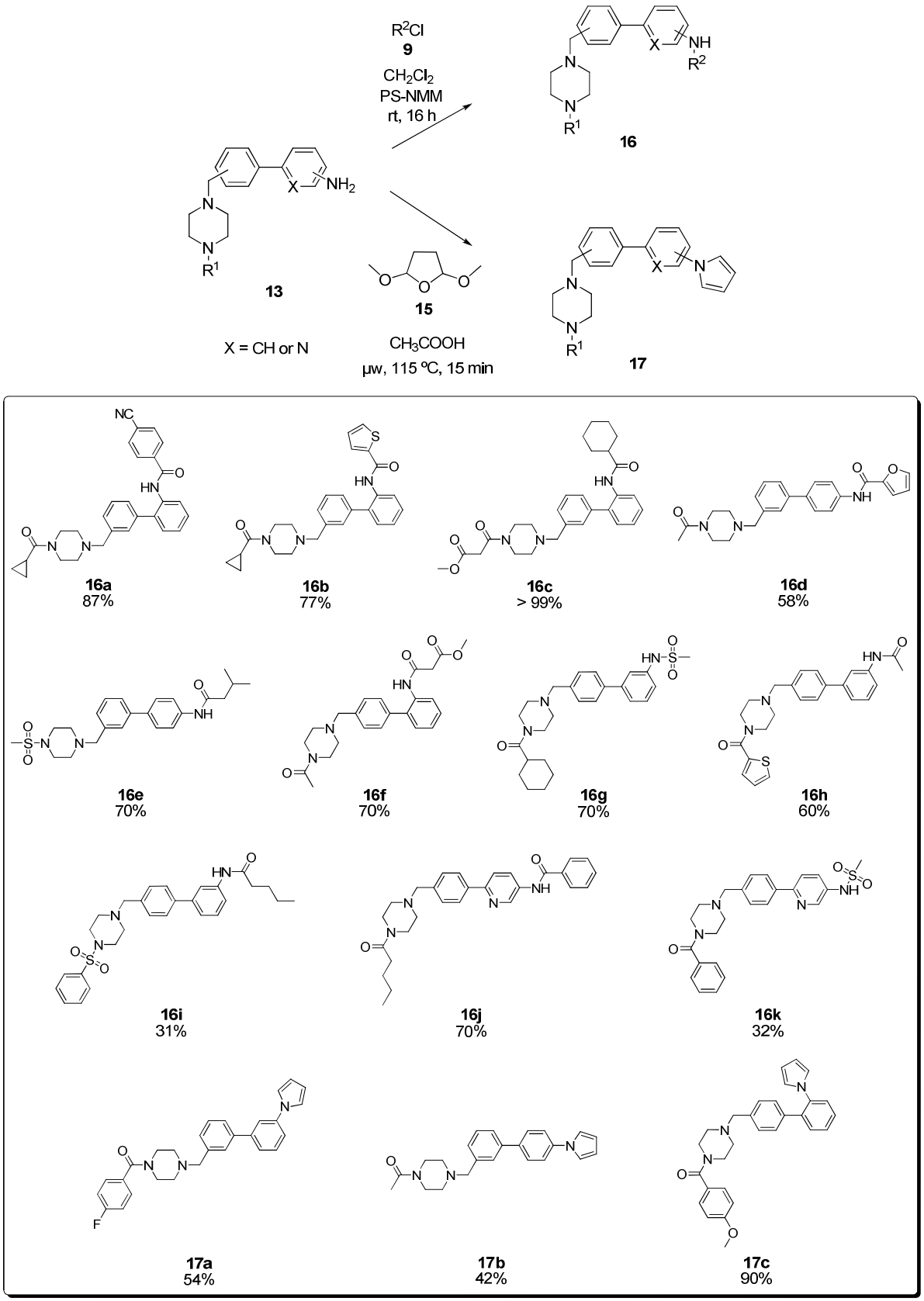
Crude reaction yield given, product used without further purification.

Figure 3.4. Amines **13** synthesised using Raney Nickel/H-Cube conditions.

Many of the products **13** were obtained in very good yields without any further purification. **13e** was the only product to be obtained in moderate yield which could have been due to the fact that the catalyst cartridge needed to be changed, which resulted in the reduction not taking place efficiently.

3.6. Amino group functionalisation

The amine group in **13** could next be functionalised by amidation and sulphonylation reactions with the corresponding acid, or sulphonyl, chlorides **9** in the presence of a supported base (PS-NMM). Pyrrole derivatives were synthesised by reaction of **13** with 2,5-dimethoxytetrahydrofuran (**15**) in acetic acid (Scheme 3.6).[125]

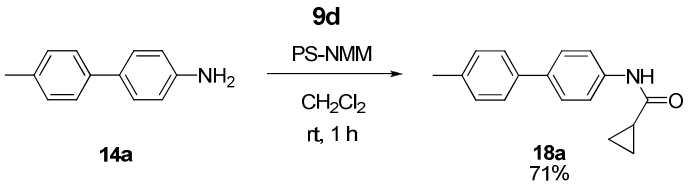


Reaction yields given after purification by chromatography.

Scheme 3.6. Amine functionalisation of compounds **13** and biaryls **16** and **17** library.

The elaborated biaryl products were obtained in moderate to good yields after purification by chromatography.

An amide coupling of **14a** led to an interesting biphenyl derivative **18a** in good yield (71%; Scheme 3.7).



Scheme 3.7. Amine functionalisation reaction of compound **14a**.

Very small crystals of **18a** were grown and analysed by a synchrotron X-ray diffraction crystal structure determination, which showed a very interesting structure with and Z' value of 3 (Figure 3.5).

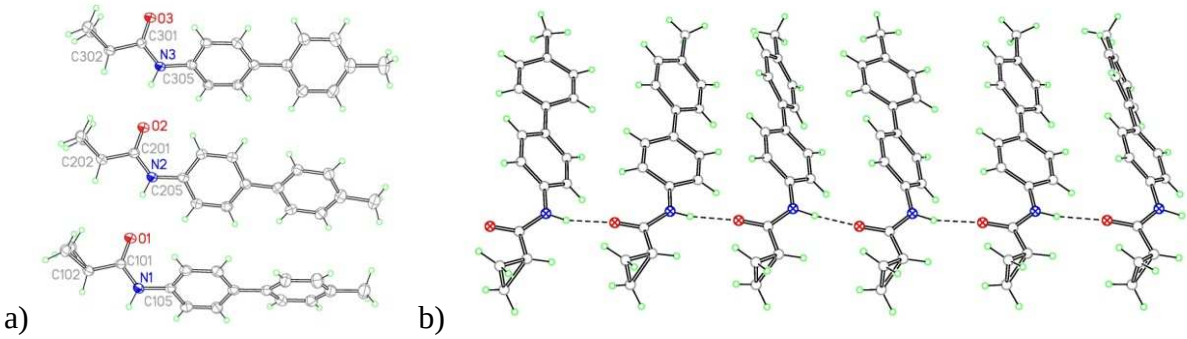


Figure 3.5. Crystal structure of **18a**: a) Three molecules in the asymmetric unit (40% probability displacement ellipsoids). b) Chains formed by intermolecular N–H···O hydrogen bonds, running along the *b* axis, viewed here along the *c* axis.

The asymmetric unit consists of three independent molecules (Figure 3.5a), which have similar orientations in the unit cell but vary in their detailed conformations, particularly in the torsional twist within the biphenyl unit [19.7(5)°, 21.2(5)° and −26.8(5)°] and in the extent to which the amide group lies out of the plane of the aromatic ring to which it is attached [torsion angles 41.9(5)°, 19.4(5)° and 45.3(5)°]. The molecules form chains along the crystallographic *b* axis through approximately linear intermolecular N–H···O hydrogen bonds (Figure 3.5b).

3.7. Conclusion

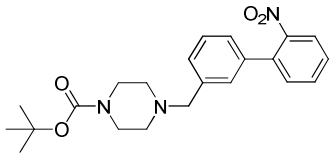
In conclusion, a (piperazin-1-ylmethyl)biaryl library has been synthesised over a few steps using, *inter alia*, the MAOS-mediated Suzuki-Miyaura coupling reaction. This library is composed of a number of very interesting drug-like molecules. The crystal structure of **18a** has stimulated our interest into examining analogues in the solid state and results will be disclosed in due course.

3.8. Experimental procedures and data

Experimental conditions and analytical methods are as for Chapter 2

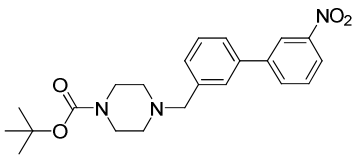
General procedure for the synthesis of compounds 10:

tert-Butyl 4-((2'-nitrobiphenyl-3-yl)methyl)piperazine-1-carboxylate **10a**



1a (1.02 mmol, 410 mg), **7e** (1.02 mmol, 207 mg), palladium(II) acetate (0.01 mmol, 2 mg), sodium carbonate (3.07 mmol, 324 mg), tetrabutylammonium bromide (1.02 mmol, 329 mg) and water (4 mL) were placed in a sealed microwave vial and stirred under microwave irradiation (initial power 300 W) at 150 ºC for 10 min. The mixture was cooled to rt, diluted with EtOAc (20 mL) and water (10 mL) and extracted with EtOAc. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 640 mg of a brown oil. The crude product was purified by chromatography on silica gel, hexane/EtOAc 7:3, to give 290 mg of the pure expected product as a brown oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.83 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.7 Hz), 7.60 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.1 Hz), 7.50-7.40 (m, 2H), 7.37 (m, 1H), 7.34 (m, 1H), 7.27 (m, 1H), 7.21 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 3.52 (s, 2H), 3.41 (m, 4H), 2.37 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 149.4, 138.6, 137.4, 136.3, 132.2, 131.9, 128.9, 128.7, 128.4, 128.1, 126.7, 124.1, 79.5, 62.7, 52.9 (2C), 43.7 (2C), 28.4 (3C). HRMS-ES (m/z) found 398.2072, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

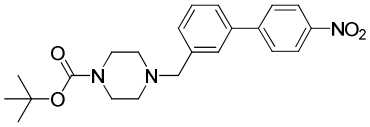
tert-Butyl 4-((3'-nitrobiphenyl-3-yl)methyl)piperazine-1-carboxylate **10b**



Brown oil, 521 mg, 87% yield (1.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.43 (dd, 1H, J = 1.8 Hz), 8.18 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 7.90 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.8 Hz, J_3 = 1.1 Hz), 7.59 (dd, 1H, J = 7.7 Hz), 7.57 (s, 1H), 7.51 (d, 1H, J = 7.3 Hz),

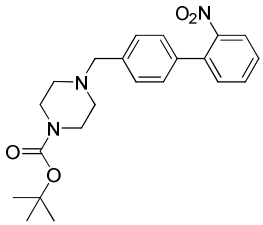
7.43 (dd, 1H, *J* = 7.3 Hz), 7.36 (d, 1H, *J* = 7.3 Hz), 3.57 (s, 2H), 3.42 (m, 4H), 2.41 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 148.7, 142.8, 139.1, 138.8, 133.1, 129.7, 129.3, 129.1, 127.8, 126.0, 122.1, 122.0, 79.6, 62.9, 52.9 (2C), 43.5 (2C), 28.4 (3C). HRMS-ES (m/z) found 398.2074, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

tert-Butyl 4-((4'-nitrobiphenyl-3-yl)methyl)piperazine-1-carboxylate **10c**



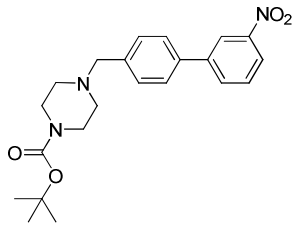
Orange oil, 381 mg, 72% yield (1.77 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, *J* = 9.2 Hz), 7.72 (d, 2H, *J* = 8.8 Hz), 7.57 (s, 1H), 7.50 (d, 1H, *J* = 7.0 Hz), 7.43 (dd, 1H, *J* = 7.3 Hz), 7.38 (d, 1H, *J* = 7.3 Hz), 3.57 (s, 2H), 3.41 (m, 4H), 2.40 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 147.6, 139.2 (2C), 138.9, 129.7, 129.2, 128.0, 127.9 (2C), 126.3, 124.1 (2C), 79.7, 62.9, 53.0 (2C), 44.1 (2C), 28.5 (3C). HRMS-ES (m/z) found 398.2071, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

tert-Butyl 4-((2'-nitrobiphenyl-4-yl)methyl)piperazine-1-carboxylate **10d**



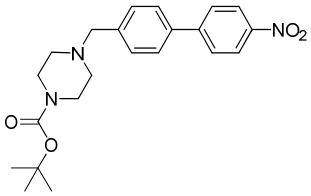
Total irradiation time: 20 minutes (2 x 10 min). Yellow oil, 170 mg, 85% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.83 (d, 1H, *J* = 7.7 Hz), 7.59 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.47 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.43 (m, 1H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 7.0 Hz), 3.53 (s, 2H), 3.42 (m, 4H), 2.39 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 149.3, 138.1, 136.2, 136.1, 132.2, 131.9, 129.3 (2C), 128.1, 127.8 (2C), 124.0, 79.6, 62.6, 52.9 (2C), 43.6 (2C), 28.4 (3C). HRMS-ES (m/z) found 398.2073, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

tert-Butyl 4-((3'-nitrobiphenyl-4-yl)methyl)piperazine-1-carboxylate **10e**



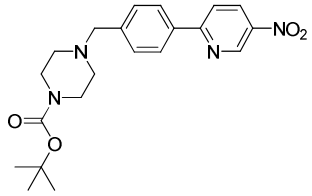
Off-white solid, 543 mg, 75% yield (1.83 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.45 (s, 1H), 8.20 (d, 1H, *J* = 7.0 Hz), 7.90 (d, 1H, *J* = 7.7 Hz), 7.62 (m, 4H), 7.50 (m, 1H), 3.48 (m, 6H), 3.46 (m, 4H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 148.7, 142.6, 138.5, 137.5, 132.9, 129.8 (2C), 129.7, 127.0 (2C), 121.9, 121.8, 79.6, 62.5, 52.9 (2C), 43.9 (2C), 28.4 (3C). HRMS-ES (m/z) found 398.2073, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074. Elemental analysis CHN (%) found C: 66.5, H: 6.9, N: 10.7, calcd for $C_{22}H_{27}O_4N_3$ C: 66.5, H: 6.9, N: 10.7.

tert-Butyl 4-((4'-nitrobiphenyl-4-yl)methyl)piperazine-1-carboxylate **10f**



Yellow solid, 480 mg, 81% yield (1.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (d, 2H, *J* = 8.8 Hz), 7.71 (d, 2H, *J* = 8.8 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 3.55 (s, 2H), 3.42 (m, 4H), 2.40 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.9, 147.4, 147.1, 139.2, 137.7, 129.9 (2C), 127.7 (2C), 127.4 (2C), 124.2 (2C), 79.7, 62.7, 53.0 (2C), 43.8 (2C), 28.5 (3C). HRMS-ES (m/z) found 398.2068, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074. Elemental analysis CHN (%) found C: 66.5, H: 6.9, N: 10.5, calcd for $C_{22}H_{27}O_4N_3$ C: 66.5, H: 6.9, N: 10.6.

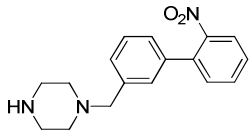
tert-Butyl 4-(4-(5-nitropyridin-2-yl)benzyl)piperazine-1-carboxylate **10g**



Total irradiation time: 20 minutes (2 x 10 min). The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 1:1, to give 285 mg of the pure expected product as a yellow solid in 70% yield (1.02 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.47 (s, 1H), 8.51 (d, 1H, *J* = 8.1 Hz), 8.03 (d, 2H, *J* = 7.0 Hz), 7.88 (d, 1H, *J* = 7.3 Hz), 7.47 (d, 2H, *J* = 7.3 Hz), 3.57 (s, 2H), 3.43 (m, 4H), 2.40 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.3, 154.8, 145.3, 141.3, 134.8, 131.9, 129.8 (2C), 128.5, 127.7 (2C), 119.9, 79.7, 62.6, 52.9 (2C), 44.0, 43.6, 28.4 (3C). HRMS-ES (m/z) found 399.2027, calcd for $[C_{21}H_{26}O_4N_4 + H]^+$ 399.2027.

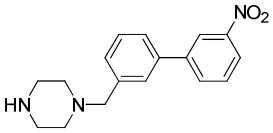
General procedure for Boc group removal:

1-((2'-Nitrobiphenyl-3-yl)methyl)piperazine **11a**



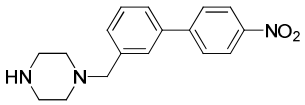
3a (1.58 mmol, 626 mg), TFA (6 mL) and CH_2Cl_2 (60 mL) were mixed and left under magnetic stirring at room temperature overnight. The volatiles were removed under reduced pressure. The product was dissolved in CH_2Cl_2 and washed with a sodium carbonate solution (1 M). The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced to give 466 mg of the pure expected product as an orange oil in 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.82 (d, 1H, *J* = 8.1 Hz), 7.59 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 7.45 ppm (dd, 2H, *J* = 7.7 Hz), 7.40-7.16 (m, 4H), 3.55 (s, 2H), 2.89 (m, 4H), 2.42 (m, 4H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 138.6, 137.3, 136.3, 132.2, 131.9, 129.0, 128.6, 128.5, 128.1, 126.6, 124.0, 63.2, 54.2 (2C), 45.9 (2C). HRMS-ES (m/z) found 298.1551, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((3'-Nitrobiphenyl-3-yl)methyl)piperazine **11b**



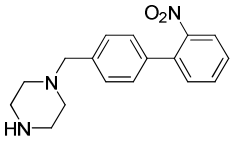
Orange oil, 352 mg, 93% yield (1.28 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.44 (dd, 1H, J = 2.2 Hz), 8.80 (ddd, 1H, J_1 = 8.4 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 7.91 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.8 Hz, J_3 = 1.1 Hz), 7.59 (dd, 1H, J = 7.8 Hz), 7.57 (s, 1H), 7.50 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.8 Hz), 7.42 (dd, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 7.3 Hz), 3.56 (s, 2H), 2.90 (m, 4H), 2.45 (m, 4H), 1.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 142.8, 139.0, 138.8, 133.1, 129.7, 129.3, 129.1, 127.8, 126.0, 125.6, 122.0 (2C), 63.2, 53.2 (2C), 45.4 (2C). HRMS-ES (m/z) found 298.1554, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((4'-Nitrobiphenyl-3-yl)methyl)piperazine **11c**



Orange oil, 249 mg, 98% yield (0.86 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, J = 8.8 Hz), 7.73 (d, 2H, J = 9.2 Hz), 7.57 (s, 1H), 7.50 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.8 Hz), 7.42 (dd + d, 2H, J_{dd} = 7.3 Hz), 3.56 (s, 2H), 2.90 (m, 4H), 2.45 (m, 4H), 1.92 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.6, 147.1, 139.3, 138.8, 129.7, 129.0, 128.0, 127.8 (2C), 126.1, 124.1 (2C), 63.4, 54.2 (2C), 45.9 (2C). HRMS-ES (m/z) found 298.1552, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

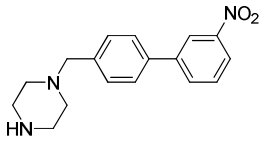
1-((2'-Nitrobiphenyl-4-yl)methyl)piperazine **11d**



Orange oil, 496 mg, 94% yield (1.77 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.82 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.59 (dd, 1H, J = 8.4 Hz), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 7.42 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.1 Hz), 3.51 (s, 2H), 2.89 (m, 4H), 2.43 (m, 4H), 1.77 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 138.4,

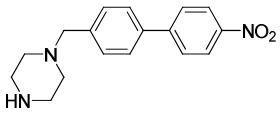
136.2, 136.0, 132.2, 131.9, 129.4 (2C), 128.0, 127.7 (2C), 124.0, 63.2, 54.4 (2C), 46.1 (2C). HRMS-ES (m/z) found 298.1552, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((3'-Nitrobiphenyl-4-yl)methyl)piperazine **11e**



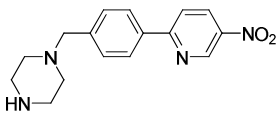
Yellow oil, 407 mg, > 99% yield (1.38 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.43 (dd, 1H, *J* = 1.8 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 7.7 Hz), 7.58 (dd, 1H, *J* = 8.1 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 8.1 Hz), 3.53 (s, 2H), 2.89 (m, 4H), 2.43 (m, 4H), 1.64 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.7, 142.7, 138.8, 137.4, 132.9 (2C), 129.9, 129.7, 127.0 (2C), 121.9, 121.8, 63.2, 54.4 (2C), 46.0 (2C). HRMS-ES (m/z) found 298.1552, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((4'-Nitrobiphenyl-4-yl)methyl)piperazine **11f**



Yellow solid, 328 mg, > 99% yield (1.08 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (d, 2H, *J* = 9.2 Hz), 7.71 (d, 2H, *J* = 9.2 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 2H, *J* = 8.4 Hz), 3.53 (s, 2H), 2.90 (m, 4H), 2.44 (m, 4H), 1.62 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.4, 147.0, 139.1, 137.6, 129.9 (2C), 127.6 (2C), 127.3 (2C), 124.1 (2C), 63.0, 53.8 (2C), 45.7 (2C). HRMS-ES (m/z) found 298.1550, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550. Elemental analysis CH (%) found C: 64.9, H: 6.0, calcd for $C_{17}H_{19}O_2N_3.0.26\ CH_2Cl_2$ C: 64.9, H: 6.2.

1-(4-(5-Nitropyridin-2-yl)benzyl)piperazine **11g**

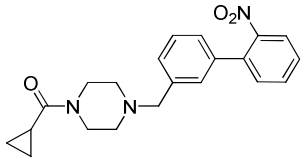


Orange solid, 201 mg, 73% yield (0.92 mmol scale). ^{1}H NMR (dmso-d_6) δ (ppm): 9.43 (d, 1H, *J* = 2.2 Hz), 8.65 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 8.26 (d, 1H, *J* = 8.8 Hz), 8.18 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 3.52 (s, 2H), 2.74 (m, 4H), 2.30 (m, 5H). ^{13}C NMR

(dmso-d_6) δ (ppm): 160.9, 144.9, 141.5, 135.2, 132.6, 131.5, 129.5 (2C), 127.4 (2C), 120.3, 62.2, 53.7 (2C), 45.4 (2C). MS-ES (m/z) found 299.2, calcd for $[C_{16}H_{18}O_2N_4 + H]^+$ 299.2. Elemental analysis CH (%) found C: 62.1, H: 5.6, calcd for $C_{16}H_{18}O_2N_4.0.175\ CH_2Cl_2$ C: 62.0, H: 5.9. Used as such for the next step.

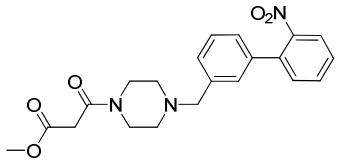
General procedure for the synthesis of functionalised compounds 12:

Cyclopropyl-[4-(2'-nitro-biphenyl-3-ylmethyl)-piperazin-1-yl]-methanone **12a**



4a (0.63 mmol, 187 mg), **9d** (0.70 mmol, 1.152 $g.mL^{-1}$, 73 µL), PS-NMM (0.70 mmol, 175 mg) and CH_2Cl_2 (10 mL) were stirred at rt for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 316 mg of a brown oil. The product was purified by chromatography on silica gel, CH_2Cl_2/MeOH from 0% to 20% of MeOH, to give 217 mg of the pure expected product as a yellow oil in 94% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (d, 1H, *J* = 8.1 Hz), 7.62 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.51-7.40 (m, 4H), 7.36 (s, 1H), 7.28 (d, 1H, *J* = 7.3 Hz), 3.80 (m, 6H), 2.65 (m, 4H), 1.69 (m, 1H), 0.96 (m, 2H), 0.75 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.0, 149.2, 137.7, 135.8, 132.4, 131.9 (2C), 129.6, 129.1, 128.3, 127.8, 124.1 (2C), 61.9, 52.5, 52.3, 44.3, 41.1, 10.9, 7.5 (2C). HRMS-ES (m/z) found 366.1813, calcd for $[C_{21}H_{23}O_3N_3 + H]^+$ 366.1812.

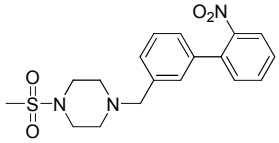
3-[4-(2'-Nitro-biphenyl-3-ylmethyl)-piperazin-1-yl]-3-oxo-propionic acid methyl ester **12b**



Yellow oil, 137 mg, 68% yield (0.51 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.86 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.1 Hz), 7.63 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.51 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.46 (m, 1H), 7.40 (d, 1H, *J* = 7.3 Hz), 7.34 (d, 1H, *J* = 7.7 Hz), 7.30 (m, 1H), 7.26 (d, 1H, *J* = 7.0 Hz), 3.74 (s, 3H), 3.69 (m, 2H), 3.60 (s, 2H), 3.47 (s + m, 4H), 2.50 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.0, 164.2, 137.8, 137.5 (2C), 136.1, 132.3, 131.8, 128.9,

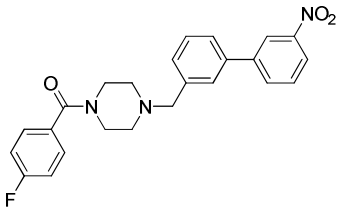
128.8, 128.5, 128.2, 126.9, 124.1, 62.3, 52.5 (2C), 46.3, 41.8, 41.0 (2C). HRMS-ES (m/z) found 398.1707, calcd for $[C_{21}H_{23}O_5N_3 + H]^+$ 398.1710.

1-Methanesulphonyl-4-(2'-nitro-biphenyl-3-ylmethyl)-piperazine **12c**



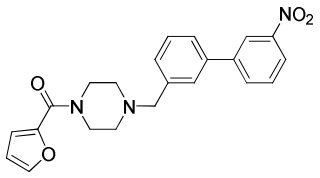
The product was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 47 mg of the pure expected product as a yellow oil in 48% yield (0.26 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (d, 1H, *J* = 7.7 Hz), 7.63 (dd, 1H, *J* = 7.7 Hz), 7.51 (d, 1H, *J* = 8.1 Hz), 7.46 (m, 1H), 7.39 (d, 1H, *J* = 7.3 Hz), 7.34-7.23 (m, 3H), 3.58 (s, 2H), 3.26 (m, 4H), 2.78 (s, 3H), 2.56 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 138.2, 137.5, 136.1, 132.3, 131.8, 128.8 (2C), 128.3, 128.2, 126.9, 124.1, 62.2, 52.2 (2C), 45.9 (2C), 34.0. HRMS-ES (m/z) found 376.1330, calcd for $[C_{18}H_{21}O_4N_3S + H]^+$ 376.1326.

(4-Fluoro-phenyl)-[4-(3'-nitro-biphenyl-3-ylmethyl)-piperazin-1-yl]-methanone **12d**



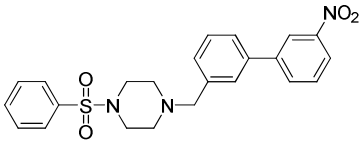
Yellow oil, 135 mg, 83% yield (0.39 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.47 (s, 1H), 8.23 (d, 1H, *J* = 7.0 Hz), 8.07 (m, 2H), 7.80-7.30 (m, 6H), 7.10 (m, 2H), 4.11-3.60 (m, 6H), 2.81 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.6 (2C), 148.7 (2C), 141.5, 139.8, 133.6, 130.2, 130.1, 130.0, 129.9, 122.7 (2C), 121.9 (2C), 116.2, 115.9, 115.8, 115.4, 68.0, 62.2, 52.5, 25.6 (2C). HRMS-ES (m/z) found 420.1726, calcd for $[C_{24}H_{22}O_3N_3F + H]^+$ 420.1718.

Furan-2-yl-[4-(3'-nitro-biphenyl-3-ylmethyl)-piperazin-1-yl]-methanone **12e**



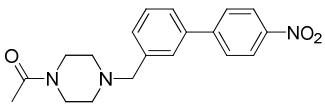
Yellow oil, 57 mg, 50% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.47 (m, 1H), 8.22 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 2.2 Hz), 7.93 (d, 1H, J = 8.1 Hz), 7.65-7.59 (m, 2H), 7.55 (d, 1H, J = 8.1 Hz), 7.49-7.44 (m, 2H), 7.40 (d, 1H, J = 7.3 Hz), 6.99 (d, 1H, J = 3.3 Hz), 6.47 (dd, 1H, J_1 = 3.1 Hz, J_2 = 1.8 Hz), 3.84 (m, 4H), 3.64 (s, 2H), 2.56 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 183.0, 159.9, 159.0, 148.7, 147.9, 143.6, 138.8, 133.1, 129.7, 129.3, 129.2, 127.9, 126.2, 122.1, 122.0, 116.4, 111.3, 62.7, 53.2 (2C), 42.8 (2C). MS-ES (m/z) found 392.2, calcd for $[C_{22}H_{21}O_4N_3 + H]^+$ 392.2. Used as such for the next step.

1-Benzenesulphonyl-4-(3'-nitro-biphenyl-3-ylmethyl)-piperazine **12f**



Yellow oil, 116 mg, 70% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.41 (m, 1H), 8.18 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 2.2 Hz, J_3 = 0.9 Hz), 7.88 (d, 1H, J = 7.9 Hz), 7.75 (d, 2H, J = 7.0 Hz), 7.64-7.48 (m, 6H), 7.41 (dd, 1H, J = 7.4 Hz), 7.31 (d, 1H, J = 7.9 Hz), 3.57 (s, 2H), 3.06 (m, 4H), 2.57 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.8, 142.7, 138.9, 138.8, 135.6, 133.2, 133.0, 129.8, 129.4, 129.3, 129.2 (2C), 127.9 (3C), 126.3, 122.2, 122.0, 62.6, 52.3 (2C), 46.1 (2C). HRMS-ES (m/z) found 438.1476, calcd for $[C_{23}H_{23}O_4N_3S + H]^+$ 438.1482.

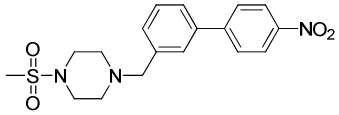
1-[4-(4'-Nitro-biphenyl-3-ylmethyl)-piperazin-1-yl]-ethanone **12g**



Brown oil, 130 mg, 92% yield (0.42 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, J = 9.2 Hz), 7.72 (d, 2H, J = 9.2 Hz), 7.57 (s, 1H), 7.52 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.8 Hz), 7.44 (dd, 1H, J = 7.7 Hz), 7.38 (d, 1H, J = 7.3 Hz), 3.40-3.70 (s + 2m, 6H), 2.44 (m, 4H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.7, 147.4, 138.8, 133.1, 130.3, 129.9, 129.6, 129.4,

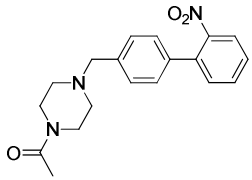
128.0, 127.8, 126.4, 124.1 (2C), 62.7, 53.1, 52.7, 46.2, 41.4, 21.3. HRMS-ES (m/z) found 340.1653, calcd for $[C_{19}H_{21}O_3N_3 + H]^+$ 340.1656.

1-Methanesulphonyl-4-(4'-nitro-biphenyl-3-ylmethyl)-piperazine **12h**



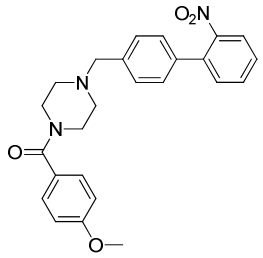
Brown solid, 103 mg, 65% yield (0.42 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.30 (d, 2H, *J* = 8.9 Hz), 7.74 (d, 2H, *J* = 8.9 Hz), 7.57 (s, 1H), 7.53 (d, 1H, *J* = 8.0 Hz), 7.45 (dd, 1H, *J* = 7.6 Hz), 7.39 (d, 1H, *J* = 7.5 Hz), 3.63 (s, 2H), 3.26 (m, 4H), 2.78 (s, 3H), 2.59 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.4, 147.2, 139.0, 138.7, 129.6, 129.2, 127.9, 127.8 (2C), 126.5, 124.1 (2C), 62.4, 52.3 (2C), 45.9 (2C), 34.3. MS-ES (m/z) found 376.2, calcd for $[C_{18}H_{21}O_4N_3S + H]^+$ 376.1. Used as such for the next step.

1-[4-(2'-Nitro-biphenyl-4-ylmethyl)-piperazin-1-yl]-ethanone **12i**



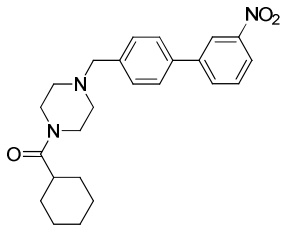
Orange oil, 79 mg, 69% yield (0.34 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.83 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.1 Hz), 7.60 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 7.48 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.42 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.36 (d, 2H, *J* = 8.1 Hz), 7,26 (d, 2H, *J* = 8.8 Hz), 3.62 (m, 2H), 3.54 (s, 2H), 3.45 (m, 2H), 2.43 (m, 4H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.9, 149.3, 137.9, 136.3, 136.1, 132.2, 131.9, 129.3 (2C), 128.1, 127.9 (2C), 124.1, 62.5, 53.1, 52.8, 46.3, 41.4, 21.3. HRMS-ES (m/z) found 340.1655, calcd for $[C_{19}H_{21}O_3N_3 + H]^+$ 340.1656.

(4-Methoxy-phenyl)-[4-(2'-nitro-biphenyl-4-ylmethyl)-piperazin-1-yl]-methanone **12j**



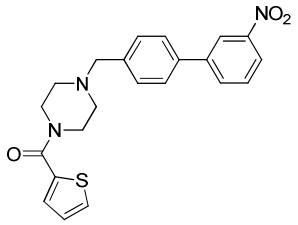
Orange oil, 112 mg, 74% yield (0.35 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.82 (d, 1H, *J* = 8.1 Hz), 7.59 (dd, 1H, *J* = 7.7 Hz), 7.47 (d, 1H, *J* = 8.1 Hz), 7.42 (d, 1H, *J* = 8.1 Hz), 7.37 (d, 4H, *J* = 8.8 Hz), 7.25 (d, 2H, *J* = 7.3 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 3.84 (s, 3H), 3.6 (m, 4H), 3.56 (s, 2H), 2.47 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 160.7, 149.3, 137.8, 136.3, 136.1, 132.2, 131.9 (2C), 129.3 (2C), 129.1 (2C), 128.1, 127.9 (2C), 124.0, 113.6 (2C), 62.5, 55.3, 53.1 (2C), 47.9, 42.3. HRMS-ES (m/z) found 432.1918, calcd for $[C_{25}H_{25}O_4N_3 + H]^+$ 432.1918.

Cyclohexyl(4-((3'-nitrobiphenyl-4-yl)methyl)piperazin-1-yl)methanone **12k**



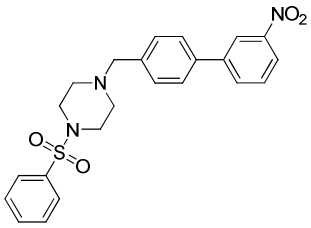
Yellow oil, 104 mg, 91% yield (0.28 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.43 (m, 1H), 8.17 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 0.7 Hz, J_3 = 0.2 Hz), 7.89 (d, 1H, *J* = 8.1 Hz), 7.58 (dd + d, 3H, J_d = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 3.56 (s + m, 6H), 2.43 (m, 4H), 2.00-1.00 (m, 11H). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.5, 148.7, 142.5, 138.2, 137.7, 132.9 (2C), 129.9, 129.7, 127.1 (2C), 122.0, 121.8, 62.4, 53.5, 52.9, 45.3, 42.8, 41.5, 40.4, 29.4, 28.9, 25.8, 25.4. HRMS-ES (m/z) found 408.2285, calcd for $[C_{24}H_{29}O_3N_3 + H]^+$ 408.2282.

(4-((3'-Nitrobiphenyl-4-yl)methyl)piperazin-1-yl)(thiophen-2-yl)methanone **12l**



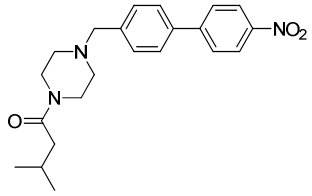
Yellow oil, 97 mg, 92% yield (0.26 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.43 (m, 1H), 8.17 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 7.89 (d, 1H, J = 7.7 Hz), 7.59 (dd + d, 3H, J_d = 7.7 Hz), 7.42 (d + dd, 3H, J_d = 8.1 Hz, J_{2dd} = 1.1 Hz), 7.25 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.1 Hz), 7.01 (dd, 1H, J_1 = 4.8 Hz, J_2 = 3.7 Hz), 3.76 (m, 4H), 3.59 (s, 2H), 2.51 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.5, 148.7, 142.5, 138.3, 137.7, 137.1, 132.9, 129.8 (2C), 129.7, 128.8, 128.5, 127.1 (2C), 126.6, 122.0, 121.8, 62.4, 53.1 (2C), 45.6 (2C). HRMS-ES (m/z) found 408.1372, calcd for $[C_{22}H_{21}O_3N_3S + H]^+$ 408.1376.

1-((3'-Nitrobiphenyl-4-yl)methyl)-4-(phenylsulphonyl)piperazine **12m**



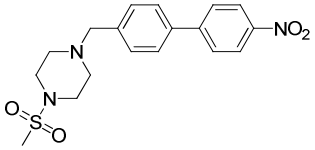
The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc from 0% to 5% of EtOAc, to give 72 mg of the pure expected product as a yellow oil in 61% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ: 8.40 ppm (m, 1H), 8.17 ppm (ddd, 1H, J_1 = 8.1 Hz, J_3 = 1.1 Hz), 7.86 ppm (d, 1H, J = 7.7 Hz), 7.74 ppm (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 7.48-7.63 ppm (m, 6H), 7.34 ppm (d, 2H, J = 8.4 Hz), 3.53 ppm (s, 2H), 3.04 ppm (m, 4H), 2.54 ppm (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.7, 142.5, 138.1, 137.7, 135.6, 132.9, 132.8, 129.8 (2C), 129.7, 129.0 (2C), 127.8 (2C), 127.1 (2C), 122.0, 121.8, 62.1, 52.2 (2C), 46.1 (2C). HRMS-ES (m/z) found 438.1479, calcd for $[C_{23}H_{23}O_4N_3S + H]^+$ 438.1482.

3-Methyl-1-(4-((4'-nitrobiphenyl-4-yl)methyl)piperazin-1-yl)butan-1-one **12n**



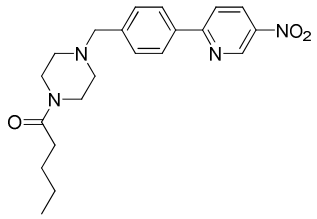
The crude product was tereated with PS-Trisamine (0.10 mmol, 3.48 mmol/g, 30 mg) overnight in CH_2Cl_2 then filtered. The filtrate was concentrated under reduced pressure to give 498 mg of the pure expected compound as a yellow solid in 100% yield (1.30 mmol scale). Recrystallized from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.31 (d, 2H, J = 8.8 Hz), 7.85-7.65 (m, 6H), 4.74 (m, 2H), 4.16 (m, 2H), 3.95 (m, 2H), 3.47 (m, 2H), 2.68 (m, 2H), 2.17 and 2.10 (m and sept, 3H, J_{sept} = 6.6 Hz), 0.94 (d, 6H, J = 6.6 Hz). HRMS-ES (m/z) found 382.2123, calcd for $[C_{22}H_{27}O_3N_3 + H]^+$ 382.2125. Elemental analysis CHN (%) found C: 63.0, H: 6.7, N: 9.8, calcd for $C_{22}H_{27}O_3N_3$.0.38 $CHCl_3$ C: 63.0, H: 6.5, N: 9.8.

1-(Methylsulphonyl)-4-((4'-nitrobiphenyl-4-yl)methyl)piperazine **12o**



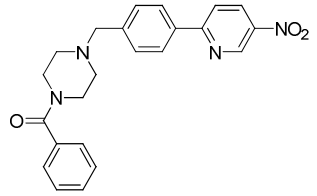
Yellow solid, 219 mg, 48% yield (1.22 mmol scale). Recrystallised from $CHCl_3$. ^{1}H NMR (dmso-d_6) δ (ppm): 8.32 (d, 2H, J = 9.0 Hz), 8.00 (d, 2H, J = 8.6 Hz), 7.90 (m, 2H), 7.74 (m, 2H), 4.43 (s, 2H), 3.70 (m, 2H), 3.40 (m, 2H), 3.19 (m, 4H), 2.99 (s, 3H). ^{13}C NMR (dmso-d_6) δ (ppm): 146.9, 145.7, 132.2, 130.2, 128.2 (2C), 127.6 (2C), 124.1 (4C), 58.1, 50.1 (2C), 42.3 (2C), 35.1. HRMS-ES (m/z) found 376.1322, calcd for $[C_{18}H_{21}O_4N_3S + H]^+$ 376.1326. Elemental analysis CHN (%) found C: 52.3, H: 5.3, N: 9.8, calcd for $C_{18}H_{21}O_4N_3S$.0.40 $CHCl_3$ C: 52.2, H: 5.1, N: 9.9.

1-{4-[4-(5-Nitro-pyridin-2-yl)-benzyl]-piperazin-1-yl}-pentan-1-one **12p**



Yellow solid, 106 mg, 84% yield (0.33 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.47 (d, 1H, *J* = 2.9 Hz), 8.51 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 8.04 (d, 2H, *J* = 8.1 Hz), 7.89 (d, 1H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 8.1 Hz), 3.62 (m, 2H), 3.59 (s, 2H), 3.47 (m, 2H), 2.44 (m, 4H), 2.31 (m, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.90 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.6, 145.3, 132.2, 132.0, 130.3, 129.9, 128.6, 128.4, 128.3, 127.8, 120.9, 119.9, 62.3, 53.1, 52.8, 45.3, 41.2, 33.4, 26.8, 22.2, 13.9. HRMS-ES (m/z) found 383.2077, calcd for $[C_{21}H_{26}O_3N_4 + H]^+$ 383.2078.

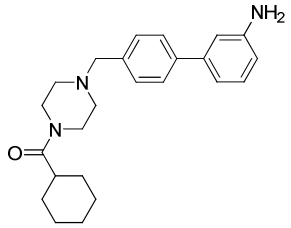
{4-[4-(5-Nitro-pyridin-2-yl)-benzyl]-piperazin-1-yl}-phenyl-methanone **12q**



Yellow solid, 91 mg, 75% yield (0.30 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.47 (d, 1H, *J* = 2.6 Hz), 8.51 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 8.08 (d, 1H, *J* = 7.3 Hz), 8.04 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 1H, *J* = 8.8 Hz), 7.35-7.70 (m, 4H), 7.47 (d, 2H, *J* = 8.1 Hz), 3.81 (m, 2H), 3.46 (m, 2H), 3.61 (s, 2H), 2.49 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.4, 162.3, 145.4, 142.9, 141.0, 136.3, 135.8, 132.0 (2C), 129.9 (2C), 128.6 (2C), 127.8 (2C), 127.1 (2C), 120.0, 62.5, 53.5, 52.7, 47.8, 42.1. HRMS-ES (m/z) found 403.1764, calcd for $[C_{23}H_{22}O_3N_4 + H]^+$ 403.1765.

General procedure for the nitro group reduction of compounds 12:

(4-((3'-Aminobiphenyl-4-yl)methyl)piperazin-1-yl)(cyclohexyl)methanone **13a**



Raney Nickel method

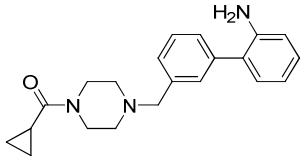
6k (0.19 mmol, 78 mg) was dissolved in an EtOH/EtOAc 1:1 mixture (50 mL) and reduced by hydrogenation catalyzed by Raney Nickel in an H-Cube at 65 ºC at a flow rate of 0.8 mL.min^{-1}, using full hydrogen mode. The solution obtained was concentrated under reduced pressure to give 70 mg of a yellow oil which was purified by chromatography on silica gel, CH_2Cl_2/MeOH 98:2, to give 68 mg of the pure expected product as a yellow oil in 94% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.50 (d, 2H, J = 8.1 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.20 (dd, 1H, J = 7.7 Hz), 6.96 (d, 1H, J = 7.7 Hz), 6.88 (m, 1H), 6.65 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 4.00-3.40 (m, 6H), 3.53 (s, 2H), 2.42 (m, 4H), 1.60-1.80 (m, 5H), 1.50 (m, 2H), 1.24 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.5, 146.7, 129.9, 129.7 (2C), 129.5 (2C), 127.0 (2C), 117.6, 114.1, 113.8, 62.2, 53.1, 52.6, 44.8, 40.9, 40.4, 29.4 (2C), 25.8 (3C) (1 quaternary C missing). HRMS-ES (m/z) found 378.2535, calcd for $[C_{24}H_{31}ON_3 + H]^+$ 378.2540.

Tin(II) chloride reduction

6k (0.025 mmol, 10 mg) was dissolved in EtOH (1 mL) then tin(II) chloride (0.125 mmol, 28 mg) was added and the mixture was stirred under microwave irradiation at 130 ºC for 30 minutes. The mixture was cooled to room temperature, poured in a saturated potassium carbonate solution (10 mL) and stirred at room temperature for 1 h. EtOAc was added and the mixture was filtered on Celite®. The two phases were separated and the aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 11 mg of a yellow oil which was purified by chromatography on silica gel, CH_2Cl_2/MeOH 98:2, to give 6 mg of the pure expected product as a yellow oil in 67% yield.

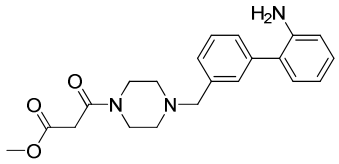
All the following were reduced by the Raney Nickel method.

(4-((2'-Aminobiphenyl-3-yl)methyl)piperazin-1-yl)(cyclopropyl)methanone **13b**



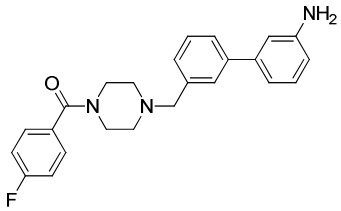
Brown solid, 177 mg, 92% yield (0.58 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.57-7.38 (m, 4H), 7.18 (d, 1H, *J* = 8.8 Hz), 7.13 (d, 1H, *J* = 7.0 Hz), 6.83 (dd, 1H, *J* = 7.3 Hz), 6.78 (d, 1H, *J* = 7.7 Hz), 3.90 (m, 8H), 2.73 (m, 4H), 1.68 (m, 1H), 0.99 (m, 2H), 0.77 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.0, 143.5, 140.1, 130.7, 130.5 (2C), 129.3 (2C), 128.9, 128.8, 126.9, 118.7, 115.9, 62.2, 52.7, 52.2, 44.1, 40.8, 10.9, 7.7 (2C). HRMS-ES (m/z) found 336.2070, calcd for $[C_{21}H_{25}ON_3 + H]^+$ 336.2070.

Methyl 3-(4-((2'-aminobiphenyl-3-yl)methyl)piperazin-1-yl)-3-oxopropanoate **13c**



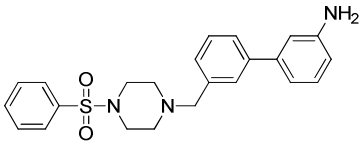
Yellow oil, 106 mg, 88% yield (0.33 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.42 (s, 1H), 7.41 (d, 2H, *J* = 8.4 Hz), 7.33-7.29 (m, 1H), 7.18 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 7.13 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.5 Hz), 6.83 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 6.78 (d, 1H, *J* = 8.1 Hz), 3.80-3.67 (m, 2H), 3.74 (s, 3H), 3.64 (s, 2H), 3.50 (m, 2H), 3.47 (s, 2H), 3.20 (m, 2H, NH_2), 2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.0, 164.2, 143.4, 139.7, 130.4 (2C), 130.0, 128.9, 128.6, 128.4, 128.2, 127.3, 118.7, 115.7, 62.5, 52.7, 52.5, 52.3, 46.1, 41.6, 41.0. HRMS-ES (m/z) found 368.1965, calcd for $[C_{21}H_{25}O_3N_3 + H]^+$ 368.1969.

(4-((3'-Aminobiphenyl-3-yl)methyl)piperazin-1-yl)(4-fluorophenyl)methanone **13d**



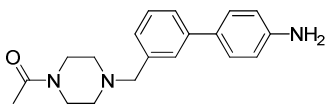
Brown oil, 113 mg, 99% yield (0.29 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70-7.50 (m, 2H), 7.48-7.35 (m, 4H), 7.22 (d, 1H, *J* = 7.7 Hz), 7.09 (dd, 2H, *J* = 8.8 Hz), 7.02-6.89 (m, 2H), 6.69 (d, 1H, *J* = 7.7 Hz), 4.30-3.40 (m, 8H), 2.71 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.4, 162.4, 146.8, 142.0, 141.5, 132.6, 130.9, 129.8 (2C), 129.6 (2C), 129.5, 129.2, 128.8, 117.6, 115.9, 115.6, 114.4, 113.8, 62.2, 52.4, 52.0, 46.0, 40.8. HRMS-ES (m/z) found 390.1982, calcd for $[C_{24}H_{24}ON_3F + H]^+$ 390.1976.

3'-((4-(Phenylsulphonyl)piperazin-1-yl)methyl)biphenyl-3-amine **13e**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 9:1, to give 33 mg of the pure expected product as a yellow oil in 35% yield (0.23 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (d, 2H, *J* = 8.1 Hz), 7.59 (d, 1H, *J* = 7.1 Hz), 7.55 (d, 1H, *J* = 7.3 Hz), 7.50 (m, 1H), 7.44 (m, 2H), 7.33 (dd, 1H, *J* = 7.7 Hz), 7.21 (m, 2H), 6.94 (d, 1H, *J* = 7.7 Hz), 6.87 (m, 1H), 6.67 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 3.73 (m, 2H, NH_2), 5.53 (s, 2H), 3.04 (m, 4H), 2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 146.8, 142.0, 141.6, 135.5, 132.9 (2C), 129.7, 129.1 (2C), 128.7, 128.1, 127.9, 127.8 (2C), 126.3, 117.6, 114.2, 113.9, 62.6, 52.1 (2C), 30.9 (2C). HRMS-ES (m/z) found 408.1740, calcd for $[C_{23}H_{25}O_2N_3S + H]^+$ 408.1740.

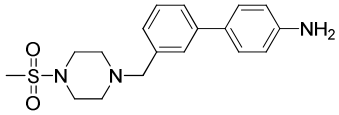
1-(4-((4'-Aminobiphenyl-3-yl)methyl)piperazin-1-yl)ethanone **13f**



Brown oil, 104 mg, 91% yield (0.37 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.50-7.40 (m, 3H), 7.40 (d, 2H, *J* = 8.8 Hz), 7.34 (dd, 1H, *J* = 7.7 Hz), 7.21 (m, 1H), 6.74 (d, 1H, *J* = 8.8

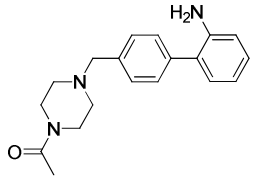
Hz), 3.70-3.30 (m, 8H), 2.46 (m, 4H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.9, 145.9, 142.7, 141.2, 141.0, 128.7, 128.0 (2C), 127.2, 127.1, 125.4, 115.4 (2C), 63.0, 53.0, 52.7, 46.2, 41.4, 21.4. MS-ES (m/z) found 310.2, calcd for $[C_{19}H_{23}ON_3 + H]^+$ 310.2. Used as such for the next step.

3'-((4-(Methylsulphonyl)piperazin-1-yl)methyl)biphenyl-4-amine **13g**



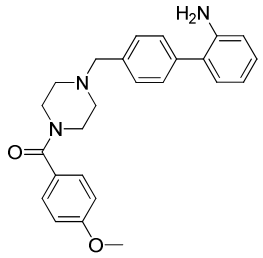
Brown oil, 80 mg, 90% yield (0.26 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.50-7.42 (m, 2H), 7.41 (d, 2H, *J* = 8.8 Hz), 7.34 (dd, 1H, *J* = 7.3 Hz), 7.21 (d, 1H, *J* = 7.7 Hz), 6.75 (d, 2H, *J* = 8.8 Hz), 3.60 (s, 2H), 3.27 (m, 6H), 2.77 (s, 3H), 2.60 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 146.0, 141.4, 131.1, 128.8 (2C), 128.0 (3C), 127.2, 125.7, 115.4 (2C), 62.6, 52.2 (2C), 45.7 (2C), 34.2. HRMS-ES (m/z) found 346.1588, calcd for $[C_{18}H_{23}O_2N_3S + H]^+$ 346.1584.

1-(4-((2'-Aminobiphenyl-4-yl)methyl)piperazin-1-yl)ethanone **13h**



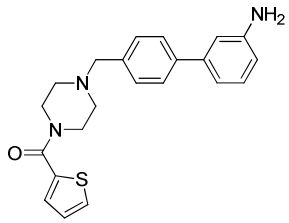
Yellow oil, 65 mg, 92% yield (0.23 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.34-7.44 (m, 4H), 7.08-7.17 (m, 2H), 6.80 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.1 Hz), 6.75 (d, 1H, *J* = 8.1 Hz), 3.90-3.30 (m, 2H), 3.62 (m, 2H), 3.54 (s, 2H), 3.46 (m, 2H), 2.45 (m, 4H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.9, 143.5, 138.5, 136.5, 130.4, 129.5 (2C), 129.0 (2C), 128.5, 127.3, 118.6, 115.6, 62.6, 53.1, 52.7, 46.3, 41.4, 21.3. HRMS-ES (m/z) found 310.1913, calcd for $[C_{19}H_{23}ON_3 + H]^+$ 310.1914.

(4-((2'-Aminobiphenyl-4-yl)methyl)piperazin-1-yl)(4-methoxyphenyl)methanone **13i**



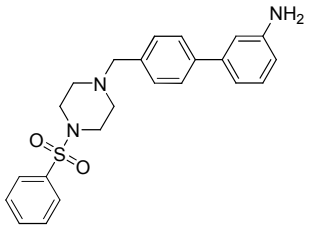
Yellow oil, 95 mg, 97% yield (0.24 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.43-7.37 (m, 6H), 7.15 (dd, 1H, J = 7.6 Hz), 7.12 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.82 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 6.76 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 3.82 (s, 3H), 3.90-3.40 (m, 6H), 3.58 (s, 2H), 2.50 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 160.7, 143.5 (2C), 138.7, 136.3, 130.4, 129.6, 129.1 (2C), 129.0 (2C), 128.5, 127.8, 127.1, 118.6, 115.6, 113.7 (2C), 62.6, 55.3, 53.1 (2C), 47.8, 42.6. HRMS-ES (m/z) found 402.2171, calcd for $[C_{25}H_{27}O_2N_3 + H]^+$ 402.2176.

(4-((3'-Aminobiphenyl-4-yl)methyl)piperazin-1-yl)(thiophen-2-yl)methanone **13j**



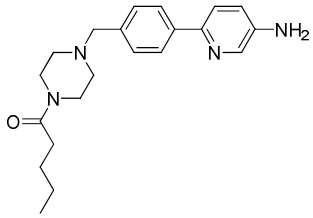
The crude product was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 70 mg of the pure expected product as a yellow oil in 80% yield (0.23 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.51 (d, 2H, J = 8.4 Hz), 7.41 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.26 (dd, 1H, J_1 = 3.7 Hz, J_2 = 1.1 Hz), 7.20 (dd, 1H, J = 7.7 Hz), 7.01 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.7 Hz), 6.96 (d, 1H, J = 7.7 Hz), 6.88 (m, 1H), 6.66 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 3.90-3.60 (m, 6H), 3.56 (s, 2H), 2.50 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.5, 146.7, 142.0, 140.6, 137.0, 129.7 (2C), 129.5, 129.2, 128.8, 128.5, 127.1 (2C), 126.6, 117.6, 114.1, 113.8, 62.5, 53.0 (2C), 45.5 (2C). HRMS-ES (m/z) found 378.1631, calcd for $[C_{22}H_{23}ON_3S + H]^+$ 378.1635.

4'-((4-(Phenylsulphonyl)piperazin-1-yl)methyl)biphenyl-3-amine **13k**



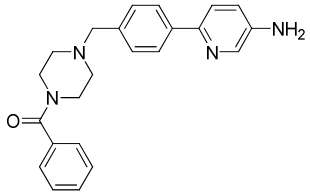
Yellow oil, 65 mg, 100% yield (0.16 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 7.57 (d, 1H, J = 7.0 Hz), 7.52 (d, 2H, J = 7.3 Hz), 7.46 (d, 2H, J = 8.1 Hz), 7.25 (d, 2H, J = 7.0 Hz), 7.19 (dd, 1H, J = 8.1 Hz), 6.93 (d, 1H, J = 7.7 Hz), 6.85 (s, 1H), 6.65 (dd, 1H, J_1 = 7.7 Hz, J_2 = 2.2 Hz), 3.49 (s, 2H), 3.03 (m, 6H), 2.53 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.5, 146.7, 142.0, 129.7, 129.5, 129.2, 128.8 (2C), 128.5, 127.0 (2C), 126.6, 117.6 (2C), 114.1 (2C), 113.8 (2C), 62.5, 53.1 (2C), 45.4 (2C). MS-ES (m/z) found 408.2, calcd for $[C_{23}H_{23}O_2N_3S + H]^+$ 408.2. Used as such for the next step.

1-(4-(4-(5-Aminopyridin-2-yl)benzyl)piperazin-1-yl)pentan-1-one **13l**



Yellow oil, 70 mg, > 99% yield (0.19 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.16 (d, 1H, J = 2.9 Hz), 7.82 (d, 2H, J = 8.4 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.03 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.6 Hz), 3.80 (m, 2H), 3.62 (m, 2H), 3.53 (s, 2H), 3.44 (m, 2H), 2.42 (m, 4H), 2.29 (t, 2H, J = 7.0 Hz), 1.58 (m, 2H), 1.33 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.7, 147.5, 141.5, 137.0, 132.1, 132.0, 129.8, 128.6, 128.4, 126.1, 122.4, 120.8, 62.3, 52.9, 52.6, 45.2, 41.1, 33.0, 27.4, 22.5, 13.8. HRMS-ES (m/z) found 353.2340, calcd for $[C_{21}H_{28}ON_4 + H]^+$ 353.2336.

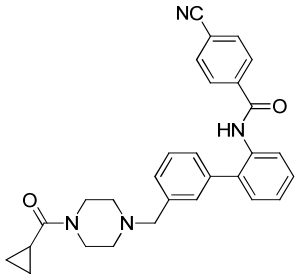
(4-(4-(5-Aminopyridin-2-yl)benzyl)piperazin-1-yl)(phenyl)methanone **13m**



Yellow oil, 70 mg, 100% yield (0.19 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.19 (d, 1H, *J* = 2.6 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 8.1 Hz), 7.72-7.63 (m, 1H), 7.60-7.35 (m, 6H), 7.06 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 4.00 (m, 2H), 3.83 (m, 2H), 3.60 (s, 2H), 3.45 (m, 2H), 2.47 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 147.8, 141.4, 137.1, 133.2, 132.0, 130.0, 129.6 (2C), 128.6, 128.4 (2C), 127.0 (2C), 126.0 (2C), 122.4, 120.8, 62.5, 53.1, 52.6, 47.6, 42.0. HRMS-ES (m/z) found 373.2026, calcd for $[C_{23}H_{24}ON_4 + H]^+$ 373.2023.

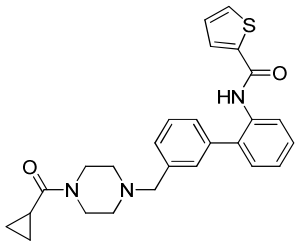
General procedure for the synthesis of compounds 16:

4-Cyano-*N*-(3'-((4-(cyclopropanecarbonyl)piperazin-1-yl)methyl)biphenyl-2-yl)benzamide **16a**



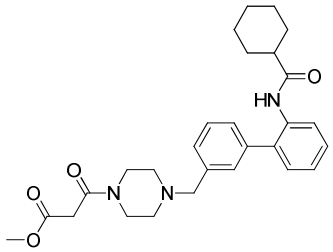
7b (0.22 mmol, 74 mg), **9k** (0.25 mmol, 41 mg), PS-NMM (0.25 mmol, 63 mg) and CH_2Cl_2 (10 mL) were mixed and stirred at rt for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 114 mg of an orange solid. The crude product was purified by chromatography on silica gel, CH_2Cl_2/MeOH from 0% to 10% of MeOH, to give 89 mg of the pure expected product as a yellow solid in 87% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22 (m, 1H), 8.12 (d, 1H, *J* = 8.3 Hz), 7.86-7.64 (m, 5H), 7.55-7.37 (m, 4H), 7.36-7.27 (m, 2H), 3.75 (m, 6H), 2.64 (m, 4H), 1.67 (m, 1H), 1.00 (m, 2H), 0.79 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.1, 163.4, 138.5, 138.4, 134.1 (2C), 132.5 (2C), 132.0, 130.5, 130.1, 129.3, 129.2, 128.8, 128.5, 127.6 (2C), 125.4, 122.4, 117.8, 115.2, 62.2, 53.7, 52.7, 44.6, 41.3, 10.9, 7.6 (2C). HRMS-ES (m/z) found 465.2284, calcd for $[C_{29}H_{28}O_2N_4 + H]^+$ 465.2285. Elemental analysis CH (%) found C: 70.0, H: 5.9, calcd for $C_{29}H_{28}O_2N_4$.0.49 CH_2Cl_2 C: 70.0, H: 5.8.

N-(3'-((4-(Cyclopropanecarbonyl)piperazin-1-yl)methyl)biphenyl-2-yl)thiophene-2-carboxamide **16b**



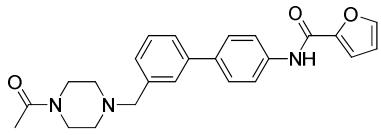
Yellow solid, 99 mg, 77% yield (0.29 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.45 (d, 1H, J = 8.1 Hz), 7.85 (s, 1H), 7.53-7.18 (m, 9H), 7.02 (dd, 1H, J_1 = 4.7 Hz, J_2 = 3.7 Hz), 3.90-3.50 (m, 6H), 2.45 (m, 4H), 1.69 (m, 1H), 0.97 (m, 2H), 0.74 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 159.5, 139.5, 139.1, 138.0, 134.6, 132.0, 130.8, 130.0 (2C), 129.3, 128.8, 128.7, 128.2, 128.1, 127.8, 124.4, 121.1, 62.7, 53.4, 53.0, 45.4, 42.0, 10.9, 7.4 (2C). HRMS-ES (m/z) found 446.1889, calcd for $[C_{26}H_{27}O_2N_3S + H]^+$ 446.1897. Elemental analysis CHN (%) found C: 68.6, H: 6.1. N: 9.1, calcd for $C_{26}H_{27}O_2N_3S.0.145\ CH_2Cl_2$ C: 68.6, H: 6.0, N: 9.2.

Methyl 3-(4-((2'-(cyclohexanecarboxamido)biphenyl-3-yl)methyl)piperazin-1-yl)-3-oxo-propanoate **16c**



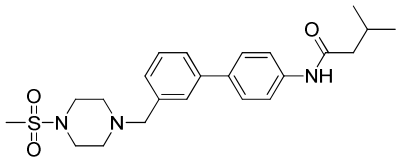
Yellow oil, 130 mg, > 99% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 1H, J = 8.1 Hz), 7.50-7.33 (m, 4H), 7.29 (d, 1H, J = 7.3 Hz), 7.26-7.12 (m, 3H), 3.75 (s, 3H), 3.68 (m, 2H), 3.60 (s, 2H), 3.47 (m, 4H), 2.51 (m, 4H), 2.07 (m, 1H), 1.75 (m, 4H), 1.28 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.0, 168.0, 164.2, 138.4, 134.8, 132.1, 130.0 (2C), 129.1, 128.6, 128.5 (2C), 128.4, 124.3, 121.8, 62.5, 52.9, 52.5 (2C), 46.3, 41.7, 41.0 (2C), 29.5 (2C), 25.6 (3C). HRMS-ES (m/z) found 478.2700, calcd for $[C_{28}H_{35}O_4N_3 + H]^+$ 478.2700.

N-(3'-((4-Acetylpiperazin-1-yl)methyl)biphenyl-4-yl)furan-2-carboxamide **16d**



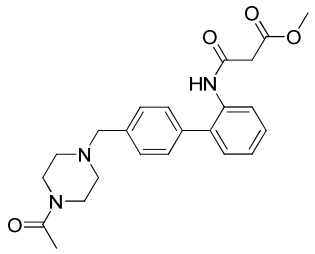
Brown oil, 37 mg, 58% yield (0.16 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.13 (s, 1H), 7.74 (d, 2H, J = 8.6 Hz), 7.63-7.50 (d + m, 5H, J_d = 8.6 Hz), 7.41 (m, 1H), 7.36-7.24 (m, 2H), 6.58 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.2 Hz), 3.70-3.30 (m, 6H), 2.49 (m, 4H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.0, 156.1, 147.8, 144.3, 140.7, 136.9, 129.0, 128.3, 128.0, 127.8 (4C), 126.3, 120.2 (2C), 115.4, 112.7, 62.6, 52.8, 52.5, 45.8, 40.9, 21.3. HRMS-ES (m/z) found 404.1967, calcd for $[C_{24}H_{25}O_3N_3 + H]^+$ 404.1969.

3-Methyl-*N*-(3'-((4-(methylsulphonyl)piperazin-1-yl)methyl)biphenyl-4-yl)butanamide **16e**



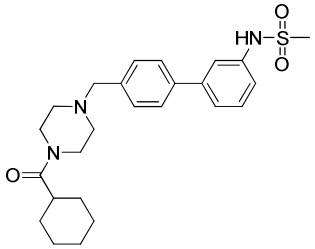
Beige solid, 60 mg, 70% yield (0.20 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.67-7.48 (m, 2H), 7.56 (d, 2H, J = 6.2 Hz), 7.46 (d, 1H, J = 7.7 Hz), 7.36 (dd, 1H, J = 7.3 Hz), 7.25 (m, 2H), 7.17 (m, 1H), 3.59 (s, 2H), 3.24 (m, 4H), 2.76 (s, 3H), 2.58 (m, 4H), 2.26-2.14 (m, 3H), 1.03-0.92 (m, 6H), 0.98-0.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.8, 140.7, 137.3, 136.8, 129.3, 128.8, 128.4, 127.9, 127.6 (2C), 127.5, 125.9, 120.1, 62.6, 52.2 (2C), 47.1, 45.8 (2C), 34.1, 26.3, 22.5 (2C). HRMS-ES (m/z) found 430.2155, calcd for $[C_{23}H_{31}O_3N_3S + H]^+$ 430.2159. Elemental analysis CHN (%) found C: 63.5, H: 7.3. N: 9.1, calcd for $C_{23}H_{31}O_3N_3S.0.085\ CH_2Cl_2$ C: 63.5, H: 7.2, N: 9.6.

Methyl 3-(4'-((4-acetylpiperazin-1-yl)methyl)biphenyl-2-ylamino)-3-oxopropanoate **16f**



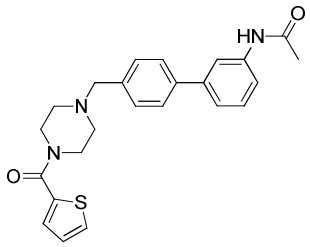
Orange oil, 63 mg, 70% yield (0.22 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.71 (m, 1H), 8.25 (d, 1H, *J* = 7.7 Hz), 7.42 (d, 2H, *J* = 8.1 Hz), 7.36 (m, 1H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.14-7.26 (m, 2H), 3.70-3.48 (m, 9H), 3.36 (s, 2H), 2.55 (m, 4H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.3, 169.0, 162.8, 137.2, 136.8, 134.5, 132.8, 130.2, 129.7 (2C), 129.4 (2C), 128.4, 124.7, 121.9, 62.5, 53.2, 52.4, 46.2, 42.1, 41.3, 24.9, 21.3. HRMS-ES (m/z) found 410.2074, calcd for $[C_{23}H_{27}O_4N_3 + H]^+$ 410.2074.

N-(4'-((4-(Cyclohexanecarbonyl)piperazin-1-yl)methyl)biphenyl-3-yl)methanesulphonamide **16g**



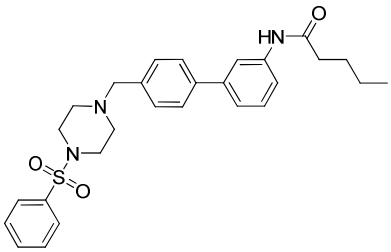
Yellow oil, 57 mg, 70% yield (0.18 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.53 (d, 2H, *J* = 8.2 Hz), 7.49 (m, 1H), 7.41-7.36 (m, 4H), 7.28-7.24 (m, 1H), 6.70 (m, 1H), 3.64 (m, 2H), 3.55 (s, 2H), 3.51 (m, 2H), 3.03 (s, 3H), 2.46 (m, 4H), 1.84-1.64 (m, 5H), 1.59-1.46 (m, 2H), 1.31-1.19 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 174.6, 142.6, 139.2, 137.3 (2C), 130.1, 129.7 (2C), 127.1 (3C), 124.1, 119.3, 62.5, 53.5, 52.9, 45.3, 41.4, 40.4, 39.5, 31.0, 29.4 (2C), 25.9 (2C). HRMS-ES (m/z) found 456.2320, calcd for $[C_{25}H_{33}O_3N_3S + H]^+$ 456.2315.

N-(4'-((4-(Thiophene-2-carbonyl)piperazin-1-yl)methyl)biphenyl-3-yl)acetamide **16h**



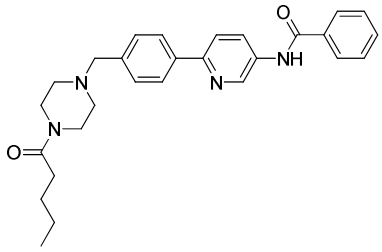
Brown solid, 34 mg, 60% yield (0.14 mmol scale). Recrystallisation from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79-7.72 (m, 2H), 7.53 (d, 2H, J = 8.6 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.43 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.2 Hz), 7.38-7.29 (m, 4H), 7.27 (dd, 1H, J_1 = 3.5 Hz, J_2 = 0.8 Hz), 7.03 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 3.77 (m, 4H), 3.57 (s, 2H), 2.51 (m, 4H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.6, 163.6, 141.6, 139.8, 138.5, 137.0, 136.7, 129.5 (2C), 129.3, 128.8, 128.6, 127.1 (2C), 126.7, 122.9, 118.7, 118.5, 62.5, 53.0 (2C), 45.6 (2C), 24.6. HRMS-ES (m/z) found 420.1747, calcd for $[C_{24}H_{25}O_2N_3S + H]^+$ 420.1740. Elemental analysis CHN (%) found C: 61.0, H: 5.4, N: 8.7, calcd for $C_{24}H_{25}O_2N_3S$.0.5 $CHCl_3$ C: 61.4, H: 5.4, N: 8.8.

N-(4'-((4-(Phenylsulphonyl)piperazin-1-yl)methyl)biphenyl-3-yl)pentanamide **16i**



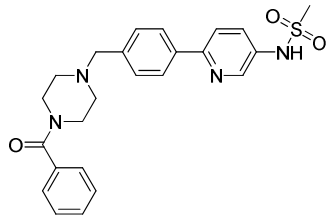
Off white solid, 22 mg, 31% yield (0.15 mmol scale). Recrystallisation from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.74 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 7.59 (m, 1H), 7.53 (d, 2H, J = 7.3 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.41 (d, 1H, J = 7.7 Hz), 7.35 (dd, 1H, J = 7.3 Hz), 7.26 (m, 3H), 7.17 (m, 1H, NH), 3.50 (s, 2H), 3.04 (m, 4H), 2.53 (m, 4H), 2.36 (t, 2H, J = 7.3 Hz), 1.71 (m, 2H), 1.40 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.2, 141.7, 138.3, 132.8 (2C), 129.5 (2C), 129.3 (2C), 129.0 (3C), 127.8 (3C), 127.1 (2C), 122.8, 118.4, 62.2, 52.1 (2C), 46.0, 37.6, 29.3, 27.6, 22.4, 13.8. HRMS-ES (m/z) found 492.2314, calcd for $[C_{28}H_{33}O_3N_3S + H]^+$ 492.2315. Elemental analysis CHN (%) found C: 62.6, H: 6.3, N: 7.6, calcd for $C_{28}H_{33}O_3N_3S$.0.46 $CHCl_3$ C: 62.5, H: 6.2, N: 7.7.

N-(6-(4-((4-Pentanoylpiperazin-1-yl)methyl)phenyl)pyridin-3-yl)benzamide **16j**



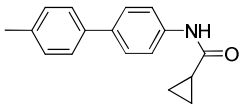
Brown solid, 57 mg, 70% yield (0.18 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.73 (d, 1H, J = 1.8 Hz), 8.42 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 8.03 (m, 1H, NH), 7.93 (2d, 4H, J_{d1} = 8.4 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.64-7.48 (m, 3H), 7.43 (d, 2H, J = 8.4 Hz), 3.65 (m, 2H), 3.59 (s, 2H), 3.48 (m, 2H), 2.46 (m, 4H), 2.32 (t, 2H, J = 7.3 Hz), 1.60 (m, 2H), 1.36 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.7, 166.1, 153.2, 141.2 (2C), 138.1, 134.2, 133.6, 132.3, 129.6 (2C), 129.3 (2C), 128.3, 127.1 (2C), 126.6 (2C), 120.5, 62.5, 53.1, 52.8, 45.6, 41.4, 33.0, 27.5, 22.6, 13.9. HRMS-ES (m/z) found 457.2591, calcd for $[C_{28}H_{32}O_2N_4 + H]^+$ 457.2598. Elemental analysis CHN (%) found C: 71.5, H: 6.8, N: 11.4, calcd for $C_{28}H_{32}O_2N_4$.0.205 CH_2Cl_2 C: 71.5, H: 6.9, N: 11.8.

N-(6-(4-((4-Benzoylpiperazin-1-yl)methyl)phenyl)pyridin-3-yl)methanesulphonamide **16k**



Beige solid, 26 mg, 32% yield (0.18 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.50 (d, 1H, J = 2.3 Hz), 7.90 (d, 2H, J = 8.6 Hz), 7.76 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.3 Hz), 7.69 (d, 1H, J = 8.6 Hz), 7.43-7.37 (m, 8H), 3.81 (m, 2H), 3.59 (s, 2H), 3.44 (m, 2H), 3.01 (s, 3H), 2.60-2.35 (2m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.4, 154.1, 142.3, 138.5, 137.5, 135.6, 132.5, 129.7, 129.5 (2C), 129.2, 128.5 (2C), 127.0 (2C), 126.6 (2C), 120.7, 62.4, 53.3, 52.7, 47.7, 42.2, 39.7. HRMS-ES (m/z) found 451.1795, calcd for $[C_{24}H_{26}O_3N_4S + H]^+$ 451.1798. Elemental analysis CH (%) found C: 62.4, H: 5.9, calcd for $C_{24}H_{26}O_3N_4S$.0.17 CH_2Cl_2 C: 62.4, H: 5.7.

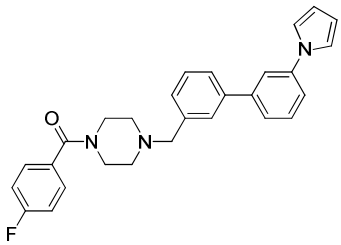
N-(4'-Methylbiphenyl-4-yl)cyclopropanecarboxamide **18**



White solid, 90 mg, 71% yield (0.50 mmol scale). Crystallisation from CH_2Cl_2 to give light brown/colorless crystals. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.60-7.50 (m, 4H), 7.74 (d, 2H, *J* = 8.4 Hz), 7.36 (m, 1H), 7.23 (d, 2H, *J* = 8.1 Hz), 2.39 (s, 3H), 1.51 (m, 1H), 1.11 (m, 2H), 0.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.8, 137.6, 137.1, 136.8, 129.5 (3C), 127.4 (2C), 126.6 (3C), 119.9, 21.1, 15.8, 8.0 (2C). HRMS-ES (m/z) found 252.1386, calcd for $[C_{17}H_{17}ON + H]^+$ 252.1383. Elemental analysis CHN (%) found C: 81.2, H: 6.8, N: 5.4, calcd for $C_{17}H_{17}ON$ C: 81.2, H: 6.8, N: 5.6.

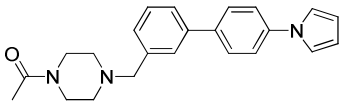
General procedure for the pyrrole synthesis of 17:

(4-((3'-(*1H*-Pyrrol-1-yl)biphenyl-3-yl)methyl)piperazin-1-yl)(4-fluorophenyl)methanone **17a**



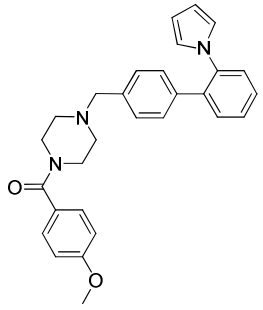
7d (0.26 mmol, 103 mg), **9** (0.29 mmol, 1.02 g.mL^{-1}, 37 µL) and acetic acid (3 mL) were mixed in a sealed microwave vial and stirred under microwave irradiation at 115 ºC for 15 min. Acetic acid was removed under reduced pressure. The product was dissolved in CH_2Cl_2, washed with a sodium carbonate solution (1 M), water and a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated to give 109 mg of a brown solid which was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5-9:1, to give 62 mg of the pure expected product as an orange oil in 54% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.59 (d, 2H, *J* = 8.4 Hz), 7.55-7.31 (m, 8H), 7.15 (m, 2H), 7.08 (dd, 2H, *J* = 8.8 Hz), 6.38 (m, 2H), 3.90-3.30 (m, 6H), 2.50 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.4, 165.2, 161.5, 142.6, 141.2, 140.6, 138.4, 131.8, 129.9, 129.4, 129.3, 128.9, 128.5, 127.8, 126.2, 124.5, 119.6, 119.5 (2C), 115.7, 115.4, 110.5 (2C), 62.9, 53.1 (2C), 47.6, 42.3. HRMS-ES (m/z) found 440.2137, calcd for $[C_{28}H_{26}ON_3F + H]^+$ 440.2133.

1-(4-((4'-(*1H*-Pyrrol-1-yl)biphenyl-3-yl)methyl)piperazin-1-yl)ethanone **17b**



Orange solid, 24 mg, 42% yield (0.16 mmol scale). Recrystallisation from $CHCl_3$. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.66 (d, 2H, *J* = 8.6 Hz), 7.57 (s, 1H), 7.52 (d, 1H, *J* = 7.8 Hz), 7.47 (d, 2H, *J* = 8.6 Hz), 7.42 (dd, 1H, *J* = 7.8 Hz), 7.32 (d, 1H, *J* = 7.4 Hz), 7.14 (dd, 2H, *J* = 2.0 Hz), 6.38 (dd, 2H, J = 2.0 Hz), 3.65 (m, 2H), 3.62 (s, 2H), 3.49 (m, 2H), 2.50 (m, 4H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.0, 140.3, 140.0, 138.3 (2C), 128.9, 128.2 (2C), 127.6, 125.9, 124.5, 120.7 (2C), 119.2 (2C), 110.6 (2C), 62.9, 53.1, 52.8, 46.3, 41.4, 21.3. HRMS-ES (m/z) found 360.2074, calcd for $[C_{23}H_{25}ON_3 + H]^+$ 360.2070. Elemental analysis CHN (%) found C: 70.1, H: 6.3, N: 10.0, calcd for $C_{23}H_{25}ON_3$.0.34 $CHCl_3$ C: 70.1, H: 6.4, N: 10.5.

(4-((2'-(*1H*-Pyrrol-1-yl)biphenyl-4-yl)methyl)piperazin-1-yl)(4-methoxyphenyl)methanone **17c**

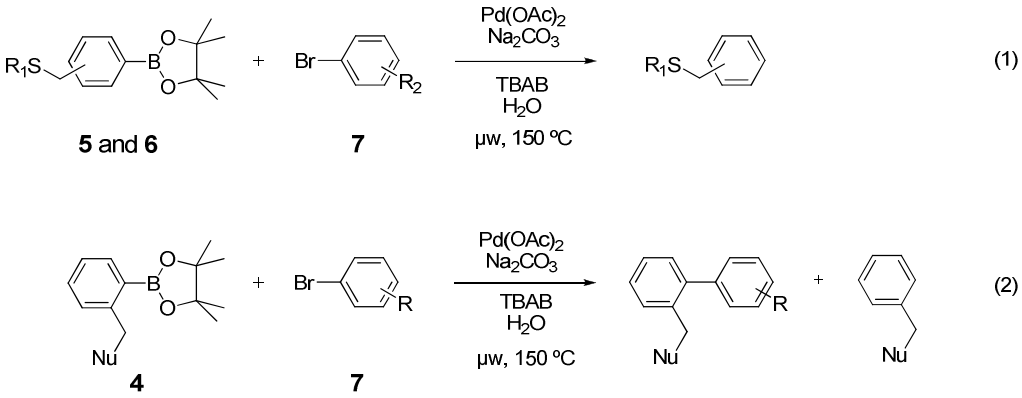


The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 6:4, to give 35 mg of the pure expected product as a yellow oil in 90% yield (0.09 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.43-7.33 (m, 5H), 7.29-7.17 (m, 3H), 7.03 (d, 2H, *J* = 8.1 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 6.54 (m, 2H), 6.10 (m, 2H), 3.81 (s, 3H), 3.80-3.40 (m, 4H), 3.50 (s, 2H), 2.44 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.2, 160.7, 138.9, 137.8, 136.8, 136.5, 131.1, 129.1 (2C), 129.0 (2C), 128.2 (3C), 127.9, 127.3, 126.4, 122.0 (2C), 113.4 (2C), 108.9 (2C), 62.5, 55.3, 53.1 (2C), 47.9, 42.5. HRMS-ES (m/z) found 452.2337, calcd for $[C_{29}H_{29}O_2N_3 + H]^+$ 452.2333.

Chapter 4: Suzuki-Miyaura coupling of *S*- and *ortho*-substituted phenylboronic esters

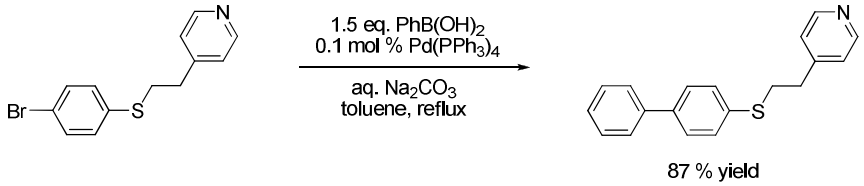
4.1. Introduction

The SM coupling of sulphur-containing phenylboronic esters and *ortho*-substituted phenylboronic esters with aryl bromides was previously found to be inefficient leading to mixtures of expected biaryls, protodeborylated product and starting materials (See Chapter 2) (Scheme 4.1).



Scheme 4.1. SM coupling of *S*- and *o*-substituted methylphenylboronic esters.

Itoh *et al.* found that $Pd(PPh_3)_4$ was an effective catalyst for the thermally-mediated SM coupling of bromobenzenethioethers with aqueous Na_2CO_3 in toluene (Scheme 4.2).[126]



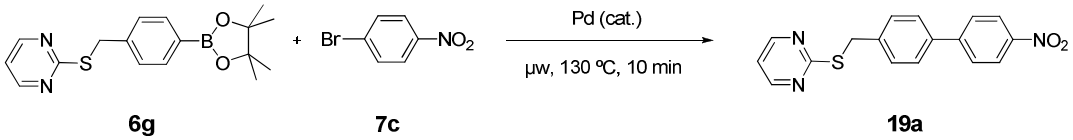
Scheme 4.2. SM coupling reaction of a thioether.

In order to find the most suitable conditions for the SM coupling of these arylboronic esters, a range of catalysts, bases, ligands and solvents were tested in a parallel optimisation method using automated solution dispensers, an auto-sampler microwave (Biotage®) and an automated LC-MS analyser.

4.2. SM coupling of *S*-substituted methylphenylboronic esters

4.2.1. Optimisation of conditions for the SM coupling of *S*-substituted methylphenylboronic esters

The reaction optimisation experiments were carried out on compound **6g** with 1-bromo-4-nitrobenzene **7c** under microwave irradiation at 130 °C for 10 minutes (Scheme 4.3).



Scheme 4.3. SM coupling reaction on **6g**.

This optimisation process consisted of 27 reactions using:

- 3 catalysts: $PdCl_2$, $Pd(OAc)_2$ and $Pd(PPh_3)_4$.
- 3 bases: CsF, K_3PO_4 and Na_2CO_3.
- 3 solvent systems: water, THF and toluene/EtOH/H_2O (1:1:1).

The catalysts and bases (when no water was used) were weighed directly in a microwave vial, **6g** and **7c** were mixed and solublised in each solvent system (without the water for the last one), the bases were solublised in water, where appropriate, and all the solutions were added to the vials using an automated solution dispenser. The conditions applied for this parallel synthesis test were: **6g** (0.2 mmol), **7c** (1 equiv.), catalyst (5 mol %), base (3 equiv.), solvent (2 mL), 130 ºC, 10 min, microwave irradiation (maximum power 300 W). The solutions obtained were analysed by LC-MS in MeOH (Figure 4.1; retention time of the expected product **19a**: 1.29 min; FW: 323 $g.mol^{-1}$; peak in green). The best conditions found were when $Pd(PPh_3)_4$ was used as pre-catalyst with CsF as base in THF (conditions A) and when $Pd(PPh_3)_4$ was used as a pre-catalyst with Na_2CO_3 as base in toluene/EtOH/H_2O (1:1:1) (conditions B).

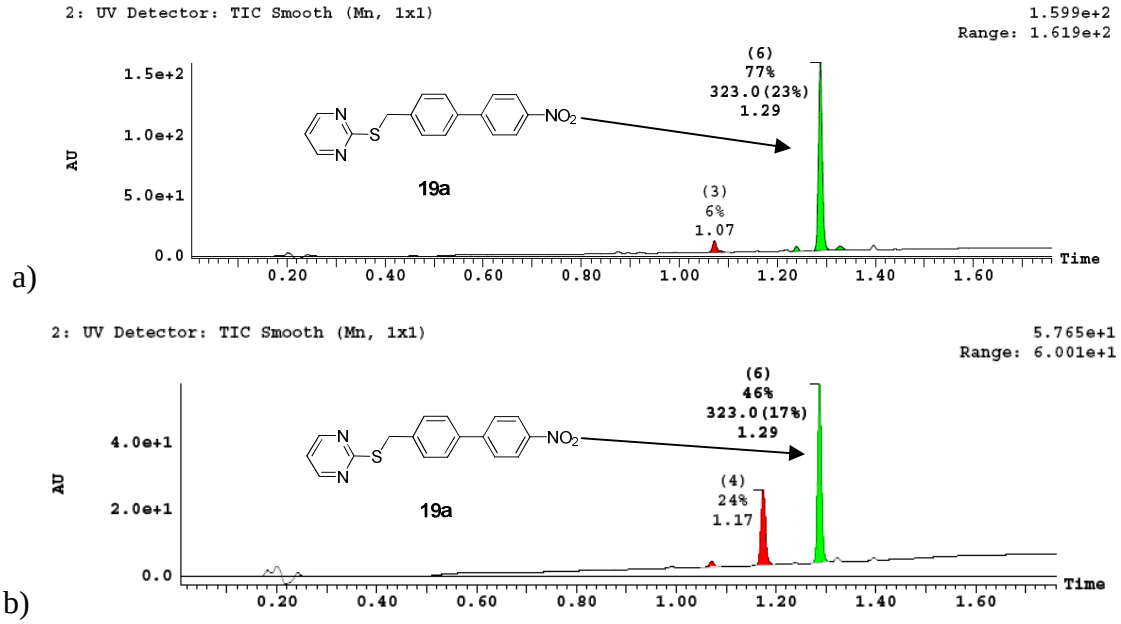
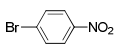
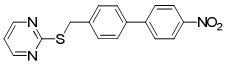
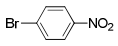
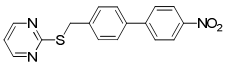
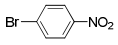
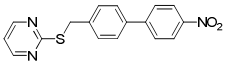
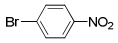
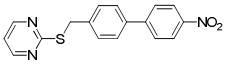
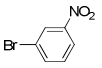
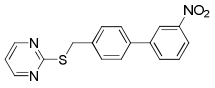
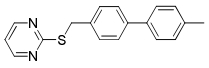
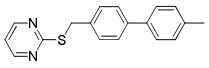


Figure 4.1. LC-MS graph for the reaction mixtures under conditions A (a) and B (b).

The ensuing reactions were optimised using conditions A (a) and B (b) (Table 4.1).

Table 4.1. Optimisation of the SM coupling reaction on **6g**.

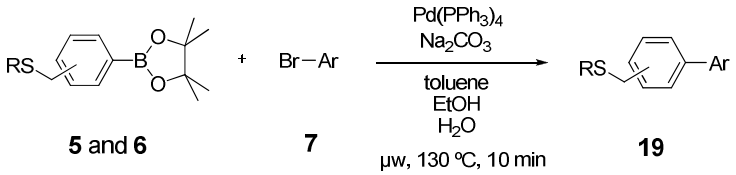
Entry	**7**		% mol cat.	Conditions	Product (**8**)		Yield (%)[a]
1		**7c**	5	A		**19a**	91
2		**7c**	3	A		**19a**	50
3		**7c**	1	A		**19a**	66
4		**7c**	0.5	A		**19a**	–
5		**7d**	3	B		**19b**	85[b]
6		**7h**	5	A		**19c**	50
7		**7h**	3	B		**19c**	81

Conditions: (A) **7** (1.1 equiv), $Pd(PPh_3)_4$, CsF (3 equiv), THF, 130 ºC, 10 min, microwave irradiation (maximum power 300 W); (B) **7** (1.1 equiv), $Pd(PPh_3)_4$, Na_2CO_3 (3 equiv), toluene/EtOH/H_2O (1:1:1), 130 ºC, 10 min, microwave irradiation (maximum power 300 W).
[a] Isolated yields after purification by chromatography. [b] Reaction achieved at 150 ºC.

It was also observed that the coupling reaction did not work if the thioether-substituted boronic ester had not been purified previously by chromatography on silica gel. This might be a necessary process in order to remove any traces of thiol, which is known to act as a poison towards the palladium catalyst.[126] A change in temperature does not seem to influence the reaction yield. Good yields were obtained at 150 ºC (e.g. 85% yield for **19b**, Table 4.1, entry 5) and at 130 ºC (e.g. 91% yield for **19a**, Table 4.1, entry 1). The reaction was first achieved using an electron withdrawing aryl bromide to make sure that all the favourable conditions for the SM coupling were met. Very good yields were obtained when using **7c** or **7d** under both conditions (e.g. 91% yield with conditions A, Table 4.1, entry 1 and 85% yield with conditions B, Table 4.1, entry 5). However, in order to obtain the biphenyl in good yield, conditions A require a larger amount of catalyst than conditions B (e.g. 91% yield with 5 mol % of $Pd(PPh_3)_4$ (conditions A), Table 4.1, entry 1; 50% yield with 3 mol % of $Pd(PPh_3)_4$ (conditions A), Table 4.1, entry 2; 85% yield with 3 mol % of $Pd(PPh_3)_4$ (conditions B), Table 4.1, entry 5). An electron rich aryl bromide, 1-bromotoluene, **7h**, was also tested. A moderate yield was obtained when using conditions A (e.g. 50% yield, Table 4.1, entry 6) and a very good yield was obtained when using conditions B (e.g. 81% yield, Table 4.1, entry 7). Conditions B were found to be the optimum conditions because the biphenyl products were obtained in good yields employing a relatively low catalyst loading.

4.2.2. SM coupling of *S*-substituted methylphenylboronic esters using the optimised conditions

A range of *S*-containing phenylboronic acid pinacol esters (Figure 4.2) were coupled in a SM reaction with several aryl bromides using conditions B previously established (Scheme 4.4).



Scheme 4.4. SM coupling of *S*-substituted methylphenylboronic esters.

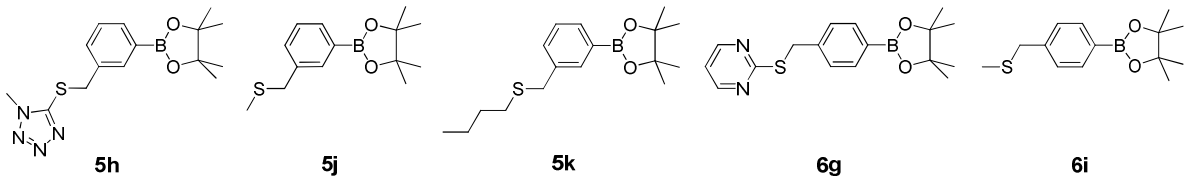


Figure 4.2. Arylboronic esters **5** and **6** used in the SM coupling of *S*-substituted derivatives.

Different aryl bromides were used in this SM coupling (Figure 4.3) affording a library of *S*-substituted biaryls **19** (Figure 4.4).

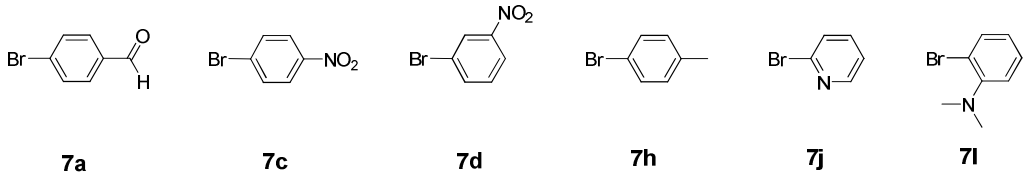
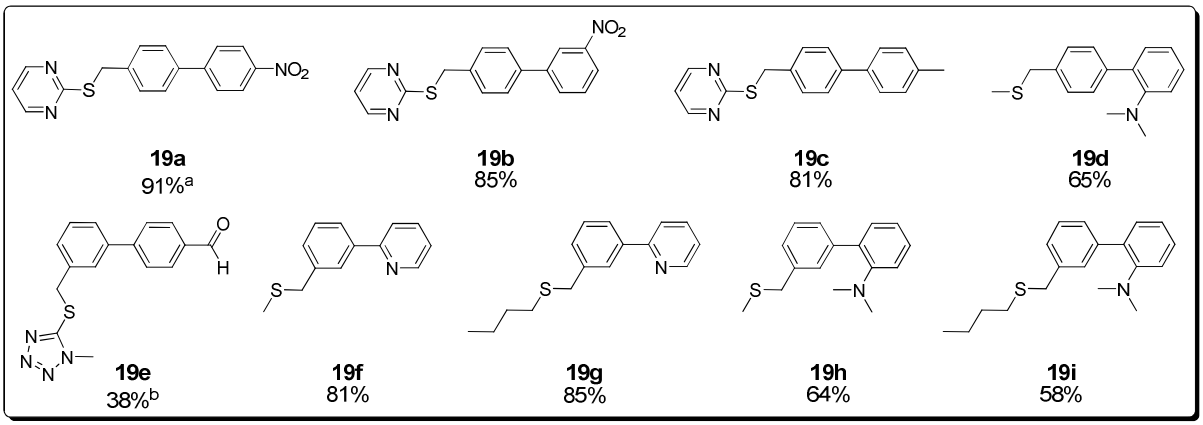


Figure 4.3. Aryl bromides **7** used in the SM coupling of *S*-substituted arylboronates.



Isolated yields given.
Conditions: $Pd(PPh_3)_4$ (3 % mol.), Na_2CO_3 (3 equiv.), toluene/EtOH/H_2O (1:1:1), 150 ºC, 10 min, microwave irradiation (maximum power 300 W). Percentage yields obtained after purification by chromatography.
[a] Conditions A used. [b] Mixture with biphenyl/boronic ester (84:16), calculated yield by ^{1}H NMR.

Figure 4.4. *S*-substituted biaryls **19**.

The biaryls were generally obtained in very good yields (e.g. 85% for **19g**). Moderate yields were obtained when using an *ortho*-substituted aryl bromide (e.g. 58% for **19i**).

4.2.3. Synthesis of biaryl palladacycles

Biaryl compounds are found in many fields of application. Biaryls **19f-i** were deemed to be suitable ligands for transition metal chemistry especially for forming palladacycles. The latter are one of the most popular classes of organopalladium derivatives and comprise a C-Pd bond and display intramolecular coordination *via* a heteroatom which stabilises the organometallic unit. They are extremely useful as precatalysts in a range of organic reactions (Figure 4.5).[127]

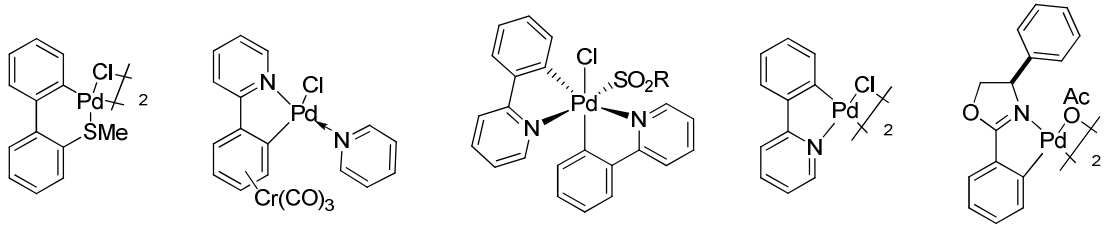
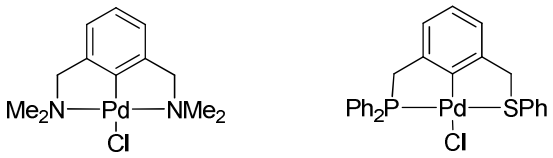


Figure 4.5. Examples of biaryl palladacycles.

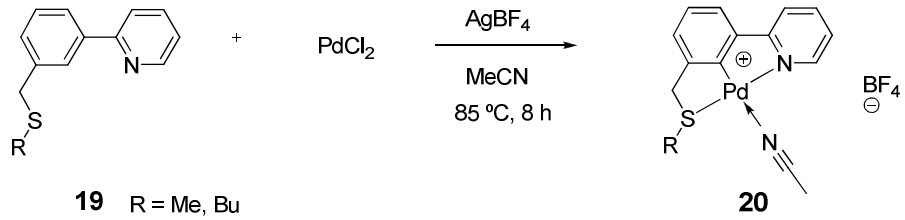
One particular class of palladacycles are called pincers (Figure 4.6).[128] Unsymmetrical pincers are relatively rare.[129] Palladium-pincers are very useful catalysts in organic synthesis.[130]



Symmetric NCN Non symmetric PCS

Figure 4.6. Examples of aryl palladium pincers.

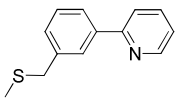
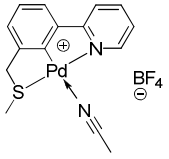
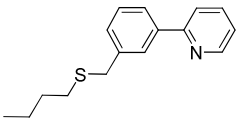
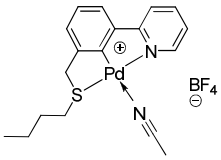
In order to form unsymmetric pincers, a few reactions were attempted. **19f** and **19g** were treated by palladium chloride in acetonitrile in the presence of silver tetrafluoroborate under reflux (Scheme 4.5 and Table 4.2).[131]



19 R = Me, Bu **20**

Scheme 4.5. Synthesis of palladium pincers from **19**.

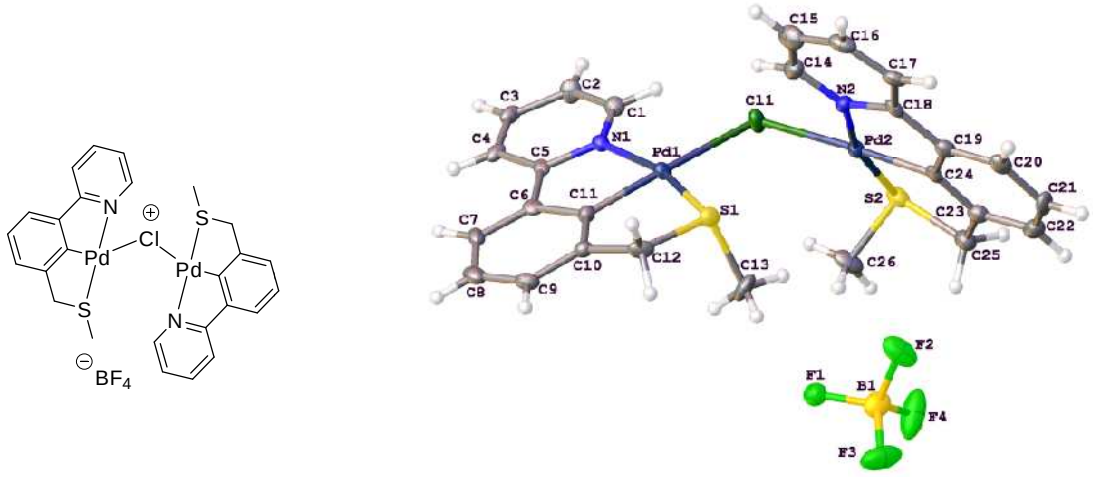
Table 4.2. Attempted synthesis of palladium pincers from **19**.

Entry	**19**	$AgBF_4$ (equiv.)	**20**	Yield (%)
1	 **19f**	2	 **20a**	–
2	 **19g**	1.2	 **20b**	–

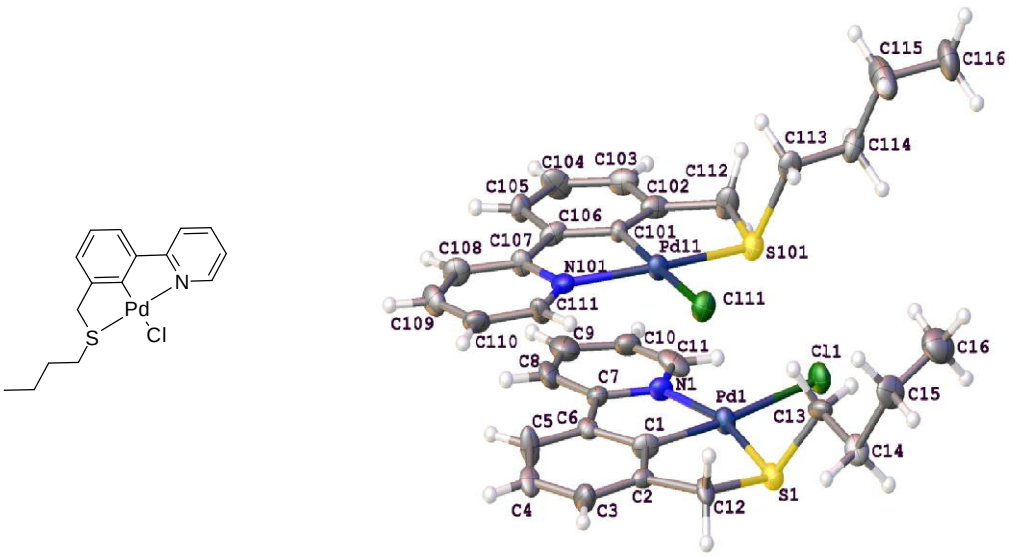
Conditions: **19** (0.95 equiv.), $PdCl_2$ (1 equiv.), $AgBF_4$, acetonitrile (35 mL) reflux under nitrogen atmosphere.

The products obtained after purification by chromatography (yellow solids) appeared to be mixtures according to mass spectrometric analysis. Crystals of the products expected to be **20a** and **20b** were grown and analysed by X-ray crystallography.

However, the structures found were not as expected. The palladacycle from **19f** was found to be a cationic chlorido-bridged palladium(II) complex (**20c**) and the palladacycle from **19g** was found to be a chloropalladacycle (**20d** with two independent molecules in the unit cell) (Figure 4.7).



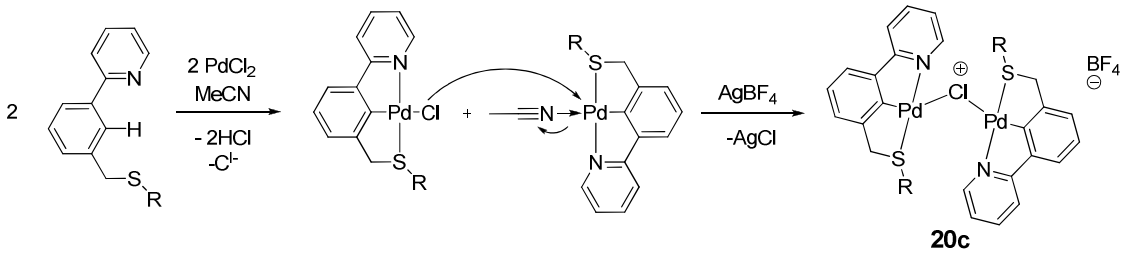
20c



20d

Figure 4.7. Crystal structures of **20c** and **20d**.

During the reaction, a mixture of chloropalladacycle and acetonitrile-bound palladacycle complexes was formed and these two entities are likely to have reacted together to form the cationic chlorido-bridged palladium(II) complex **20c** (Scheme 4.6).



Scheme 4.6. Purported mechanism of the formation of the chloropalladacycle and the cationic chlorido-bridged palladium(II) complex.

Cationic chlorido-bridged palladacycles complexes (Figure 4.8) are rather rare examples of palladacycles but a number of related palladacycles and other palladium containing complexes have been synthesised and studied.[132]

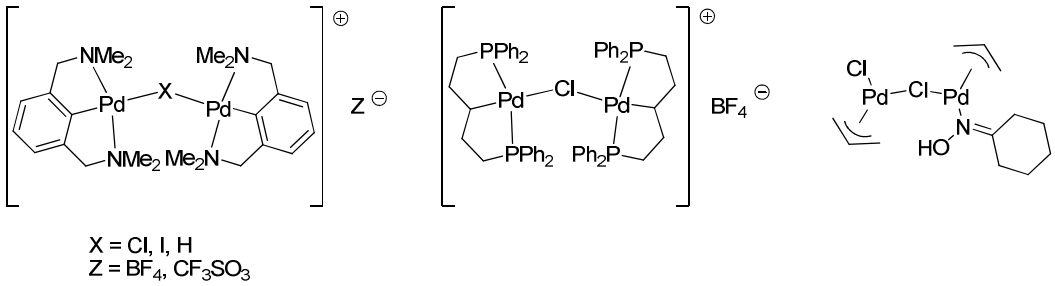
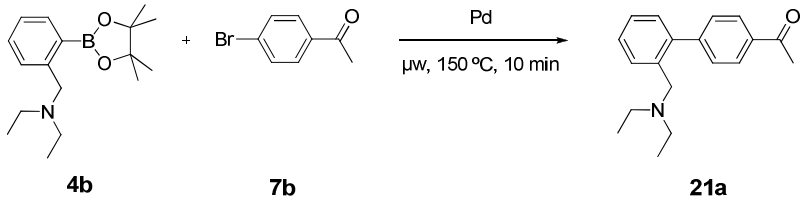


Figure 4.8. Examples of chlorido-bridged palladium(II) complexes.

4.3. SM coupling of *ortho*-substituted methylphenylboronic esters

4.3.1. Optimistation of the conditions for the SM coupling of *ortho*-substituted methylphenylboronic esters

As previously shown, *o*-substituted arylboronate derivatives were unsuccessfully employed in the SM coupling in the conditions used. A screening of catalysts, bases, ligands and solvent systems was achieved (Scheme 4.7) using 2-(*N*,*N*-diethylaminomethyl)phenylboronic acid pinacol ester **4b** as the boronate coupling partner and 4-bromoacetophenone **7b** as the aryl bromide for the SM coupling in a parallel approach.



Scheme 4.7. SM coupling reaction of *o*-substituted phenylboronic ester.

This optimisation process consisted of 36 reactions using:

- 3 catalysts: $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$.
- 3 bases: CsF, K_3PO_4 and Na_2CO_3.
- 2 solvent systems: THF and toluene/EtOH/H_2O (1:1:1).
- 2 ligands: dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine and 1,3-bis(2,6-diisopropylphenyl)-*1H*-imidazol-3-ium chloride.

The reaction mixtures were prepared as for the SM coupling of *S*-substituted arylboronates and the conditions applied for this parallel synthesis test were: **4b** (0.2 mmol), **7b** (1 equiv.), catalyst (5 mol %), base (3 equiv.), ligand (none or 10 mol %), solvent (2 mL), 130 ºC, 10 min, microwave irradiation (maximum power 300 W). The solutions obtained were then analysed by LC-MS in MeOH (Figure 4.9; retention time of the expected product **21a**: 0.87 min; FW: 281 $g.mol^{-1}$; peak in green). The best conditions found were when $Pd(PPh_3)_4$ was used as pre-catalyst with CsF as base in THF and when $Pd(PPh_3)_4$ was used as a pre-catalyst with K_3PO_4 or Na_2CO_3 as base in toluene/EtOH/H_2O (1:1:1).

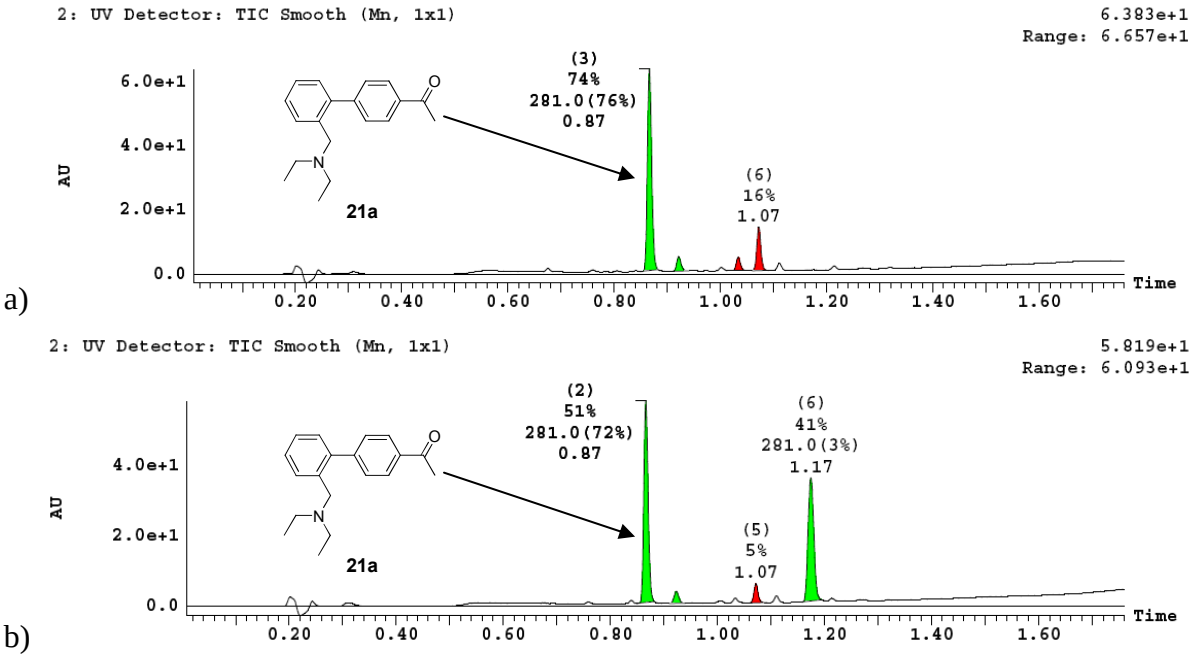
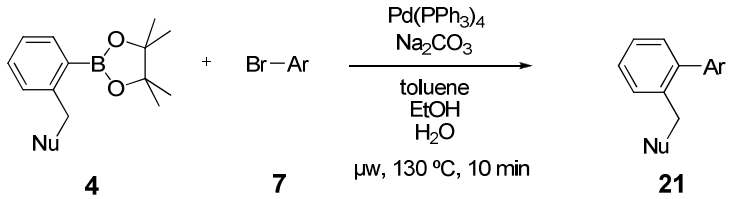


Figure 4.9. LC-MS graph of reaction mixtures under conditions A (a) and B (b).

The latter conditions were chosen for the SM coupling of *o*-substituted phenylboronic esters in order to synthesise a small library of *o*-substituted biaryls (**21**), because of the low catalyst loading.

4.3.2. SM coupling of *ortho*-substituted methylphenylboronic esters using the optimised conditions

The SM coupling (Scheme 4.8) was carried out on *o*-substituted methylphenylboronic acid pinacol esters **4** (Figure 4.10) with different aryl bromides **7** (Figure 4.11) to give a small library of *o*-substituted biaryls **21** (Figure 4.12).



Scheme 4.8. SM coupling of *o*-substituted methylphenylboronic esters.

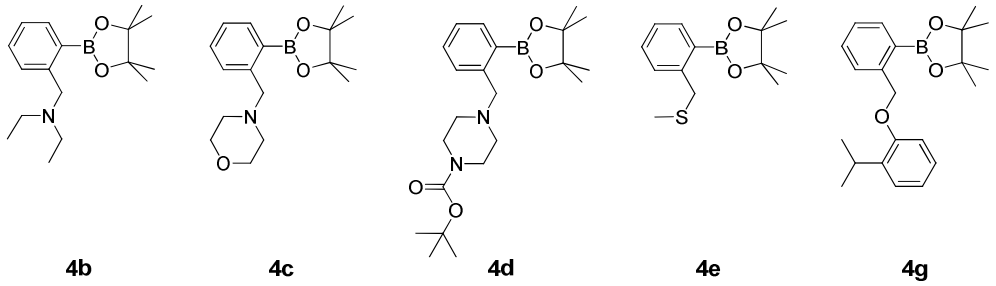


Figure 4.10. Arylboronates **4** used in the SM coupling.

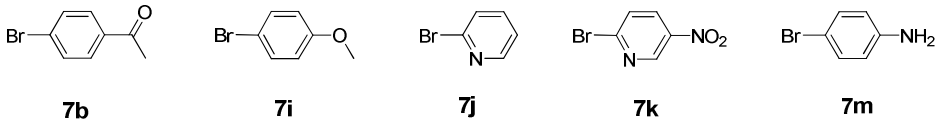
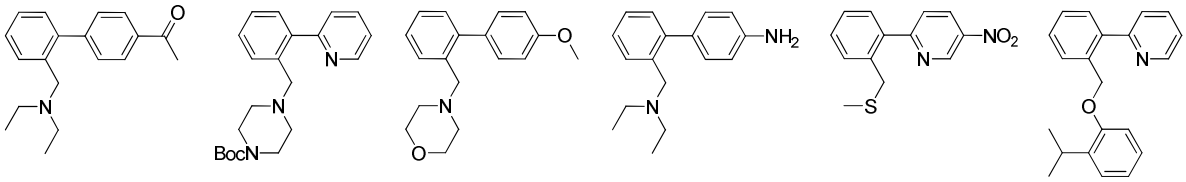


Figure 4.11. Aryl bromides **7** used in the SM coupling of **4**.



Conditions: $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (3 equiv.), toluene/EtOH/H_2O (1:1:1), 150 °C, 10 min, microwave irradiation (maximum power 300 W). Percentage yields given after purification by chromatography.
[a] Mixture with protodeborylated product (87:13), calculated yield by ^1H NMR.

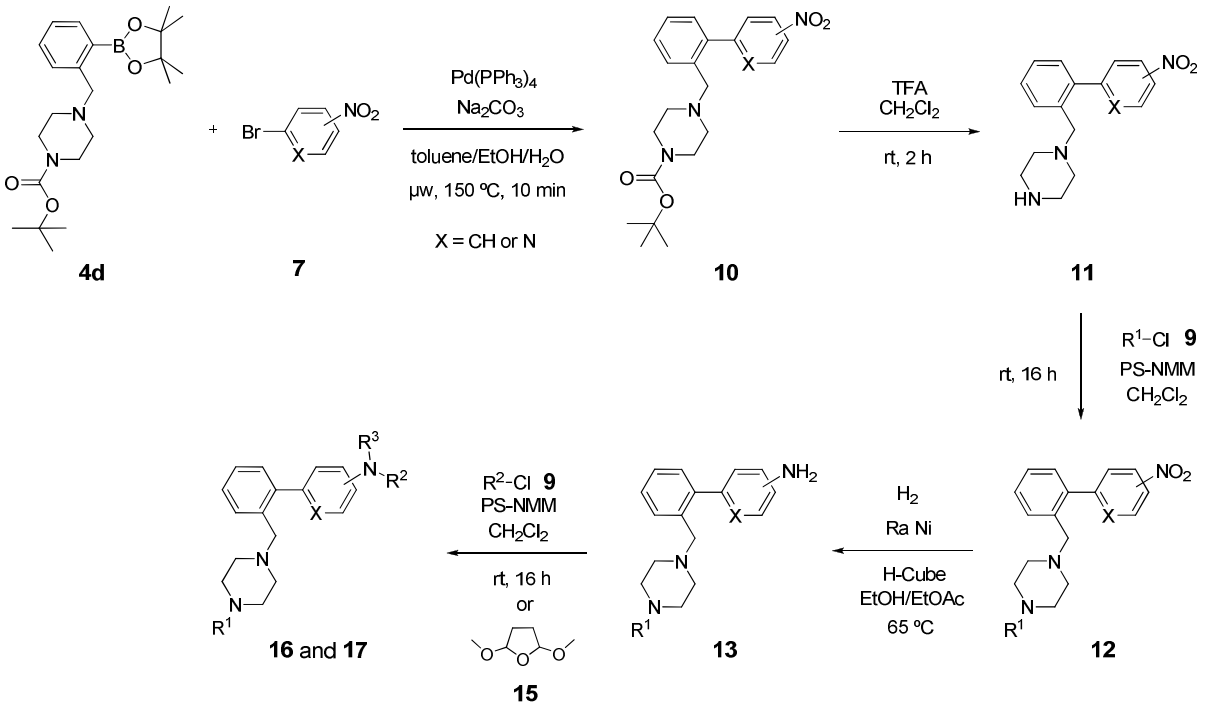
Figure 4.12. *o*-Substituted biaryls **21**.

o-Substituted biaryls **21** were obtained in good yields (e.g. 92% for **21a**) apart from **21d** which was obtained in less than 9% yield. This shows that *o*-substituted (*N*-, *S*- and *O*-methyl)phenylboronic esters are able to couple in a SM coupling reaction with electron withdrawing and electron rich aryl bromides to afford the respective biaryls.

Once the optimal conditions for the SM coupling of *o*-substituted phenylboronic esters were ascertained, the synthesis of a small library of *o*-substituted piperazin-1-ylmethylbiaryls was undertaken.

4.4. Synthesis of an *ortho*-substituted (piperazin-1-ylmethyl)biaryl library

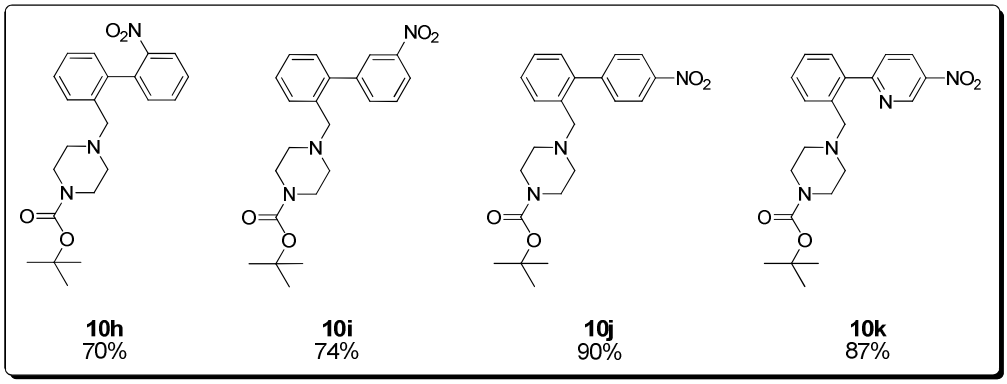
As described in Chapter 3, a (piperazin-1-ylmethyl)biaryl library can be synthesised from (Boc-piperazin-1-ylmethyl)phenylboronic acid pinacol esters **5d** and **6d**. This synthetic scheme was applied to **4d** in order to synthesise a small library of *o*-substituted (piperazin-1-ylmethyl)biaryls (Scheme 4.9). Compound **4d** was coupled with bromonitrobenzenes or bromonitropyridine in a SM coupling, then the Boc group could be removed and the amino group of the piperazine could be functionalised as an amide or a sulphonamide. The nitro group would be reduced and the resulting amino group would be functionalised into an amide, a sulphonamide or a pyrrole.



Scheme 4.9. Synthetic sequence to an *o*-(piperazin-1-ylmethy)biaryl library.

4.4.1. SM coupling

The SM coupling was achieved by using the previously optimised conditions for *o*-substituted methylphenylboronic esters. Hence, the *o*-substituted **4d** was coupled with *o*-, *m*- and *p*-bromonitrobenzenes and a bromopyridine to yield to a 2'-(Bocpiperazin-1-ylmethyl)nitrobiaryl library (Figure 4.13).



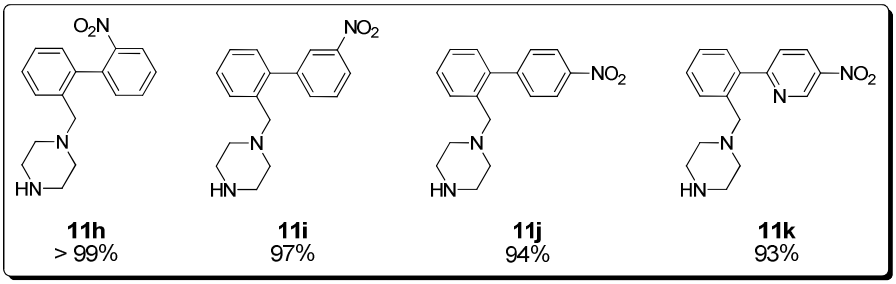
Percentage yields obtained after purification by chromatography.

Figure 4.13. A 2'-(Bocpiperazin-1-ylmethyl)nitrobiaryl library.

2'-(Bocpiperazin-1-ylmethyl)nitrobiaryls **10** were obtained in good yields and were then treated with TFA in order to remove the Boc protecting group.

4.4.2. Boc group removal

The Boc-protecting group on compounds **10h-k** was easily removed with TFA in CH_2Cl_2 in an overnight reaction to give 2'-(*NH*-piperazin-1-ylmethyl)nitrobiaryls **11h-k** (Figure 4.14).



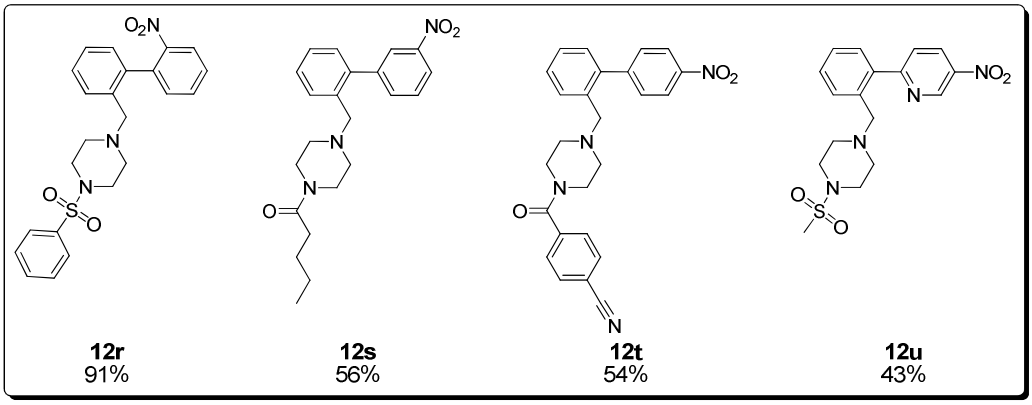
Percentage yield given.

Figure 4.14. A 2'-(*NH*-piperazin-1-ylmethyl)nitrobiaryl library.

2'-(*NH*-piperazin-1-ylmethyl)nitrobiaryls **11** were obtained in good yields and purities after a basic wash without any further purification.

4.4.3. Piperazine functionalisation

Compounds **11h-k** were reacted with acid or sulphonyl chlorides **9** to give **12r-u** (Figure 4.15).



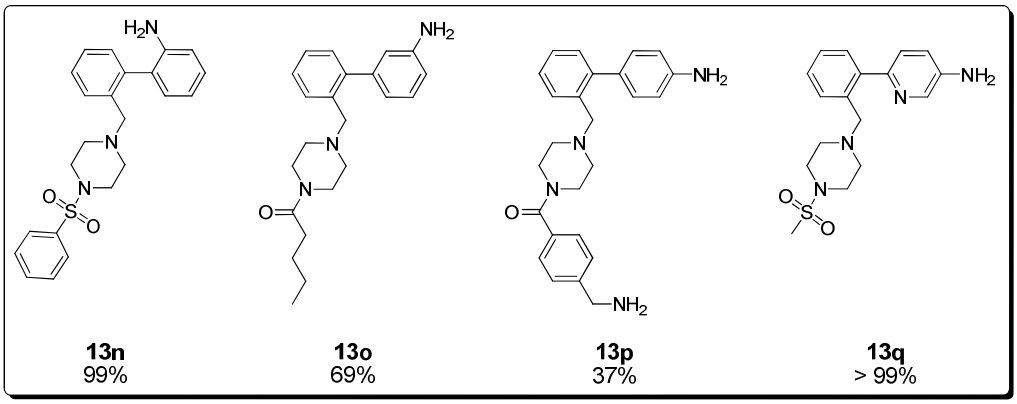
Percentage yields obtained after purification by chromatography.

Figure 4.15. A 2'-(piperazin-1-ylmethyl)nitrobiaryl library.

Derivatives **12r-u** were obtained in moderate to good yields.

4.4.4. Nitro group reduction

Compounds **12r-u** were then reduced by a flow chemistry hydrogenation (H-Cube) catalysed by Raney Nickel (see Chapter 3) to yield to the aniline derivatives **13n-q** (Figure 4.16).



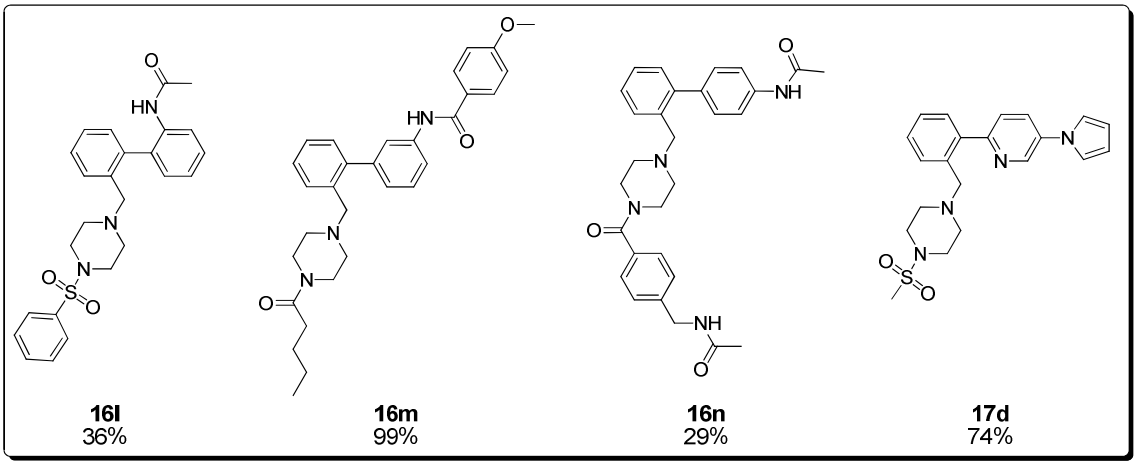
Percentage yield given.

Figure 4.16. A 2'-(piperazin-1-ylmethyl)phenylaniline library.

The aniline derivatives **13n-q** were obtained in moderate to good yields. It was observed that the cyano group in **12t** was also reduced to a benzylamine **13p** under the reaction conditions.

4.4.5. Aniline functionalisation

The biaryl derivatives **13** were then funtionalised to amides, sulphonamides or pyrroles (Figure 4.17).



Percentage yields obtained after purification by chromatography.

Figure 4.17. A 2'-(piperazin-1-ylmethyl)biaryl library.

A small library of 2'-(piperazin-1-ylmethyl)biaryls was obtained in moderate to very good yields and this complements the (piperazin-1-ylmethyl)biaryl library, previously synthesised in Chapter 3, now adding *o*-substituted isomers to the synthetic scope of this reaction.

4.4. Conclusion

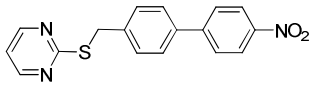
Suitable conditions were found and applied for the SM coupling reaction of *S*- and *o*-substituted methylphenylboronic esters with aryl bromides in order to synthesise a small library of biaryl derivatives in good yields. The (piperazin-1-ylmethyl)biaryl library was completed by the synthesis of *ortho*-derivatives, obtained after the optimisation of hitherto unsuccessful SM coupling conditions. Some of the *S*-substituted biaryls could be used to form unsymmetrical palladium pincers and two examples were synthesised and gave unexpected palladacycles. It would be interesting to carry on this work further in order to synthesise more palladacycle analogues and test them in palladium-catalysed reactions.

4.5. Experimental procedures and data

Experimental conditions and analytical methods are as for Chapter 2

General procedure for the SM coupling of sulphur-substituted methylphenylboronic esters using conditions A:

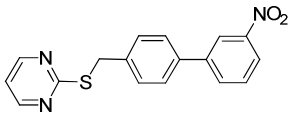
2-((4'-Nitrobiphenyl-4-yl)methylthio)pyrimidine **19a**



6g (0.5 mmol, 164 mg), **7c** (0.55 mmol, 111 mg), cesium fluoride (1.5 mmol, 228 mg), tetrakis(triphenylphosphine)palladium (0.025 mmol, 29 mg) and THF (2 mL) were placed in sealed microwave vial and stirred under microwave irradiation (maximum power 300 W) at 130 ºC for 10 min. The mixture was cooled to rt, diluted with EtOAc (20 mL) and water (10 mL) and extracted with EtOAc. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 269 mg of an orange solid. The crude product was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 147 mg of the expected product as a yellow solid in 91% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.55 (d, 2H, *J* = 4.8 Hz), 8.29 (d, 2H, *J* = 8.8 Hz), 7.72 (d, 2H, *J* = 8.8 Hz), 7.57 (m, 4H), 6.70 (dd, 1H, *J* = 4.8 Hz), 4.47 (s, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 157.3 (2C), 147.2, 147.1, 138.8, 137.6, 129.9 (2C), 127.7 (2C), 127.5 (2C), 124.1 (2C), 116.7, 34.8. HRMS-ES (m/z) found 324.0805, calcd for $[C_{17}H_{13}O_2N_3S + H]^+$ 324.0801. Elemental analysis CHN (%) found C: 62.9, H: 4.1, N: 12.9, calcd for $C_{17}H_{13}O_2N_3S$ C: 63.1, H: 4.1, N: 13.0.

General procedure for the SM coupling of sulphur-substituted methylphenylboronic esters using conditions B:

2-((3'-Nitrobiphenyl-4-yl)methylthio)pyrimidine **19b**

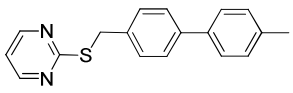


6g (0.38 mmol, 125 mg), **7d** (0.42 mmol, 85 mg), sodium carbonate (1.14 mmol, 121 mg), tetrakis(triphenylphosphine)palladium (0.01 mmol, 12 mg), toluene (1 mL), EtOH (1 mL) and

H_2O (1 mL) were placed in sealed microwave vial and stirred under microwave irradiation (maximum power 300 W) at 130 ºC for 10 min. The mixture was cooled to rt, diluted with EtOAc (20 mL) and water (10 mL) and extracted with EtOAc. The organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 195 mg of a brown oil. The crude product was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 104 mg of the expected product as a yellow solid in 85% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.53 (d, 2H, J = 4.8 Hz), 4.41 (m, 1H), 8.17 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.2 Hz), 7.87 (d, 1H, J = 7.7 Hz), 7.62-7.52 (m, 5H), 6.98 (dd, 1H, J = 4.8 Hz), 4.46 (s, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 157.3 (2C), 148.8, 142.5, 138.3, 137.5, 132.9, 129.9 (2C), 129.7, 127.2 (2C), 122.0, 121.8, 116.7, 34.8. HRMS-ES (m/z) found 324.0804, calcd for $[C_{17}H_{13}O_2N_3S + H]^+$ 324.0801. Elemental analysis CHN (%) found C: 62.9, H: 4.0, N: 13.1, calcd for $C_{17}H_{13}O_2N_3S$ C: 63.1, H: 4.1, N: 13.0.

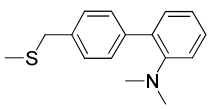
The other *S*-substituted aryl boronates were coupled in SM coupling reactions as for **19b**.

2-((4'-Methylbiphenyl-4-yl)methylthio)pyrimidine **19c**



Beige solid, 79 mg, 81% yield (on 0.3 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.53 (dd, 2H, J_1 = 4.8 Hz, J_2 = 1.7 Hz), 7.52-7.45 (m, 6H), 7.23 (d, 2H, J = 7.0 Hz), 6.97 (dd, 1H, J = 5.1 Hz), 4.45 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.2, 157.3 (2C), 140.1, 137.9, 137.0, 136.2, 129.5 (4C), 127.0 (2C), 126.9 (2C), 116.6, 35.0, 21.1. HRMS-ES (m/z) found 293.1111, calcd for $[C_{18}H_{16}N_2S + H]^+$ 293.1107. Elemental analysis CHN (%) found C: 73.0, H: 5.6, N: 9.6, calcd for $C_{18}H_{16}N_2S.0.04CHCl_3$ C: 72.9, H: 5.4, N: 9.4.

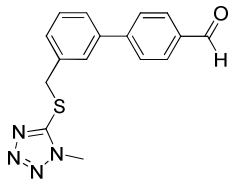
N,*N*-Dimethyl-4'-(methylthiomethyl)biphenyl-2-amine **19d**



The crude product was purified by chromatography on silica gel, hexane/CH_2Cl_2 from 0% to 50% of CH_2Cl_2, then purified on a SCX column, MeOH then MeOH/NH_3 and concentrated to

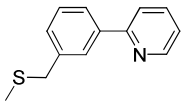
give 55 mg of the pure expected product as an orange oil in 65% yield (0.33 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.53 (d, 2H, *J* = 8.2 Hz), 7.32 (d, 2H, *J* = 7.8 Hz), 7.29-7.24 (m, 1H), 7.21 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 7.03 (d, 1H, *J* = 7.4 Hz), 6.99 (d, 1H, *J* = 7.4 Hz), 3.72 (s, 2H), 2.53 (s, 6H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, main rotamer) δ (ppm): 151.2, 140.6, 136.3, 133.8, 131.6, 128.8 (2C), 128.7 (2C), 128.0, 121.5, 117.6, 43.3, 38.1 (2C), 14.9. HRMS-ES (m/z) found 258.1314, calcd for $[C_{16}H_{19}NS + H]^+$ 258.1311.

3'-((1-Methyl-*1H*-tetrazol-5-ylthio)methyl)biphenyl-4-carbaldehyde **19e**



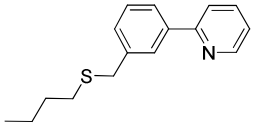
Orange oil, 38 mg in mixture with boronic ester (84/16), calcd yield 38% (by ^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.07 (s, 1H), 7.96 (d, 2H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 8.2 Hz), 7.67 (s, 1H), 7.59-7.55 (m, 1H), 7.50-7.45 (m, 2H), 4.62 (s, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 191.9, 153.5, 146.3, 140.4, 136.6, 135.5, 130.3 (2C), 129.6, 129.1, 128.1, 127.7 (2C), 127.2, 37.6, 33.4.

2-(3-(Methylthiomethyl)phenyl)pyridine **19f**



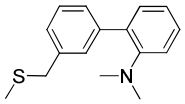
Colorless oil, 101 mg, 81% yield (0.58 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.70 (d, 1H, *J* = 4.8 Hz), 7.95 (s, 1H), 7.86 (d, 1H, *J* = 7.4 Hz), 7.78-7.72 (m, 2H), 7.44 (dd, 1H, *J* = 7.4 Hz), 7.38 (d, 1H, *J* = 7.4 Hz), 7.26-7.21 (m, 1H), 3.77 (s, 2H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.2, 149.7, 139.6, 138.9, 136.8, 129.4, 128.9, 127.4, 125.6, 122.2, 120.7, 38.3, 15.0. HRMS-ES (m/z) found 216.0845, calcd for $[C_{13}H_{13}NS + H]^+$ 216.0841.

2-(3-(Butylthiomethyl)phenyl)pyridine **19g**



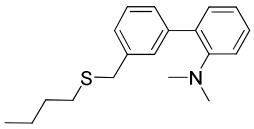
Yellow oil, 110 mg, 85% yield (0.5 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.70 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.3 Hz), 7.96 (s, 1H), 7.86 (d, 1H, J = 7.4 Hz), 7.79-7.72 (m, 2H), 7.43 (dd, 1H, J = 7.4 Hz), 7.38 (d, 1H, J = 6.5 Hz), 7.26-7.21 (m, 1H), 3.80 (s, 2H), 2.45 (t, 2H, J = 7.0 Hz), 1.56 (m, 2H), 1.37 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.3, 149.7, 139.6, 139.3, 136.7, 129.4, 128.9, 127.4, 125.5, 122.2, 120.7, 36.4, 31.3, 31.2, 22.0, 13.7. HRMS-ES (m/z) found 258.1308, calcd for $[C_{16}H_{19}NS + H]^+$ 258.1311.

N,*N*-Dimethyl-3'-(methylthiomethyl)biphenyl-2-amine **19h**



Colorless oil, 64 mg, 64% yield (0.39 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.51 (s, 1H), 7.46 (d, 1H, J = 7.8 Hz), 7.35 (dd, 1H, J = 7.8 Hz), 7.29-7.20 (m, 3H), 7.03 (d, 1H, J = 7.0 Hz), 7.00 (d, 1H, J = 7.4 Hz), 3.71 (s, 2H), 2.54 (s, 6H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 151.2, 142.0, 138.1, 133.8, 131.6, 129.2, 128.5, 128.1, 127.3, 127.0, 121.4, 117.6, 43.3 (2C), 38.4, 14.8. HRMS-ES (m/z) found 258.1311, calcd for $[C_{16}H_{19}NS + H]^+$ 258.1311.

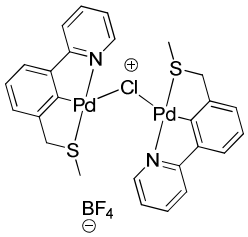
3'-(Butylthiomethyl)-*N*,*N*-dimethylbiphenyl-2-amine **19i**

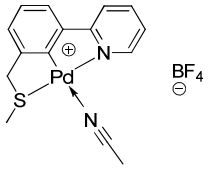


Colorless oil, 88 mg, 58% yield (0.51 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.51 (s, 1H), 7.45 (d, 1H, J = 7.4 Hz), 7.34 (dd, 1H, J = 7.9 Hz), 7.29-7.23 (m, 2H), 7.21 (d, 1H, J = 7.4 Hz), 7.03 (d, 1H, J = 7.4 Hz), 6.99 (d, 1H, J = 7.4 Hz), 3.73 (s, 2H), 2.54 (s, 6H), 2.44 (t, 2H, J = 7.4 Hz), 1.55 (m, 2H), 1.37 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 151.2, 142.0, 138.6, 133.8, 131.6, 129.2, 128.5, 128.1, 127.2, 127.0, 121.4, 117.5, 43.3 (2C), 36.3, 31.3, 30.9, 22.0, 13.7. HRMS-ES (m/z) found 300.1779, calcd for $[C_{19}H_{25}NS + H]^+$ 300.1780.

General procedure for the synthesis of a palladacycles from 19:

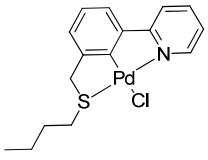
2-(3-(Methylthiomethyl)phenyl)pyridine chlorido-bridged palladacycle tetrafluoroborate **20c**

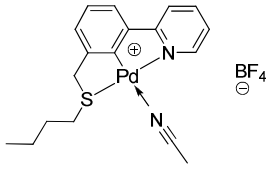




Palladium chloride (0.49 mmol, 87 mg) and MeCN (25 mL) were placed in a round bottomed flask and stirred under reflux (~ 85 °C) and nitrogen atmosphere until all $PdCl_2$ was dissolved. Silver tetrafluoroborate (0.98 mmol, 191 mg) was then added and the mixture left to stir under reflux and nitrogen atmosphere for 2 h. the mixture was cooled to rt and filtered. The solution of **19f** (0.47 mmol, 100 mg) in MeCN (10 mL) was added to the filtrate and the solution stirred under reflux and nitrogen atmosphere for 6 h. the mixture was cooled to rt and filtered. The filtrate was concentrated to give 305 mg of a yellow solid which was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 133 mg of a light yellow solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 8.38 (m, 1H), 8.07 (m, 2H), 7.56 (d, 1H, *J* = 7.3 Hz), 7.45 (ddd, 1H, J_1 = 7.3 Hz, J_2 = 1.8 Hz), 7.10 (dd, 1H, *J* = 7.3 Hz), 7.04 (d, 1H, *J* = 7.3 Hz), 4.40 (m, 2H), 2.74 (s, 3H). ^{13}C NMR (DMSO-d_6) δ (ppm): 164.1, 149.3, 148.3, 143.8, 141.0, 126.2, 125.4, 124.1, 123.1, 120.3, 46.1, 22.6 (one quaternary C missing). HRMS-ES presence of a mixture.

2-(3-(Butylthiomethyl)phenyl)pyridinechloropalladacycle **20d**

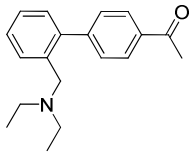




Pale yellow solid, 91 mg, (0.39 mmol scale). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.66 (m, 1H), 8.11 (m, 2H), 7.62 (d, 1H, *J* = 7.4 Hz), 7.50 (ddd, 1H, J_1 = 6.3 Hz, J_2 = 2.0 Hz), 7.14 (dd, 1H, *J* = 7.8 Hz), 7.08 (d, 1H, *J* = 6.6 Hz), 4.44 (m, 2H), 3.11 (t, 2H, *J* = 7.4 Hz), 1.81 (m, 2H), 1.43 (m, 2H), 0.89 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 164.4, 149.3, 148.7, 143.9, 140.6, 125.8, 125.0, 123.8, 122.9, 120.0, 45.0, 38.1, 31.3, 21.2, 13.4 (one quaternary C missing). HRMS-ES presence of a mixture.

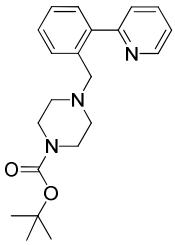
The *o*-substituted aryl boronates were coupled in SM coupling reactions as for **19b**.

1-(2'-((Diethylamino)methyl)biphenyl-4-yl)ethanone **21a**



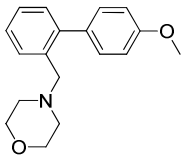
Pale yellow oil, 155 mg, 92% yield (0.6 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.99 (d, 2H, J = 8.6 Hz), 7.63 (d, 1H, J = 7.4 Hz), 7.46 (d, 2H, J = 8.2 Hz), 7.37 (ddd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 7.30 (ddd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 7.20 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 3.45 (s, 2H), 2.65 (s, 3H), 2.40 (q, 4H, J = 7.0 Hz), 0.88 (t, 6H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 198.0, 146.6, 141.4, 135.8, 130.3, 129.8 (3C), 129.7, 128.2 (3C), 127.0, 54.5, 46.5 (2C), 26.8, 11.3 (2C). HRMS-ES (m/z) found 282.1855, calcd for $[C_{19}H_{23}ON + H]^+$ 282.1852.

tert-Butyl 4-(2-(pyridin-2-yl)benzyl)piperazine-1-carboxylate **21b**



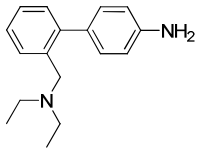
Yellow oil, 83 mg, 76% yield (0.31 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 8.66 (d, 1H J = 4.7 Hz), 7.75-7.69 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 2.0 Hz), 7.71-7.64 (m, 1H), 7.58-7.43 (m, 2H), 7.43-7.30 (m, 2H), 7.26-7.21 (m, 1H), 3.59 (s, 2H), 3.24 (m, 4H), 2.23 (m, 4H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 160.1, 154.8, 148.9, 141.2, 136.1, 135.9, 132.2, 132.1, 131.9, 130.2, 129.9, 128.6, 128.4, 128.1, 127.2, 124.2, 121.6, 79.4, 60.0, 52.5 (2C), 43.9, 42.9, 28.4 (3C). HRMS-ES (m/z) found 354.2180, calcd for $[C_{21}H_{27}O_2N_3 + H]^+$ 354.2176.

4-((4'-Methoxybiphenyl-2-yl)methyl)morpholine **21c**



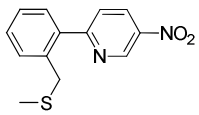
Yellow oil, 49 mg, (0.24 mmol scale). Mixture of the expected product and the protodeborylation product (87/13), yield 63% (calculated by ^{1}H NMR).

2'-((Diethylamino)methyl)biphenyl-4-amine **21d**



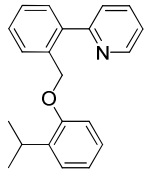
Brown oil, 13 mg, 9% yield (0.35 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73 (m, 1H), 7.32 (dd, 1H, J = 7.4 Hz), 7.27 (dd, 1H, J = 7.4 Hz), 7.21 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 6.73 (d, 2H, J = 8.2 Hz), 3.64 (m, 4H), 2.50 (q, 4H, J = 6.6 Hz), 0.96 (t, 6H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.3, 142.4, 131.5, 130.4 (3C), 130.1 (2C), 126.9 (2C), 114.7 (2C), 54.1, 46.5 (2C), 11.1 (2C). MS-ES (m/z) found 255.1, calcd for $[C_{17}H_{22}N_2 + H]^+$ 155.2.

2-(2-(Methylthiomethyl)phenyl)-5-nitropyridine **21e**



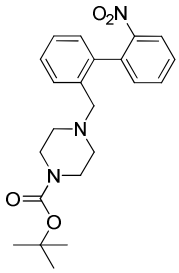
Orange oil, 85 mg, 79% yield, (0.41 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.51 (d, 1H, J = 2.6 Hz), 8.57 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.6 Hz), 7.76 (d, 1H, J = 8.7 Hz), 7.49-7.36 (m, 4H), 3.94 (s, 2H), 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 165.4, 144.6, 142.7, 138.2, 136.9, 131.7, 131.2, 130.5, 129.7, 127.7, 124.4, 36.0, 15.5. HRMS-ES (m/z) found 261.0689, calcd for $[C_{13}H_{12}O_2N_2S + H]^+$ 261.0692.

2-(2-((2-Isopropylphenoxy)methyl)phenyl)pyridine **21f**



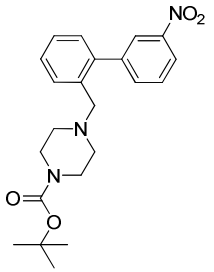
Yellow oil, 51 mg, 88% yield (0.19 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.69 (d, 1H, *J* = 5.1 Hz), 7.74 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 2.0 Hz), 7.70 (d, 1H, *J* = 7.0 Hz), 7.52 (d, 2H, *J* = 8.6 Hz), 7.50-7.40 (m, 2H), 7.28-7.22 (ddd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz), 7.20 (dd, 1H, J_1 = 7.4 Hz, J_2 = 2.0 Hz), 7.08 (ddd, 1H, J_1 = 5.9 Hz, J_2 = 1.6 Hz), 6.91 (dd, 1H, *J* = 7.4 Hz), 6.78 (d, 1H, *J* = 7.4 Hz), 5.22 (s, 2H), 3.32 (sept, 1H, *J* = 7.0 Hz), 1.16 (d, 6H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.1, 155.8, 149.2, 139.5, 137.3, 136.5, 135.6, 129.8, 128.7, 128.6, 127.8, 126.5, 126.0, 123.9, 122.0, 120.7, 111.7, 68.1, 26.6, 22.8 (2C). HRMS-ES (m/z) found 304.1687, calcd for $[C_{21}H_{21}ON + H]^+$ 304.1696.

tert-Butyl 4-((2'-nitrobiphenyl-2-yl)methyl)piperazine-1-carboxylate **10h**



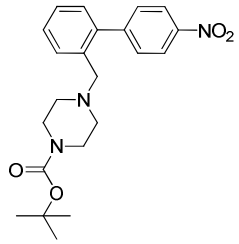
Yellow oil, 175 mg, 70% yield (0.63 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.08 (d, 1H, *J* = 8.4 Hz), 7.61 (dd, 1H, *J* = 7.2 Hz), 7.51 (dd, 1H, *J* = 8.0 Hz), 7.38-7.29 (m, 4H), 7.21-7.16 (m, 1H), 3.25-3.20 (m, 5H), 3.02 (m, 1H), 2.20-2.10 (m, 2H), 2.10-2.00 (m, 2H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.8, 149.0, 139.1, 136.6, 135.2, 132.4, 132.1, 130.0, 129.1, 128.3, 127.8, 127.8, 124.2, 79.5, 61.2, 52.7 (2C), 43.7 (2C), 28.5 (3C). HRMS-ES (m/z) found 398.2071, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

tert-Butyl 4-((3'-nitrobiphenyl-2-yl)methyl)piperazine-1-carboxylate **10i**



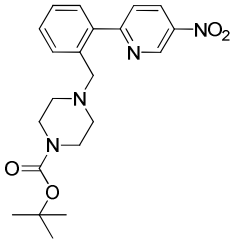
Orange oil, 273 mg, 74% yield (0.93 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.62 (m, 1H), 8.21 (ddd, 1H, J_1 = 8.2 Hz, J_2 = 2.3 Hz, J_3 = 0.8 Hz), 7.75 (d, 1H, J = 7.4 Hz), 7.56 (dd, 1H, J = 8.2 Hz), 7.42-7.35 (m, 3H), 7.32-7.27 (m, 1H), 3.37 (m, 4H), 3.28 (s, 2H), 2.31 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.7, 147.9, 143.1, 140.5, 135.5, 135.2, 131.2, 130.3, 128.8, 128.0, 127.7, 124.9, 122.0, 79.6, 60.5, 52.4 (2C), 44.2, 43.2, 28.4. HRMS-ES (m/z) found 398.2075, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

tert-Butyl 4-((4'-nitrobiphenyl-2-yl)methyl)piperazine-1-carboxylate **10j**



Yellow oil, 323 mg, 90% yield (0.90 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.25 (d, 2H, J = 8.6 Hz), 7.67 (d, 2H, J = 8.6 Hz), 7.47 (d, 1H, J = 7.0 Hz), 7.42-7.33 (m, 2H), 7.28-7.23 (m, 1H), 3.35 (s, 2H), 3.31 (m, 4H), 2.27 (m, 4H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 154.7, 148.5, 146.9, 140.6, 135.3, 130.7, 130.3 (2C), 129.9, 128.4, 127.5, 123.1 (2C), 79.6, 60.2, 52.4 (2C), 44.0, 43.2, 28.4 (3C). HRMS-ES (m/z) found 398.2077, calcd for $[C_{22}H_{27}O_4N_3 + H]^+$ 398.2074.

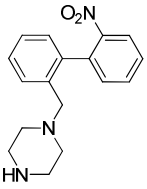
tert-Butyl 4-(2-(5-nitropyridin-2-yl)benzyl)piperazine-1-carboxylate **10k**



Orange solid, 324 mg, 87% yield (0.94 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.47 (d, 1H, J = 2.3 Hz), 9.04 (d, 0.2H, J = 2.3 Hz), 8.51 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.7 Hz), 8.22 (dd, 0.2H, J_1 = 9.8 Hz, J_2 = 2.7 Hz), 7.78 (d, 1H, J = 8.2 Hz), 7.48-7.37 (m, 4H), 7.32-7.28 (m, 0.4H), 6.56 (d, 0.2H, J = 9.8 Hz), 3.76 (m, 0.7H), 3.61 (s, 2H), 3.56 (m, 0.7H), 3.50 (s, 0.2H), 3.40 (m, 0.5H), 3.15 (m, 4H), 2.37 (m, 0.5H), 2.21 (m, 4H), 1.48 (s, 1.6H), 1.44 (s, 1H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 166.3, 154.8, 146.5, 144.4, 142.6, 139.1, 136.7, 133.2, 131.1, 130.9, 130.2, 129.5, 129.2, 128.3, 127.8, 127.2, 124.0, 104.7, 79.6, 60.4, 53.0, 52.4, 44.7, 43.2, 28.5. HRMS-ES (m/z) found 399.2031, calcd for $[C_{21}H_{26}O_4N_4 + H]^+$ 399.2027. Elemental analysis CHN (%) found C: 62.8, H: 6.5, N: 14.3, calcd for $C_{21}H_{26}O_4N_4.0.05CH_2Cl_2$ C: 62.8, H: 6.5, N: 13.9.

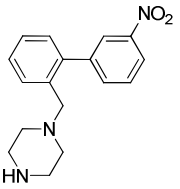
The Boc group removal of compounds **10h-k** was performed as for **11a** in Chapter 3:

1-((2'-Nitrobiphenyl-2-yl)methyl)piperazine **11h**



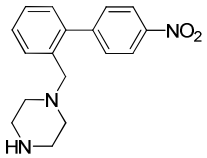
Orange oil, 131 mg, > 99% yield (0.44 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.09 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.1 Hz), 7.61 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 7.51 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.40-7.30 (m, 4H), 7.19-7.16 (m, 1H), 3.20 (d, 1H, J = 12.9 Hz), 3.03 (d, 1H, J = 13.3 Hz), 2.69 (m, 4H), 2.20 (m, 2H), 2.09 (m, 2H), 1.71 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.9, 139.0, 136.6, 135.5, 132.2, 132.1, 130.0, 129.0, 128.1, 127.6, 127.0, 124.1, 61.6, 54.2 (2C), 45.7 (2C). HRMS-ES (m/z) found 298.1554, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((3'-Nitrobiphenyl-2-yl)methyl)piperazine **11i**



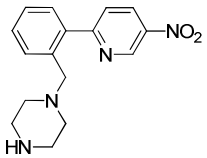
Orange oil, 196 mg, 97% yield (0.68 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.62 (m, 1H), 8.22 (d, 1H, *J* = 7.4 Hz), 7.78 (d, 1H, *J* = 7.4 Hz), 7.57 (dd, 1H, *J* = 8.2 Hz), 7.45-7.35 (m, 3H), 7.33-7.27 (m, 1H), 3.31 (s, 2H), 2.85 (m, 4H), 2.36 (m, 4H), 2.08 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm):147.9, 143.1, 140.5, 135.6, 135.4, 131.2, 130.2, 128.7, 127.9, 127.6, 124.9, 121.9, 61.0, 53.7 (2C), 46.0 (2C). HRMS-ES (m/z) found 298.1546, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-((4'-Nitrobiphenyl-2-yl)methyl)piperazine **11j**



Orange oil, 216 mg, 94% yield (0.77 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.26 (d, 2H, *J* = 8.2 Hz), 7.65 (d, 2H, *J* = 8.2 Hz), 7.47 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.3 Hz), 7.44-7.33 (m, 2H), 7.25 (dd, 1H, J_2 = 2.0 Hz), 3.33 (s, 2H), 2.80 (m, 4H), 2.32 (m, 4H), 2.30-1.90 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.6, 146.9, 140.6, 135.5, 130.8, 130.4 (2C), 129.9, 128.1, 127.4, 123.0 (2C), 60.8, 53.8 (2C), 46.0 (2C). HRMS-ES (m/z) found 298.1553, calcd for $[C_{17}H_{19}O_2N_3 + H]^+$ 298.1550.

1-(2-(5-Nitropyridin-2-yl)benzyl)piperazine **11k**

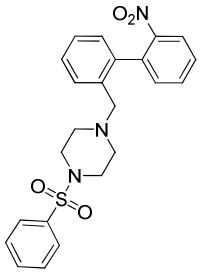


Brown oil, 211 mg, 93% yield (0.77 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 9.48 (d, 1H, *J* = 2.7 Hz), 9.04 (d, 0.2H, *J* = 3.0 Hz), 8.51 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.7 Hz), 8.20 (dd, 0.2H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 7.85 (dd, 1H, J_1 = 8.7 Hz, J_2 = 0.8 Hz), 7.50-7.38 (m, 4H), 7.34-7.30 (m, 0.3H), 6.56 (d, 0.2H, *J* = 9.5 Hz), 3.75 (m, 0.7H), 3.57 (s,

2H), 3.49 (s, 0.2H), 2.98 (m, 0.6H), 2.89 (m, 0.4H), 2.63 (m, 4H), 2.42 (m, 0.3H), 2.25 (m, 4H), 1.61 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 166.2, 146.5, 144.3, 142.6, 139.1, 136.8, 133.0, 130.9 (2C), 130.1, 129.3, 128.2, 127.6, 124.1, 104.4, 61.0, 53.8 (2C), 46.0 (2C). HRMS-ES (m/z) found 299.1506, calcd for $[C_{16}H_{18}O_2N_4 + H]^+$ 299.1503.

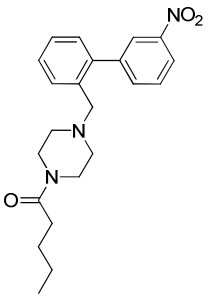
The piperazine functionalisation reaction on **11h-k** was performed as for **12a** in Chapter 3.

1-((2'-Nitrobiphenyl-2-yl)methyl)-4-(phenylsulphonyl)piperazine **12r**



The product was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 175 mg of the expected product as a yellow oil in 91% yield (0.44 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.92 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 7.73 (d, 2H, J = 7.6 Hz), 7.65 (dd, 1H, J = 7.6 Hz), 7.58 (d, 2H, J = 7.6 Hz), 7.53 (ddd. 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.43 (ddd. 1H, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.34-7.26 (m, 3H), 7.22 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.17-7.12 (m, 1H), 3.22 (d, 1H, J = 13.3 Hz), 3.02 (d, 1H, J = 12.9 Hz), 2.83 (m, 4H), 2.36-2.27 (m, 2H), 2.20-2.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.8, 138.9, 136.4, 135.6, 134.6, 132.8, 132.3, 131.8, 129.8, 129.1, 129.0 (2C), 128.1, 127.8 (3C), 127.4, 124.0, 60.5, 51.8 (2C), 45.7 (2C). HRMS-ES (m/z) found 438.1481, calcd for $[C_{23}H_{23}O_4N_3S + H]^+$ 438.1482.

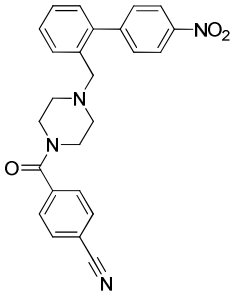
1-(4-((3'-Nitrobiphenyl-2-yl)methyl)piperazin-1-yl)pentan-1-one **12s**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 6:4, to give 133 mg of the pure expected product as a yellow oil in 56% yield (0.62 mmol scale). ^{1}H NMR

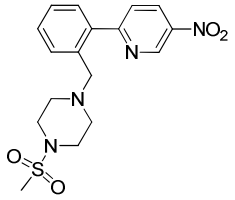
($CDCl_3$) δ (ppm): 8.66 (m, 1H), 8.22 (d, 1H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 7.6 Hz), 7.58 (dd, 1H, *J* = 8.0 Hz), 7.44-7.36 (m, 3H), 7.33-7.29 (m, 1H), 3.58 (m, 2H), 3.44 (m, 2H), 3.34 (s, 2H), 2.36 (m, 4H), 2.30 (t, 2H, *J* = 7.6 Hz), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.6, 147.8, 143.0, 140.5, 133.5, 135.0, 131.2, 130.3, 128.8, 128.0, 127.8, 124.9, 122.0, 60.4, 53.0, 52.2, 45.6, 41.5, 33.0, 27.5, 22.6, 13.9. HRMS-ES (m/z) found 382.2117, calcd for $[C_{22}H_{27}O_3N_3 + H]^+$ 382.2125.

4-(4-((4'-Nitrobiphenyl-2-yl)methyl)piperazine-1-carbonyl)benzonitrile **12t**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 8:2 and treated with PS-Trisamine in CH_2Cl_2 overnight at rt then filtered to give 154 mg of the pure expected product as a yellow oil in 54% yield (0.67 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (d, 2H, *J* = 8.7 Hz), 7.70 (d, 2H, *J* = 8.7 Hz), 7.59 (d, 2H, *J* = 8.7 Hz), 7.47 (d + m, 3H, J_d = 8.3 Hz), 7.44-7.36 (m, 2H), 7.29-7.24 (m, 1H), 3.68 (m, 2H), 3.41 (s, 2H), 3.25 (m, 2H), 2.42 (m, 2H), 2.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.1, 148.4, 147.0, 140.6, 140.1, 134.7, 132.4 (2C), 130.6, 130.2 (2C), 130.0, 128.4, 127.7 (3C), 123.1 (2C), 118.1, 113.5, 60.0, 52.9, 52.1, 47.6, 42.2. HRMS-ES (m/z) found 427.1762, calcd for $[C_{25}H_{22}O_3N_4 + H]^+$ 427.1765.

1-(Methylsulphonyl)-4-(2-(5-nitropyridin-2-yl)benzyl)piperazine **12u**

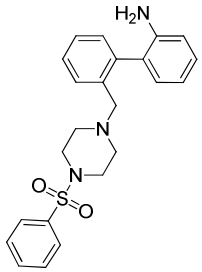


The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 8:2, to give 108 mg of the pure expected product as an orange oil in 43% yield (0.67 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.49 (d, 1H, *J* = 2.0 Hz), 8.54 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.7 Hz),

7.75 (d, 1H, *J* = 8.6 Hz), 7.52-7.40 (m, 4H), 3.69 (s, 2H), 3.02 (m, 4H), 2.72 (s, 3H), 2.41 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): (presence of rotamers) 166.2, 146.5, 144.3, 142.6, 139.1, 136.8, 133.0, 130.9 (2C), 130.1, 129.3, 128.2, 127.6, 124.1, 104.4, 61.0, 53.8 (2C), 46.0 (2C). HRMS-ES (m/z) found 377.1279, calcd for $[C_{17}H_{20}O_4N_4S + H]^+$ 377.1278.

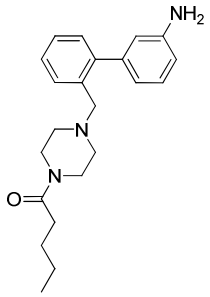
The nitro group reduction of **12r-u** was performed as for **13a** using the Raney nickel method in Chapter 3.

2'-((4-(Phenylsulphonyl)piperazin-1-yl)methyl)biphenyl-2-amine **13n**



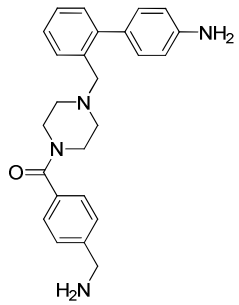
Pale yellow oil, 161 mg, 99% yield (0.40 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73 (dd, 2H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.62 (dd, 1H, *J* = 7.6 Hz), 7.54 (dd, 2H, *J* = 7.6 Hz), 7.45-7.39 (m, 1H), 7.32-7.27 (m, 2H), 7.21-7.17 (m, 1H), 7.13 (ddd. 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 6.92 (dd. 1H, J_1 =7.65 Hz, J_2 = 1.5 Hz), 6.73 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 6.67 (d, 1H, *J* = 8.0 Hz), 3.60-3.20 (m, 1H), 3.41 (d, 1H, *J* = 13.7 Hz), 3.26 (d, 1H, *J* = 13.7 Hz), 3.06-2.80 (m, 5H), 2.44-2.32 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 143.7, 139.1, 136.7, 135.6, 132.8, 130.4, 130.2, 129.5, 129.0 (2C), 128.5, 127.8 (2C), 127.7, 127.5, 126.7, 118.1, 115.1, 59.0, 51.8 (2C), 46.1 (2C). HRMS-ES (m/z) found 408.1749, calcd for $[C_{23}H_{25}O_2N_3S + H]^+$ 408.1740.

1-(4-((3'-Aminobiphenyl-2-yl)methyl)piperazin-1-yl)pentan-1-one **13o**



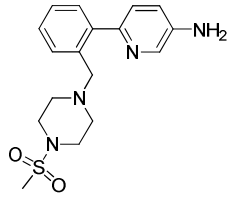
Yellow oil, 82 mg, 69% yield (0.34 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.52 (d, 1H, *J* = 7.0 Hz), 7.35-7.22 (m, 3H), 7.17 (dd, 1H, *J* = 8.6 Hz), 6.73 (d, 1H, *J* = 7.8 Hz), 6.70-6.65 (m, 2H), 3.69 (m, 2H), 3.56 (m, 2H), 3.44 (s, 2H), 3.40 (m, 2H), 2.32 (m, 4H), 2.28 (t, 2H, *J* = 7.8 Hz), 1.58 (m, 2H), 1.34 (m, 2H), 0.91 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.6, 146.0, 142.9, 142.4, 135.2, 129.9, 129.6, 128.8, 127.1, 126.8, 120.0, 116.2, 113.4, 59.5, 53.0, 52.5, 45.8, 41.6, 33.0, 27.5, 22.6, 13.9. Used as such for the next step.

(4-((4'-Aminobiphenyl-2-yl)methyl)piperazin-1-yl)(4-(aminomethyl)phenyl)methanone **13p**



Orange oil, 52 mg, 37% yield (0.35 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.45 (m, 1H), 7.40 (d, 1H, *J* = 7.5 Hz), 7.36-7.20 (m, 6H), 7.15 (d, 2H, *J* = 7.8 Hz), 6.70 (d, 2H, *J* = 8.0 Hz), 4.50-3.50 (m, 8H), 3.44 (s, 2H), 3.33 (m, 2H), 2.42 (m, 2H), 2.30 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.0, 145.4, 142.9, 135.2, 135.0, 131.5, 130.4 (2C), 130.3 (2C), 129.9 (2C), 128.1, 127.4 (2C), 127.0, 126.6, 114.6 (2C), 59.7, 53.0, 52.4, 47.8, 42.4, 30.9. Used as such for the next step.

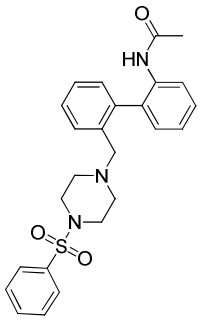
6-(2-((4-(Methylsulphonyl)piperazin-1-yl)methyl)phenyl)pyridin-3-amine **13q**



Orange oil, 97 mg, > 99% yield (0.28 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.19 (d, 1H, *J* = 2.7 Hz), 7.52-7.46 (m, 1H), 7.41-7.36 (m, 1H), 7.36-7.30 (m, 2H), 7.30-7.23 (m, 1H), 7.05 (dd, 1H, J_1 = 8.2 Hz, J_2 = 3.1 Hz), 3.80 (m, 2H), 3.66 (s, 2H), 3.14 (m, 4H), 2.75 (s, 3H), 2.46 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.6, 141.1, 141.0, 136.3, 135.2, 130.1, 130.0, 127.7, 127.3, 124.3, 121.8, 59.3, 51.9 (2C), 45.9 (2C), 34.2. HRMS-ES (m/z) found 347.1543, calcd for $[C_{17}H_{22}O_2N_4S + H]^+$ 347.1536.

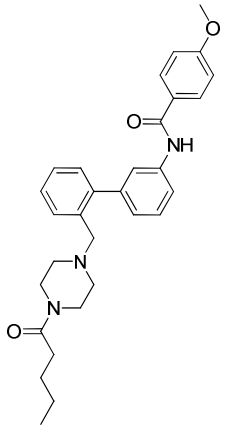
The piperazine functionalisation reaction on **131n-p** was performed as for **12a** in Chapter 3.

N-(2'-((4-(Phenylsulphonyl)piperazin-1-yl)methyl)biphenyl-2-yl)acetamide **16l**



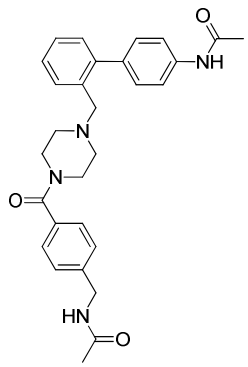
168 mg of a yellow oil were obtained and purified by chromatography on silica gel, CH_2Cl_2/EtOAc 9:1-7:3, to give 55 mg of the pure expected product as a colorless oil in 36% yield (0.34 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.19 (s, 1H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.73 (d, 2H, *J* = 7.0 Hz), 7.63 (dd, 1H, *J* = 7.4 Hz), 7.55 (dd, 2H, *J* = 7.8 Hz), 7.38-7.26 (m, 4H), 7.18-7.09 (m, 2H), 7.03 (d, 1H, *J* = 6.2 Hz), 3.35 (d, 1H, *J* = 12.9 Hz), 3.07 (d, 1H, *J* = 12.9 Hz), 2.93 (m, 4H), 2.64 (m, 2H), 2.33 (m, 2H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.7, 139.2, 135.4, 135.3, 134.9, 133.6, 133.1, 130.7, 130.2, 130.0, 129.1 (2C), 128.3, 128.1, 127.9, 127.8 (2C), 124.6, 123.6, 60.3, 51.8 (2C), 45.9 (2C), 24.0. HRMS-ES (m/z) found 450.1844, calcd for $[C_{25}H_{27}O_3N_3S + H]^+$ 450.1846.

4-Methoxy-*N*-(2'-((4-pentanoylpiperazin-1-yl)methyl)biphenyl-3-yl)benzamide **16m**



180 mg of a pale orange oil were obtained and purified by chromatography on silica gel, CH_2Cl_2/MeOH from 0% to 10% of MeOH, to give 105 mg of the pure expected product as a beige solid in 99% yield (0.22 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (d, 2H, *J* = 8.6 Hz), 7.78 (m, 1H), 7.66 (m, 1H), 7.59 (m, 1H), 7.51 (m, 1H), 7.41-7.26 (m, 4H), 7.14 (d, 1H, *J* = 6.4 Hz), 6.98 (d, 2H, *J* = 8.6 Hz), 3.88 (s, 3H), 3.54 (m, 2H), 3.46 (m, 2H), 3.38 (m, 2H), 2.33 (m, 4H), 2.27 (t, 2H, *J* = 7.5 Hz), 1.56 (m, 2H), 1.32 (m, 2H), 0.89 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.7, 165.3, 162.6, 142.4 (2C), 137.8, 130.2 (2C), 128.9 (2C), 128.7, 127.5, 127.2, 127.0, 125.5 (2C), 121.4, 118.9, 114.0 (2C), 59.5, 55.5, 52.9, 52.4, 45.5, 41.4, 33.0, 27.5, 22.6, 13.9. HRMS-ES (m/z) found 486.2744, calcd for $[C_{30}H_{35}O_3N_3 + H]^+$ 486.2751. Elemental analysis CH (%) found C: 72.1, H: 7.6, calcd for $C_{30}H_{35}O_3N_3 0.9CH_3OH$ C: 72.1, H: 7.6.

N-(4-(4-((4'-Acetamidobiphenyl-2-yl)methyl)piperazine-1-carbonyl)benzyl)acetamide **16n**

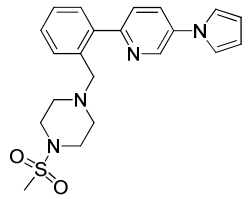


Beige solid, 18 mg, 29% yield (0.13 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (m, 1H), 7.54 (d, 2H, *J* = 8.6 Hz), 7.48 (d, 1H, *J* = 7.0 Hz), 7.40-7.20 (m, 9H), 6.34 (m, 1H), 4.40 (d,

2H, *J* = 5.9 Hz), 3.69 (m, 2H), 3.43 (s, 2H), 3.32 (m, 2H), 2.41 (m, 2H), 2.25 (m, 2H), 2.18 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 170.0, 168.7, 142.2, 140.1, 137.1 (2C), 135.0, 134.8, 130.2, 130.1, 130.0 (2C), 127.6 (2C), 127.3 (2C), 127.2 (2C), 119.3 (2C), 59.6, 53.0, 52.3, 47.8, 43.2, 42.2, 24.5, 23.2. HRMS-ES (m/z) found 485.2547, calcd for $[C_{29}H_{32}O_3N_4 + H]^+$ 485.2547.

The synthesis of pyrrole derivatives **17d** was performed as for **17a** in Chapter 3.

1-(2-(5-(*1H*-Pyrrol-1-yl)pyridin-2-yl)benzyl)-4-(methylsulphonyl)piperazine **17d**

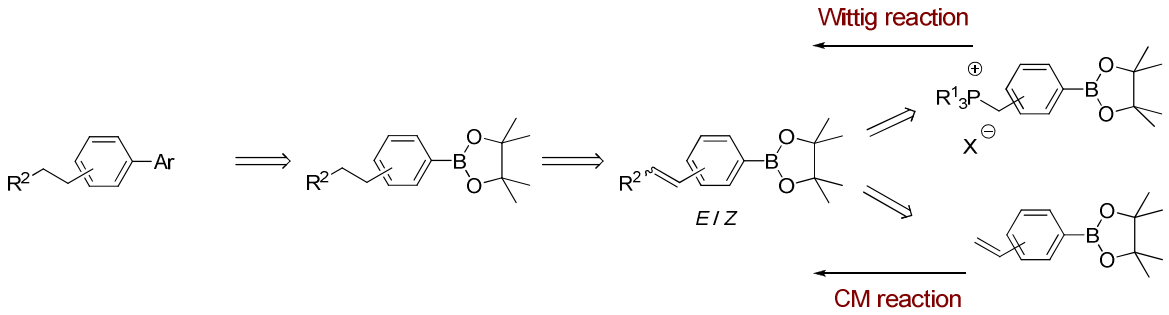


106 mg of a brown oil was obtained and purified by chromatography on silica gel, CH_2Cl_2/EtOAc 6:4, to give 79 mg of the pure expected product as a beige solid 74% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.80 (d, 1H, *J* = 2.3 Hz), 7.76 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.7 Hz), 7.58 (d, 1H, *J* = 9.0 Hz), 7.53-7.50 (m, 1H), 7.48-7.44 (m, 1H), 7.42-7.37 (m, 2H), 7.16 (dd, 2H, *J* = 2.1 Hz), 6.44 (dd, 2H, *J* = 2.1 Hz), 3.69 (s, 2H), 3.10 (m, 4H), 2.73 (s, 3H), 2.45 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.9, 140.8, 140.1, 135.7, 135.3, 130.2, 130.0, 128.4, 127.5, 127.4, 124.4, 119.1 (2C), 111.5 (2C), 59.5, 51.9 (2C), 45.9 (2C), 34.2. HRMS-ES (m/z) found 397.1686, calcd for $[C_{21}H_{24}O_2N_4S + H]^+$ 397.1693. Elemental analysis CHN (%) found C: 63.2, H: 5.9, N: 13.6, calcd for $C_{21}H_{24}O_2N_4S$ .0.04CH_2Cl_2 C: 63.2, H: 6.1, N: 14.0.

Chapter 5: Synthesis of an arylethylbiaryl library

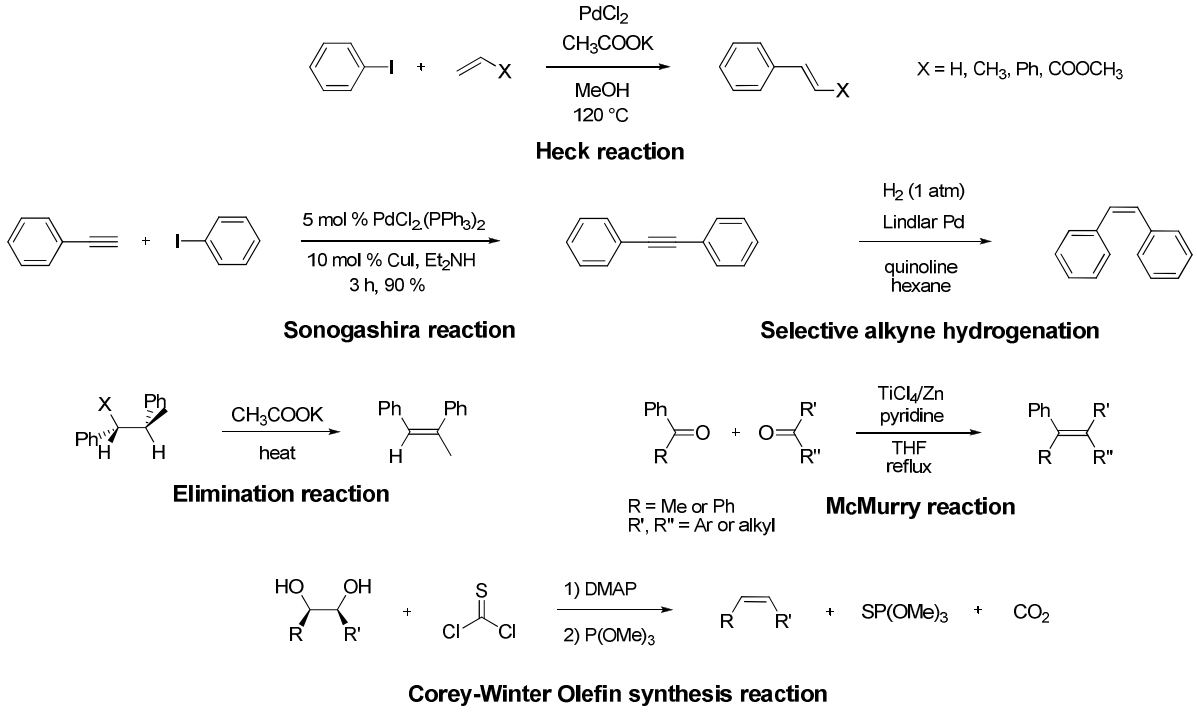
5.1. Introduction

In principle, the arylethylbiaryl unit can be obtained by the hydrogenation of the alkene function of an aryl-substituted stilbene (Scheme 5.1). Two retrosynthetic methods were envisaged *viz* Wittig and cross-metathesis (CM) reactions.



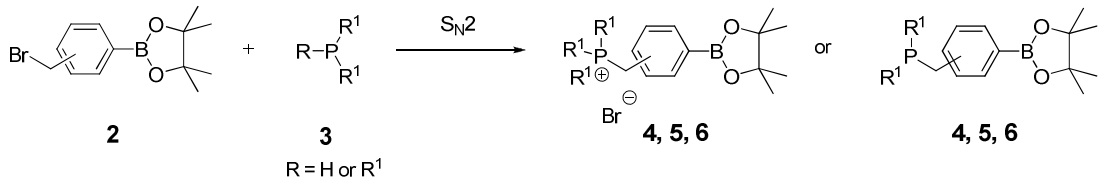
Scheme 5.1. Retrosynthesis of an arylethylbiaryl library.

Such alkenyl derivatives can be synthesised in many other ways (Scheme 5.2), e.g. *via* the following reactions: Heck reaction,[133] Sonogashira reaction[134] then selective alkyne hydrogenation,[135] dehydration, elimination, McMurry reaction,[136] Corey-Winter Olefin Synthesis,[137] etc.



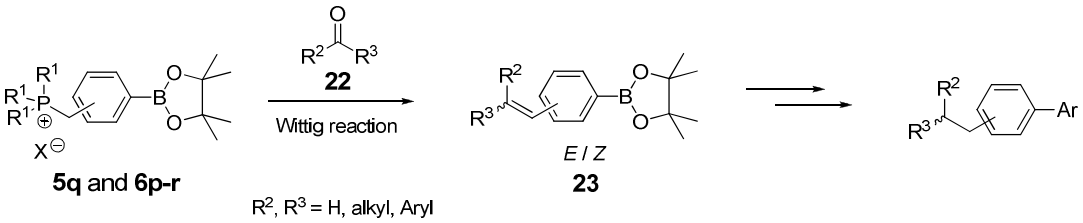
Scheme 5.2. Examples of alkene syntheses.

In order to enlarge the synthetic scope of the aryl boronate library presented in this project, phosphorus derivatives were added to the list of possible nucleophiles to use in the S_N2 reaction. Microwave-mediated S_N2 reactions were attempted with secondary and tertiary phosphines and afforded aryl boronate phosphines or phosphonium salts, respectively (Scheme 5.3).



Scheme 5.3. S_N2 reaction on compounds **2** with *P*-nucleophiles.

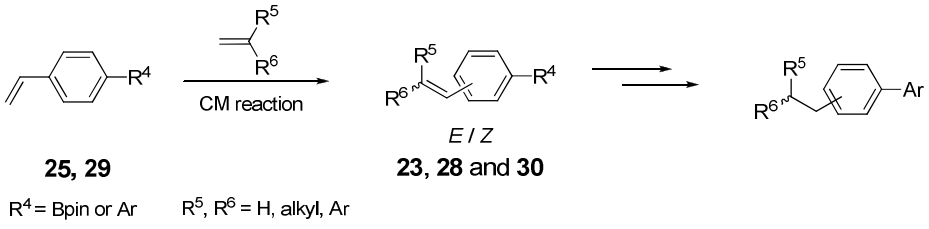
The phosphonium arylboronic ester salts obtained were considered to be interesting precursors for the Wittig reaction and the resulting alkenylarylboronic esters could lead to another family of biaryls with a different alkyl-linked functionality compared to the libraries previously made (Scheme 5.4).



Scheme 5.4. Wittig reaction on compounds **5q** and **6p-r** leading to a new biaryl library.

The alkenylarylboronic esters **23** could be reduced and then coupled in a SM reaction.

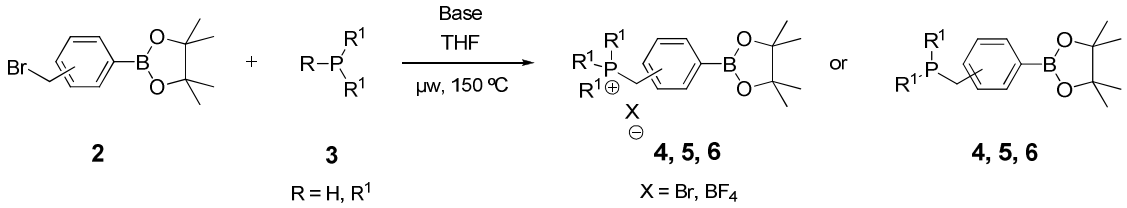
From the 4-vinylphenylboronic acid, an alternative CM reaction could be used to synthesise functionalised alkenylarylboronates (Scheme 5.5).



Scheme 5.5. CM reaction on compounds **25** and **29** leading to a new biaryl library.

5.2. Bromide displacement by phosphorus nucleophiles

Like *N*-, *S*- and *O*-nucleophiles, phosphines are also known to participate in S_N2-type reactions with benzylbromides **2**, as shown in Scheme 5.6. Secondary or tertiary phosphines (Figure 5.1) were used for the microwave-mediated S_N2 reaction to give the corresponding phosphine or phosphonium salt of the arylboronic acid pinacol ester, respectively. ^{31}P NMR spectroscopy proved to be a very useful tool for determining whether the reaction had taken place (Table 5.1).



Scheme 5.6. S_N2 reaction on compounds **2** with *P*-nucleophiles.

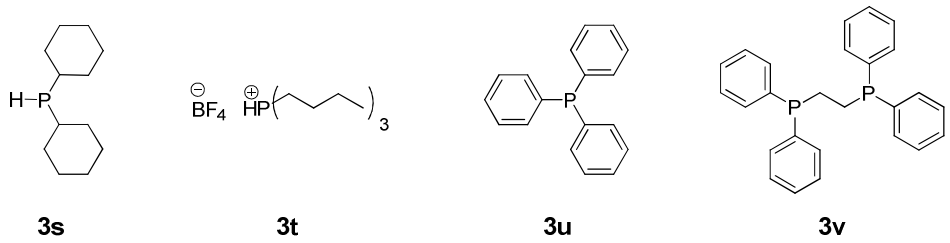
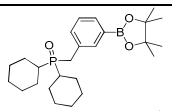
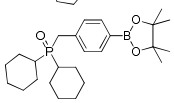
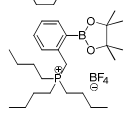
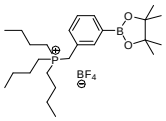
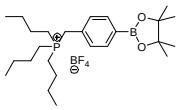
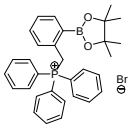
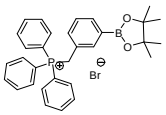
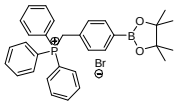
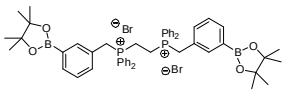
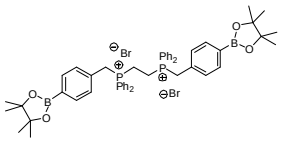


Figure 5.1. *P*-Nucleophiles.

Table 5.1. S_N2 reactions on compounds **2** with phosphorus nucleophiles.

Entry	**3**	Time (min)	Base	Product (**4**-**6**)		^{31}P NMR for **4**-**6** δ (ppm)[b]	Yield (%)
1	**3s**	30	PS-NMM		**5o**	28.9	82
2	**3s**	20	PS-NMM		**6o**	29.3	> 99
3	**3t**	15	PS-NMM		**4i**	32.1	> 99
4	**3t**	20	PS-NMM		**5p**	32.7	> 99
5	**3t**	45	PS-NMM		**6p**	32.5	> 99
6	**3u**	20	_		**4j**	24.4	> 99[a]
7	**3u**	30	_		**5q**	23.8	87[a]
8	**3u**	20	_		**6q**	23.7	> 99[a]
9	**3v**	20	_		**5r**	29.7	84[a]
10	**3v**	20	_		**6r**	28.8[c]	92[a]

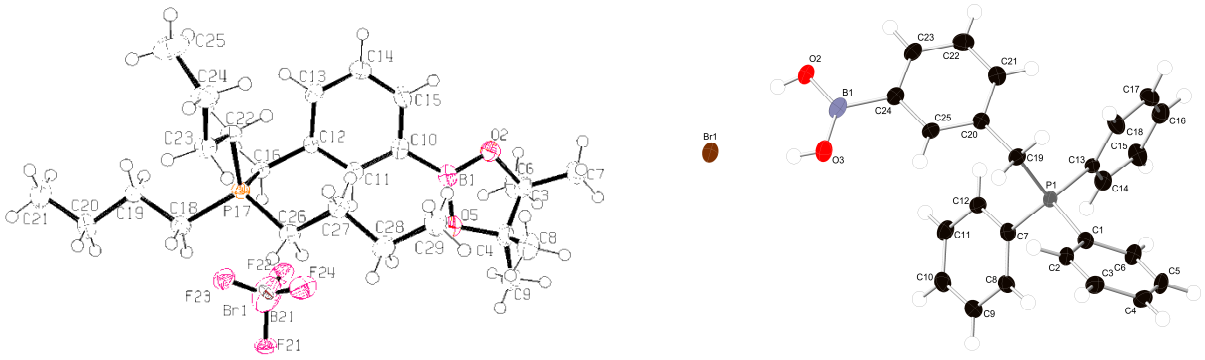
^{31}P NMR for **3** δ (ppm): **3s**[d,e]: -26.5, 18.8, 40.4, 50.8; **3t**: 14.1; **3u**: -4.8; **3v**: -11.9.

[a] Reaction achieved at 110 ºC. [b] ^{31}P NMR in $CDCl_3$. [c] ^{31}P NMR in dmso-d_6. [d] Solution 10 % in hexane. [e] ^{31}P NMR calculated $PHCy_2$ (w.r.t 85 % H_3PO_4): -30 ppm.[138]

Dicyclohexylphosphine is air sensitive and is likely to have oxidised during the S_N2 reaction and the NMR determination. Indeed, the phosphine oxides **5o** and **6o** were unexpected products. Their ^{31}P NMR chemical shifts, 28.9 ppm and 29.3 ppm, respectively, show that it is the phosphine oxides which were obtained instead of the expected phosphines (^{31}P NMR chemical shifts of phosphines are generally negative relative to TMS).

Regardless of this unexpected oxidation, phosphine oxide and phosphonium salt derivatives were easily prepared in very good to quantitative yields (Table 5.1).

Crystals of **5p** and **5q** (the pinacol ester hydrolysed) were grown and analysed by X-ray crystallographic analysis (Figure 5.2). The presence of the boronic acid derivative in the *m*- and *p*-triphenylphosphonium bromide salts **5p** and **6p** was confirmed by mass spectrometry and X-ray analyses.



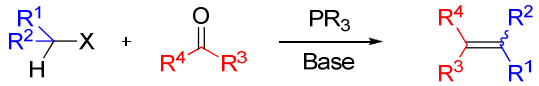
5p boronic acid of **5q**

Figure 5.2. Crystal structures of **5p** and the boronic acid of **5q**.

5.3. Wittig reaction

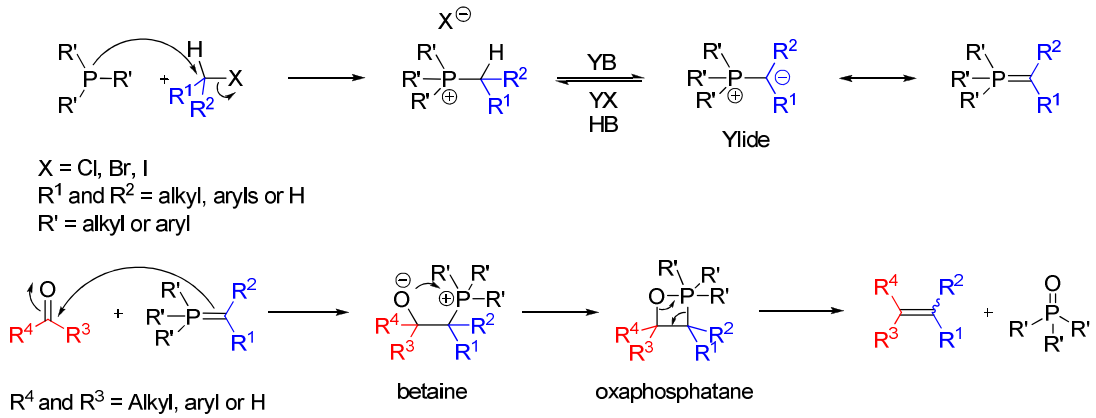
5.3.1. Introduction to the Wittig reaction

The Wittig reaction is one of the most important methods for the synthesis of alkenes from alkyl halides and aldehydes or ketones (Scheme 5.7) *via* a phosphonium ylide.[139]



Scheme 5.7. The Wittig reaction

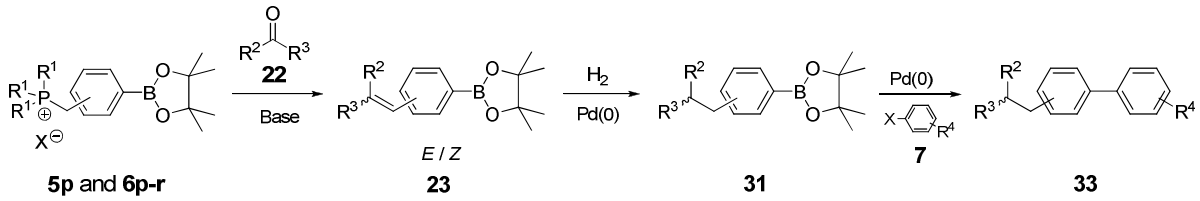
The Wittig reagent (the ylide) is prepared by the reaction of a strong base on a phosphonium salt. Subsequently, this ylide will react with an aldehyde or a ketone to form an alkene (Scheme 5.8).



Scheme 5.8. Mechanism of the Wittig reaction.

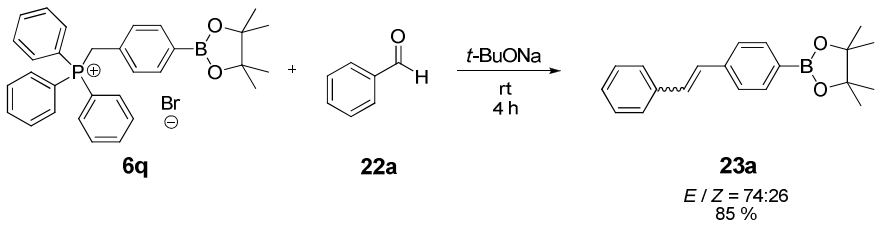
5.3.2. Wittig reaction on compounds **5q** and **6p-r**

As previously highlighted (S_N2 reaction with *P*-nucleophiles), a Wittig reaction was envisaged to synthesise arylboronic esters containing an alkene function prior to reducing the resulting double bond of the stilbene derivatives and achieving a SM coupling (Scheme 5.9).



Scheme 5.9. Synthesis of a biphenyl library from phosphonium precursors.

Unfortunately, shortly after starting the investigation of the Wittig reaction of **6q** with aldehydes, another study was published independently[57a] (Scheme 5.10) and the experimental methodologies employed gave the expected products in very good yields.



Scheme 5.10. Example of the recently published Wittig reaction on **6q**.

However, the chemistry related herein differs in that:

(i) other phosphonium precursors have been employed, such as tri-*n*-butylphosphonium tetrafluoroborate.

(ii) the phosphonium salts were synthesised using a microwave-mediated method.

The Wittig reaction using an arylboronic acid pinacol ester aldehyde component with phosphorus derivatives was also published few years ago (see Chapter 1; ref 56).

The Wittig reaction on the previously synthesised phosphorus derivatives **5q** and **6p-r** (Figure 5.3) was attempted using different aldehydes as partners (Figure 5.4) and with similar conditions, sodium *tert*-butoxide as a base in DMF or acetonitrile, under an inert atmosphere and at room temperature (Scheme 5.11), in order to compare the yield and the *E/Z* ratio of products **23** obtained, as outlined in Tables 5.2-5, since generally, semi-stabilised ylides, like benzyl ylides, yield mixtures of *Z*- and *E*- isomers when using unsymmetrical aldehydes or ketones.[139d]

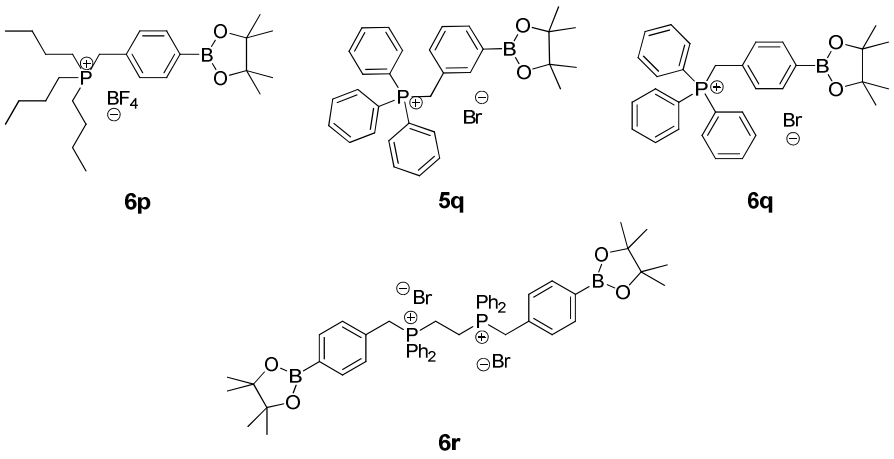


Figure 5.3. Phosphonium salts **5q** and **6p-r**.

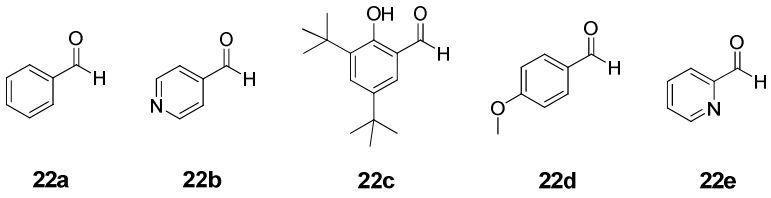
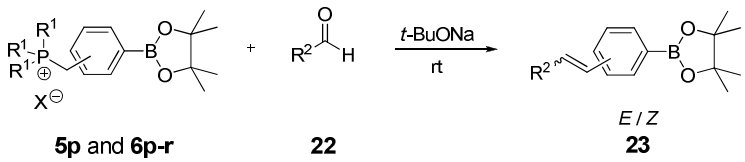


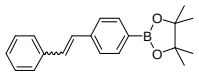
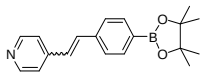
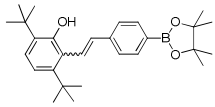
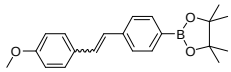
Figure 5.4. Aldehydes **22**.



Scheme 5.11. Wittig reaction on **5q** and **6p-r**.

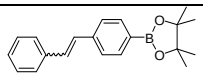
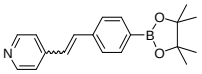
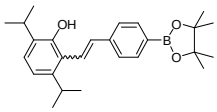
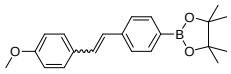
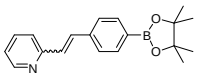
The Wittig reaction was first performed on the triphenylphosphonium salt **6q** in order to attempt to reproduce the conditions described in the literature (Table 5.2) and then on **6p** (Table 5.3), **6r** (Table 5.4) and **5q** (Table 5.5).

Table 5.2. Comparison with the literature for the Wittig reactions on **6q**.

Entry	**22**	Time (h)	Solvent	Product (**23**)	*E/Z* ratio[a]	Yield (%)
1	**22a**	3	DMF	 **23a**	15:85	22
2	**22a**	2	DMF	**23a**	44:56	69[b]
3	**22a**	2	MeCN	**23a**	19:81	56[b]
4	**22b**	4	DMF	 **23b**	64:36	29
5	**22b**	4	DMF	**23b**	43:57	49[b]
6	**22c**	20	DMF	 **23c**	67:33	29
7	**22c**	12	DMF	**23c**	48:52	11
8	**22d**	4	DMF	 **23d**	91:9	68
9	**22d**	2	DMF	**23d**	42:58	54[b]

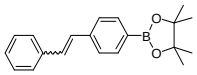
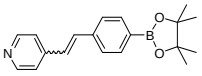
Conditions: **22** (1 equiv.), sodium *tert*-butoxide (3 equiv.), DMF or acetonitrile, inert atmosphere, rt. Percentage yields obtained after purification by chromatography.
[a] Calculated by ^{1}H NMR. [b] base added slowly.

Table 5.3. Wittig reactions on **6p**.

Entry	**22**	Time (h)	**23**	E/Z ratio[a]	Yield (%)
1	**22a**	7	 **23a**	43:57	42
2	**22a**	16	**23a**	24:76	49[b]
3	**22b**	4	 **23b**	73:27	36
4	**22b**	16	**23b**	31:69	62[b]
5	**22c**	16	 **23c**	–	–[c]
6	**22d**	20	 **23d**	93:7	84
7	**22d**	16	**23d**	–[d]	55
8	**22e**	3	 **23e**	28:72	50

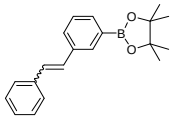
Conditions: **22** (1 equiv.), sodium *tert*-butoxide (3 equiv.), DMF, inert atmosphere, rt. Percentage yields obtained after purification by chromatography.
[a] Calculated by ^{1}H NMR. [b] base added slowly. [c] Traces of expected product (^{1}H NMR). [d] Could not be determined by ^{1}H NMR.

Table 5.4. Wittig reactions on **6r**

Entry	**22** (equiv.)	Time (h)	**23**	E/Z ratio[a]	Yield (%)
1	**22a** (2)	15	 **23a**	91:9	42
2	**22a** (4)	4	**23a**	83:17	48
3	**22b** (4)	4	 **23b**	81:19	53

Conditions: Sodium *tert*-butoxide (3 equiv.), DMF, inert atmosphere, rt. Percentage yields obtained after purification by chromatography.
[a] Calculated by ^{1}H NMR.

Table 5.5. Wittig reactions on **5q**.

Entry	**22**	Time (h)	Product	E/Z ratio[a]	Yield (%)
1	**22a**	4	 **23f**	40:60	74

Conditions: **22** (1 equiv.), sodium *tert*-butoxide (3 equiv.), DMF, inert atmosphere, rt. Percentage yields obtained after purification by chromatography.
[a] Calculated by ^{1}H NMR.

All the products were obtained and characterised after purification by chromatography and if any aldehyde was still detected, it was removed by reaction with PS-Ts-$NHNH_2$ scavenger resin.

The results obtained for the Wittig reaction were generally unsatisfactory. A maximum yield of 69% was obtained for the reaction of the triphenylphosphonium salt **6q** with benzaldehyde (**22a**) (Table 5.2, entry 2), which is poor compared with the yield (85%) reported in the literature. The Wittig reaction of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**22c**) gave poor results with a maximum yield of 29% (Table 5.2, entry 4) while a 71% yield is reported in the literature, for the corresponding reaction with **6q**. The explanation for the disparity in the yields obtained to those in the literature could not be found. However, the effect of the rate of addition of the base on the reaction yield has been investigated.[140] In some cases the yield increased from 29% to 49% (Table 5.2, entries 4 and 5) or from 36% to 62% (Table 5.3, entries 3 and 4); in one instance it did not appear to be affected by the addition rate, from 42% to 49% (Table 5.3, entries 1 and 2) and in another case it decreased from 68 % to 54% (Table 5.2, entries 10 and 11).

A good yield of 74% was obtained when the *m*-substituted triphenylphosphonium salt derivative **5q** was reacted with **22a** (Table 5.5, entry 1).

The observed *E/Z* ratios of the stilbene products **23** (calculated by ^{1}H NMR) differ from those reported in the literature and appear to depend on the nature of the solvent (Table 5.2, entries 2 and 3), the rate of the addition of the base (Table 5.2, entries 4 and 5), the reaction time (Table 5.2, entries 6 and 7) and the phosphonium derivative employed (Table 5.2, entry 2; table 5.3, entry 1; table 5.4, entry 1).

Crystals of **23d**, mixture *E* and *Z* isomers (91:9), were grown and analysed by X-ray crystallography (Figure 5.5) which confirmed the presence the olefin and boronate moieties, the former being in the (*E*)-configuration.

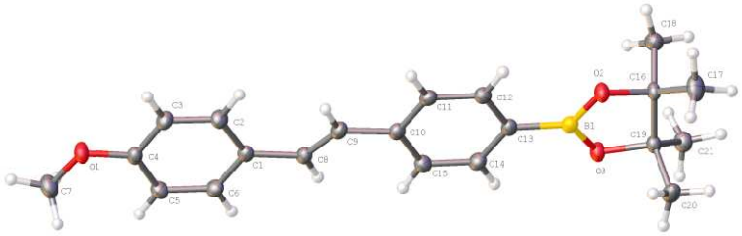
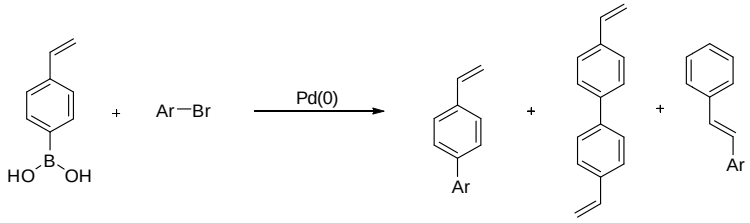


Figure 5.5. Crystal structure of the *E*-isomer of **23d**.

Although comparing the *E/Z* ratios of the Wittig products is a useful exercise, it is largely unnecessary in this approach since the alkene functionality was to be reduced by a subsequent hydrogenation. Indeed, the ultimate goal was to synthesise ethyl bridged biphenyl products by a SM reaction, such that the carbon-carbon double bond would be reduced prior to the SM coupling to avoid stereoisomeric mixtures complicating both the NMR spectroscopic analysis and the isolation of the expected product (Scheme 5.12). However, specific conditions are known for reacting arylboronates containing a carbon-carbon double bound selectively in a SM coupling rather than the Heck or homo coupling using $Pd(DIPHOS)_2$ as catalyst (Figure 5.6).[141,142]



Scheme 5.12. SM coupling with an alkenylboronate leading to a potential mixture.

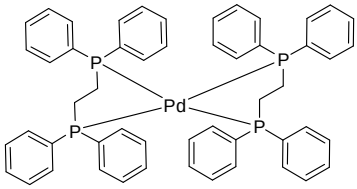


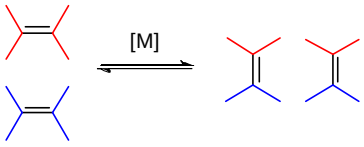
Figure 5.6. $Pd(DIPHOS)_2$: bis[1,2-bis(diphenylphosphino)ethane]palladium(0).

After employing the aforementioned Wittig reaction, a small library of vinylarylboronic esters was synthesised. These compounds will later be reduced and coupled in a SM coupling in order to obtain a library of arylethylbiaryls.

5.4. Cross-metathesis reaction

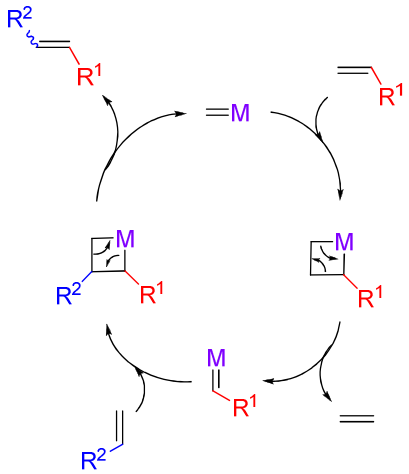
5.4.1. Background to the cross-metathesis reaction

Olefin metathesis is a reliable and efficient reaction that can be used to form carbon-carbon bonds. The metathesis reaction was used in the 1950s but no one really knew how it worked. The term "olefin metathesis" was coined in 1967,[143] which means a metal catalysed redistribution of carbon-carbon double bonds (carbene) by the scission of carbon-carbon double bonds in olefins (Scheme 5.13). The catalyst used for the metathesis reaction is a metal-carbene complex which can be made from different metals such as molybdenum, nickel, rhenium, ruthenium and tungsten. The cross-metathesis (CM) reaction is a reversible process.



Scheme 5.13. CM reaction.

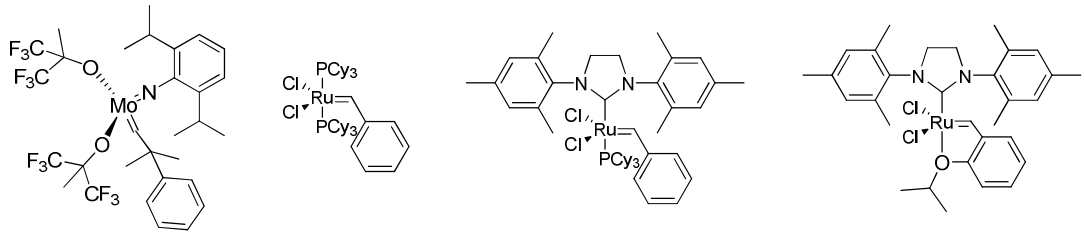
In 1971, Yves Chauvin *et al*. published their findings and understanding on the mechanism of the metathesis reaction[144] (Scheme 5.14).



Scheme 5.14. Mechanism of the CM reaction

The first step is a [2+2] cycloaddition between an olefin containing the group R^1 and a transition metal-carbene. The metallacyclobutane complex formed undergoes a concerted electron rearrangement which leads to the formation of a new alkene and a new metal-carbene complex containing the group R^1. The latter reacts with another olefin containing the group R^2 to form another metallacyclobutane complex which will then rearrange to yield the cross-coupled olefin containing both R^1 and R^2 groups and a new metallocarbene, which can then be recycled through the reaction pathway.

Chauvin's description of the metathesis process led Schrock, Grubbs and their co-workers to develop catalysts (Figure 5.7) that carried out the reaction more efficiently.[145,146,147]



27a **27b** **27c**

Figure 5.7. More commonly used CM catalysts.

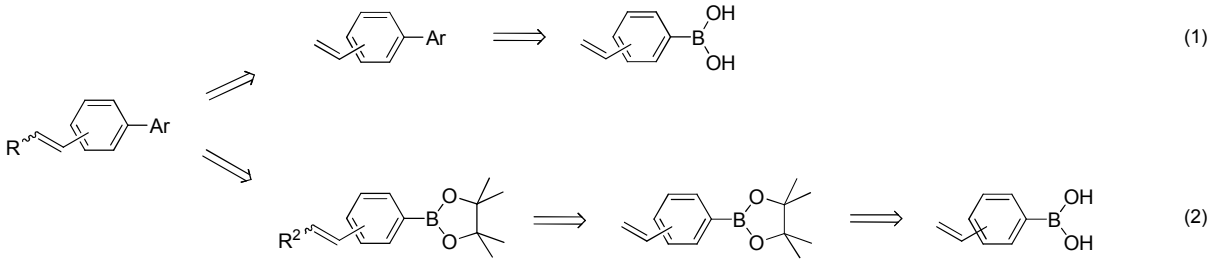
These four catalysts are molybdenum and ruthenium carbene catalysts and are commercially available. They are the more commonly used catalysts in CM reactions due to their selectivity, efficiency and functional group compatibility. However, Schrock's catalyst is more sensitive to air and moisture than Grubbs' catalysts which makes it less easy to handle.

The CM reaction is now widely used in organic synthesis.[148] Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock shared The Nobel Prize in Chemistry in 2005 for "the development of the metathesis method in organic synthesis".

5.4.2. Synthesis of vinylarylboronates and vinylbiaryls *via* CM reaction

5.4.2.1. Background

The CM reaction in the synthesis of the arylethylbiaryl library can implicate two distinct synthetic pathways (Scheme 5.15).



Scheme 5.15. Retrosynthesis of aryl ethylbiaryls *via* olefin CM reaction.

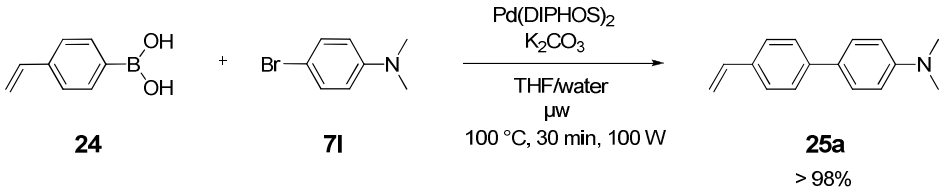
Route 1 implies a disconnection between the two alkenyl carbons first, this functionalised double bond can be constructed *via* a CM reaction, and then a disconnection between the two aryl groups, this carbon-carbon bond can be synthesised *via* a cross-coupling reaction such as SM coupling. Route 2 implies a disconnection between the two aryl groups first, then a disconnection between the two alkenyl carbons and finally a functionalisation step from the boronic acid to the boronic ester can be made in order to facilitate the handling and the purification of the intermediates throughout the steps.

5.4.2.2. Route 1: Synthesis of arylethylbiaryls *via* SM/CM

Using route 1, the SM coupling was achieved first in order to synthesise vinylbiaryl derivatives which were then reacted in a CM reaction to functionalise the vinylic group to a di-substituted alkene.

5.4.2.2.1. SM coupling

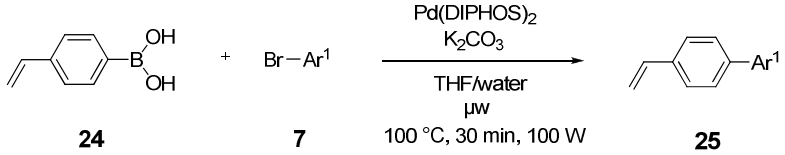
The 4-vinylphenylboronic acid (**24**) was chosen as an arylboronic acid to undergo the SM coupling. McCluskey *et al.* recently found the optimum condition for this SM coupling which avoid any secondary reactions and published it just before the start of this investigation.[142b] Their conditions were chosen for the SM coupling of **24** with different aryl bromides **7**. The SM coupling was catalysed by $Pd(DIPHOS)_2$, in a THF/H_2O mixture and using potassium carbonate as a base under microwave irradiation (100 W, with the cooling system on) at 100 °C for 30 minutes (Scheme 5.16).



24 **7l** **25a**
> 98%

Scheme 5.16. Published SM coupling on **24**.

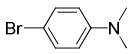
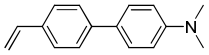
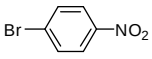
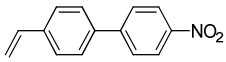
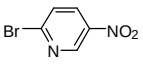
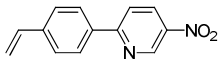
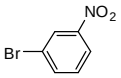
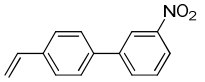
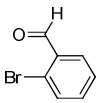
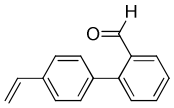
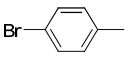
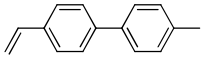
This SM coupling was repeated in the same conditions with **7l** and other aryl bromides (Scheme 5.17; Table 5.6).



24 **7** **25**

Scheme 5.17. SM coupling on **24**.

Table 5.6. SM coupling on **24**.

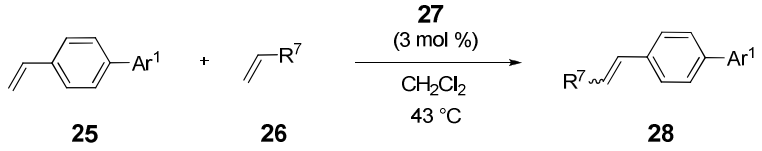
Entry	**7**		Product (**25**)		Yield (%)[a]
1		**7l**		**25a**	63
2		**7c**		**25b**	98
3		**7k**		**25c**	67
4		**7d**		**25d**	63
5		**7m**		**25e**	–
6		**7h**		**25f**	67

Conditions: ArBr (1 equiv.), $Pd(DIPHOS)_2$ (1 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O 1:1 (5 mL for 1 mmol of $ArB(OH)_2$), microwave irradiation (100 W), 100 °C, 30 min.
[a] Percentage yield after purification by chromatography.

The expected products were obtained in moderate to good yield. The yield obtained for **25a** (63%) was lower than the one reported in the literature (> 98%). The SM coupling in these conditions worked well with electron rich and electron poor aryl bromides (Table 5.6, entries 2 and 6) but no expected product was observed when using an *ortho*-substituted aryl bromide (Table 5.6, entry 5).

5.4.2.2.2. CM reaction

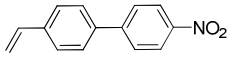
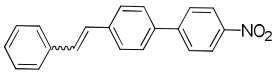
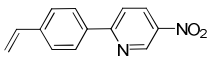
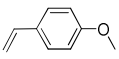
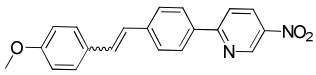
The compounds **25** were reacted in a CM reaction with vinylaryls in order to create bis-functionalised alkenes (Scheme 5.18 and Table 5.7).



25 **26** **28**

Scheme 5.18. CM reaction on compounds **25**.

Table 5.7. CM reaction on **25**.

Entry	**25**	**26** (equiv.)	**27**	Time (h)	Product (**28**)	*E/Z* ratio[a]	Yield (%)[b]
1	 **25b**	 **26a** (3)	**27a**	6	 **28a**	–	–
2	**25b**	**26a** (3)	**27b**	6	**28a**	100:0	54
3	**25b**	**26a** (1.5)	**27c**	6	**28a**	95:5	37
4	**25b**	**26a** (3)	**27c**	6	**28a**	95:5	62
5	 **25c**	 **26b** (5)	**27b**	16	 **28b**	100:0	75

[a] Calculated by ^{1}H NMR. [b] Percentage yields obtained after purification by chromatography.

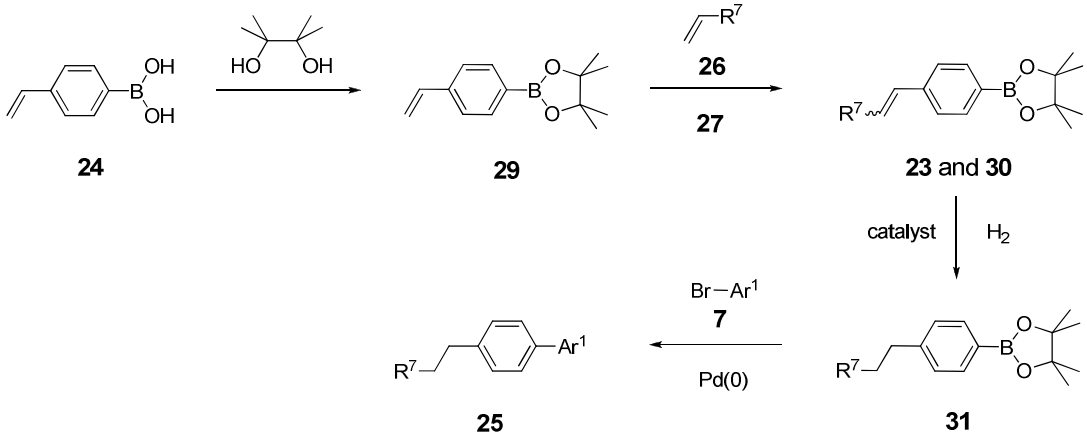
Three catalysts were tested in the CM reaction on **25b**. Grubbs' catalyst 1st generation (**27a**) was found to be inefficient in this CM reaction (Table 5.7, entry 1) but the other two, Grubbs' catalyst 2nd generation (**27b**) and Hoveyda-Grubbs' catalyst 2nd generation (**27c**) were suitable for this reaction since the expected product was obtained in moderate yields (e.g. 54% yield with **27b**, Table 5.7, entry 2 and 62% yields with **27c**, Table 5.7, entry 4). The reaction should be attempted again using a longer reaction time to examine if better yields can be obtained. The CM reaction was also attempted on **25c** with **26b** catalysed by **27b** and gave the expected product **28b** in 75% yield in 16 h (Table 5.7, entry 5).

Therefore, two arylvinylbiaryls were synthesised *via* route 1 in moderate yields.

5.4.2.3. Route 2: Synthesis of arylethylbiaryls *via* CM/SM

5.4.2.3.1. Introduction

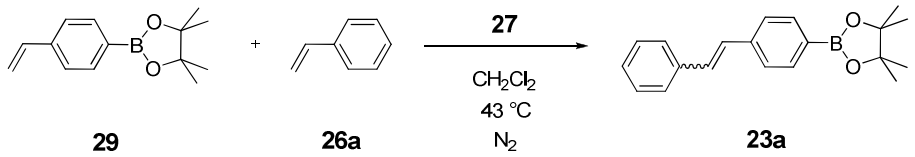
The arylethylbiaryl library can also be obtained by synthesising the bis-functionalised alkene derivatives *via* the CM reaction, reducing the carbon-carbon double bond and then coupling the boronate derivatives *via* the SM coupling reaction (Scheme 5.19). In order to be able to handle and purify the different intermediates, the 4-vinylphenylboronic acid pinacol ester **29** was easily synthesised from the boronic acid **24** (as previously outlined in chapter 2) and used as a boronic ester derivative.



Scheme 5.19. Synthesis of arylethylbiaryls *via* CM/SM.

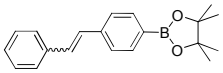
5.4.2.3.2. CM reaction

The CM reaction was first attempted on **29** with styrene (**26a**) in CH_2Cl_2 under reflux and in a nitrogen atmosphere (Scheme 5.20; Table 5.8).



Scheme 5.20. CM reaction on **29** with **26a**.

Table 5.8. CM reaction on **29** with **26a**.

Entry	**26a** equiv.	**27** (mol %)	Time (h)	Product (**23**)	*E/Z* ratio	Yields (%)[a]
1	3	**27a** (3)	24	 **23a**	–	–[b]
2	5	**27b** (5)	2.5	**23a**	100:0	55
3	5	**27b** (5)	6	**23a**	100:0	76[c]
4	5	**27b** (5)	16	**23a**	100:0	58[c]
5	5	**27b** (5)	24	**23a**	100:0	60[c]
6	5	**27b** (5)	16	**23a**	100:0	42[b,c]
7	5	**27b** (3)	6	**23a**	100:0	65
8	2	**27b** (3)	6	**23a**	100:0	58
9	1.6	**27b** (3)	6	**23a**	100:0	63
10	5	**27b** (1)	24	**23a**	100:0	52[c]
11	2	**27b** (1)	24	**23a**	100:0	65[c]
12	5	**27c** (3)	6	**23a**	100:0	51
13	5	**27b** (5)	0.5	**23a**	100:0	46[c,d]
14	5	**27b** (5)	2	**23a**	100:0	26[c,d]

[a] Percentage yields obtained after purification by chromatography. [b] Reaction achieved at room temperature. [c] Yield calculated by ^{1}H NMR spectroscopy, mixture expected product + starting material (**29**). [d] Reaction under microwave irradiation in a sealed vial, 40 °C, maximum power 300W.

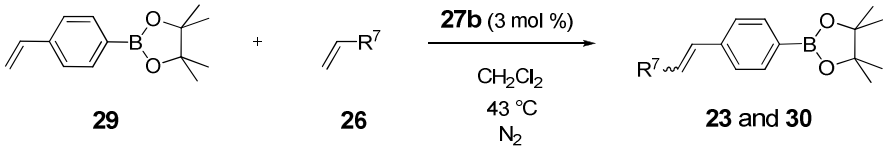
The use of an excess of **26a** led to a large amount of *E*-stilbene (styrene homocoupling product) which, was in most of the cases, difficult to separate from the expected product, **23a**, by chromatography.

As previously observed, Grubbs' catalyst 1st generation (**27a**) was inefficent in the CM on compound **29** with **26a**, even at room temperature, as only starting materials were observed (Table 5.8, entry 1). The expected product **23a** was obtained when both **27b** (Table 5.8, entries 2-11) and **27c** (Table 5.8, entry 12) were used as catalyst under reflux. The reaction time seems to affect the yields obtained. When the reaction was stopped after 2.5 h a moderate yield of 55% was obtained (Table 5.8, entry 2) and better yields were obtained after 6 h, 16 h or 24 h i.e. 76%, 58% and 60%, respectively (Table 5.8, entries 3, 4 and 5, respectively). However, the best yield was obtained after a 6 h reaction time, 76%, but the

yield decreased to around 60% when the reaction was left for a longer time. This must be due to the fact that the CM reaction is reversible.

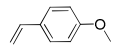
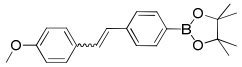
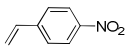
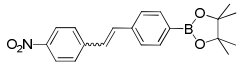
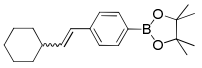
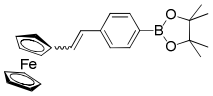
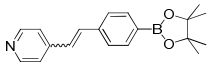
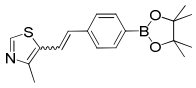
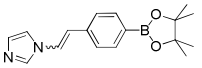
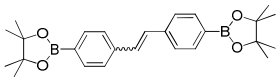
Moreover, it was difficult to monitor the reaction by TLC since, in most cases, the expected products had a similar (if not the same) R_F as the starting material **29**. A decrease in the molar percentage of catalyst led to a decrease in the yields (e.g. 76% yield with 5 mol % of **27b**, Table 5.8, entry 3; 65% yield with 3 mol % of **27b**, Table 5.8, entry 7; 52% yield with 1 mol % of **27b**, Table 5.8, entry 10). The used of a large excess of one of the alkene should lead to better yields but in this case, the yields do not seem to be affected by the difference of equivalents used of **26a**, since very similar yields were obtained when changing the number of equivalents (65%, 58% and 63% yields obtained with 5, 2 and 1.6 equiv. of **26a**, respectively, Table 5.8, entries 7, 8 and 9, respectively). The catalyst **27c** was tested and gave the expected product in a moderate yield of 51% (Table 5.8, entry 12). The reaction was also attempted by using microwave irradiation but the results were not satisfactory because of the lower yields obtained (Table 5.8, entries 13 and 14). This result can be due to the fact that the reaction took place in sealed vials where the ethylene formed could not escape and kept on reacting with the other reagents.

Other vinylic derivatives **26** were reacted with **29** in a CM reaction in order to enlarge the variety of alkene derivatives (Scheme 5.21). **27b** was chosen as catalyst (3 mol %) and the reaction was achieved under reflux in a nitrogen atmosphere (Table 5.9).



Scheme 5.21. CM reaction on **29**.

Table 5.9. CM reaction on **29**.

Entry	**26** (equiv.)		Time (h)	Product (**23** and **30**)		*E/Z* ratio[a]	Yields (%)[b]
1		**26b** (5)	6		**23d**	100:0	29[c]
2		**26c** (3)	20		**23g**	100:0	_[d]
3		**26d** (5)	6		**23h**	100:0	58
4		**26e** (5)	6		**23i**	100:0	_[d]
5		**26f** (5)	6		**23b**	_	_
6		**26g** (5)	6		**23j**	_	_
7		**26h** (5)	6		**23k**	_	_
8	_		22		**30**	100:0	89

[a] Calculated by ^{1}H NMR. [b] Percentage yield obtained after purification by chromatography. [c] Yield calculated by ^{1}H NMR, mixture expected product + homocoupling product of **26**. [d] Yield undetermined because the product is in a mixture with the homocoupling product of **26**.

The alkene derivatives **23d** and **23h** were obtained in moderate yields of 29% and 58% respectively. For the reactions resulting in **23g** and **23i**, the expected products were in a mixture with the homocoupling product of **26c** and **26e** and could not be separated by chromatography and no percentage yield could be calculated by ^{1}H NMR. These products were used as mixtures for the next steps. The reaction was attempted with heterocyclic derivatives **26** but only starting materials were observed after 6 h. This is in agreement with the literature. Kawai *et al.* have compared Grubbs' 1st generation and molybdenum-based Schrock catalysts in the homo- and cross-metathesis reaction of 2-vinylfuran and 2-vinylthiophene as aromatic heterocycles.[149] They found that Schrock's catalyst was more suitable because these aromatic heterocycles formed a stable heteroaromatic carbene with the ruthenium-based Grubbs catalyst. Moreover, vinylpyridine was found to be unreactive with both catalysts because it also formed a stable adduct with the molybdenum-based Schrock catalyst.[150] The CM reaction with **26g** and **26h** could be repeated using the molybdenum-based Schrock catalyst in order to synthesise **23j** and **23k**.

Crystals of **30** were grown and analysed by X-ray crystallography diffraction which gave the full crystal structure analysis of **30** (Figure 5.8).

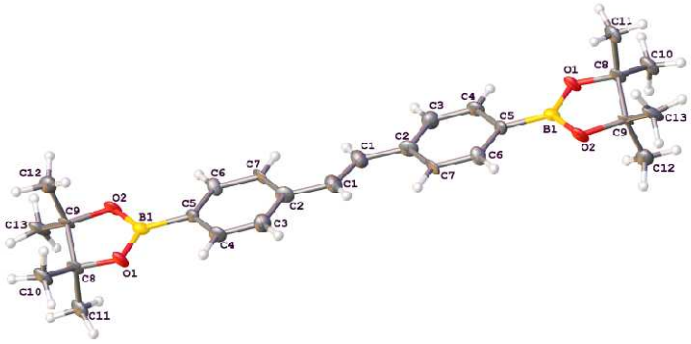


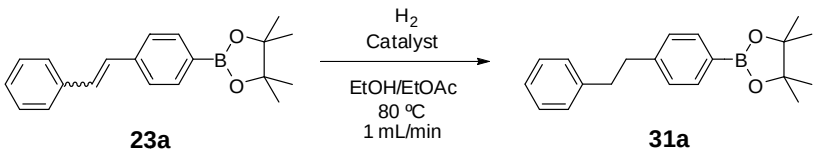
Figure 5.8. Crystal structure of **30**.

Styrylboronates **23** and styrylbiphenyls **28** synthesised *via* the Wittig, CM and SM reactions could now be reduced by hydrogenation prior to being reacted in SM couplings and functionalisation reactions.

5.5. Hydrogenation of alkene derivatives 23, 28 and 30

Hydrogenation is a chemical reaction that results from the addition of hydrogen to an unsaturated organic compound. Catalysts are necessary for the reaction to be practical because uncatalysed hydrogenation takes place only at very high temperatures. Platinum group metals, particularly platinum,[151] palladium,[152] rhodium[153] and ruthenium,[154] form highly active catalysts, which operate at lower temperatures and lower pressures of H_2. Non-precious metal catalysts, especially those based on nickel (such as Raney nickel and Urushibara nickel[155]) have also been developed as economical alternatives, but they are often slower, difficult to handle or require higher temperatures.[156]

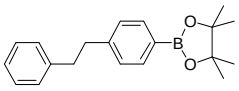
The hydrogenation of **23a** was attempted using flow chemistry in an H-Cube at 80 ºC, 1 mL.min^{-1} and full hydrogen mode (Scheme 5.22). Reductions were achieved on a 0.07 mmol scale (Table 5.10).



23a **31a**

Scheme 5.22. Hydrogenation reaction of compound **23a** using an H-Cube.

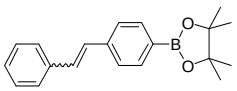
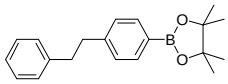
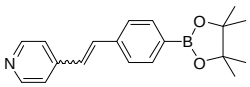
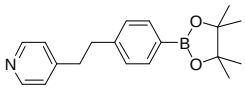
Table 5.10. Hydrogenation reaction of **23a** using the H-Cube.

Entry	Catalyst	Product (**31**)	Yield (%)
1	Raney Ni	 **31a**	–
2	PtO_2	**31a**	77

Because of the presence of a boronic ester group in the reagent, palladium was not used as a catalyst in this reaction due to potential coupling or protodeboronation side reactions. When Raney Nickel was used as catalyst no expected compound was obtained. However, with platinum oxide as catalyst, the pure expected product was obtained in 77% yield (Table 5.10, entry 2).

When the reaction was scaled-up (from 0.07 mmol to 0.88 mmol), no reduction occurred with platinum oxide as catalyst even with a high degree of dilution and with a low flow rate (Table 5.11, entry 1). Therefore other catalysts were tested including palladium on activated carbon (Table 5.11).

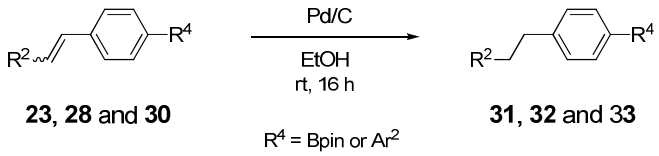
Table 5.11. Hydrogenation of **23**.

Entry	**23**	Catalyst	Conditions	Product (**31**)	Yield (%)
1	 **23a**	PtO_2	H-Cube EtOH/EtOAc 80 °C 0.8 mL.min^{-1}	 **31a**	–
2	 **23b**	Pt/C	H-Cube EtOH/EtOAc 70 °C, 40 bars 0.8 mL.min^{-1}	 **31b**	–
3	**23a**	Pd/C	H-Cube EtOH/EtOAc 80 °C, 40 bars 0.8 mL.min^{-1}	**31a**	–
4	**23a**	Pd/C	H_2 balloon EtOH rt, overnight	**31a**	100

In this case, it appeared that the use of the H-Cube was not an effective method for a scale-up reduction of alkenes by hydrogenation.

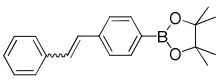
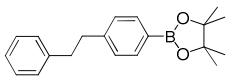
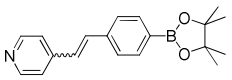
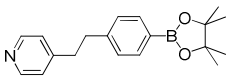
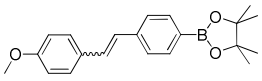
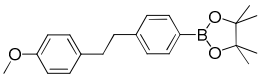
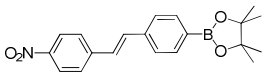
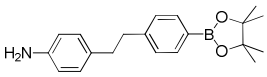
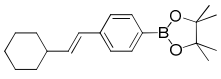
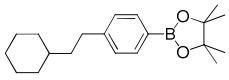
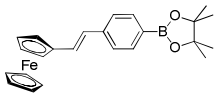
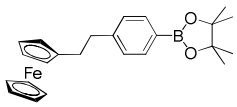
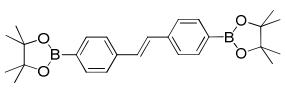
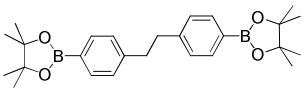
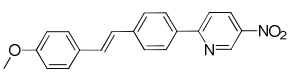
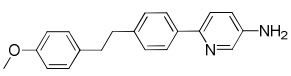
The reduced product was obtained in quantitative yield when "batch reaction" conditions were used with palladium on activated carbon as catalyst and a hydrogen balloon as source of hydrogen (Table 5.11, entry 4). No side product was obtained when palladium was used as catalyst, contrary to earlier expectations.

The other analogues **23** were then reduced by hydrogenation catalysed by palladium on activated carbon (Scheme 5.23; Table 5.12).



Scheme 5.23. Hydrogenation catalysed by Pd/C of compounds **23**, **28** and **30**.

Table 5.12. Hydrogenation of **23**, **28** and **30**.

Entry	**23**/**28**/**30**		Product (**31**/**32**)		Yield (%)
1		**23a**		**31a**	> 99
2		**23b**		**31b**	> 99
3		**23d**		**31c**	95
4		**23g**		**31d**	34[a]
5		**23h**		**31e**	94
6		**23i**		**31f**	–[b]
7		**30**		**31g**	99
8		**28b**		**32b**	75[c]

[a] Percentage yield over two steps: CM and hydrogenation reactions. [b] Percentage yield not determined, product in a mixture with the reduced bis-ferrocene ethyl homocoupling product. [c] Percentage yield obtained after purification by chromatography.

Palladium on activated carbon is an efficient catalyst for the hydrogenation of alkenes and nitro groups in products such as **23**, **28** and **30** and affords the reduced products **31** and **32** in very good yields.

Crystals of **31d** were grown and analysed by X-ray crystallography diffraction (Figure 5.9).

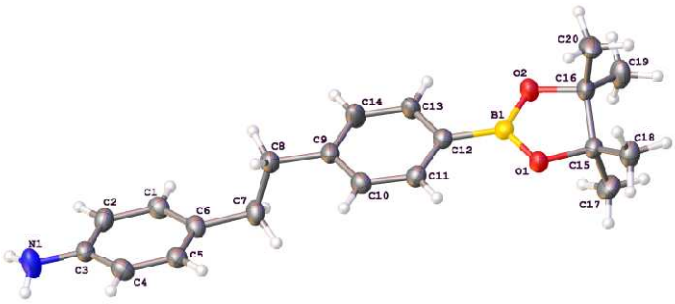
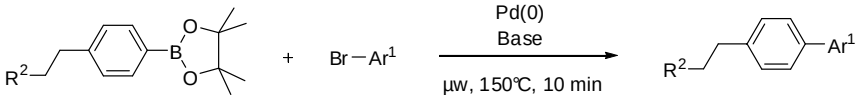


Figure 5.9. Crystal structure of **31d**.

4.6. SM coupling of compounds 31

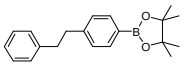
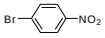
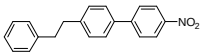
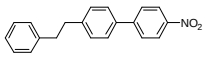
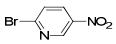
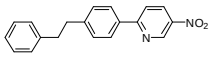
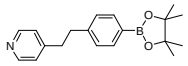
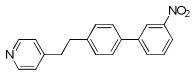
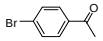
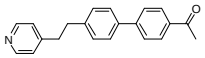
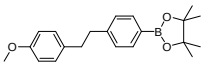
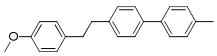
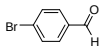
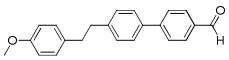
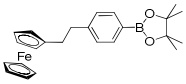
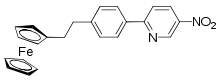
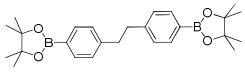
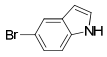
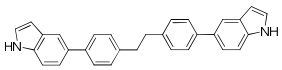
Now that the carbon-carbon double bond of the analogues **23** and **26** had been reduced, the boronic esters **31** were coupled with a range of aryl halides in SM reactions (Scheme 5.24) to yield the corresponding biaryl compounds **33** (Table 5.13).



31 **7** **33**

Scheme 5.24. SM reaction on compounds **31**.

Table 5.13. SM reaction on **31**.

Entry	**31**	**7**	Conditions	Product (**33**)		Yield (%)[a]
1	 **31a**	 **7c**	A		**33a**	67
2	**31a**	**7c**	B		**33a**	> 99
3	**31a**	 **7k**	B		**33b**	89
4	 **31b**	 **7d**	B		**33c**	82
5	**31b**	 **7b**	B		**33d**	86
6	 **31c**	 **7h**	B		**33e**	75[b]
7	**31c**	 **7a**	B		**33f**	54[b]
8	 **31f**	**7k**	B		**33g**	41[c]
9	 **31g**	 **7n**	B		**33h**	77

Conditions: A: **7** (1.1 equiv), $Pd(OAc)_2$ (1 mol %), Na_2CO_3 (3 equiv), TBAB (1 equiv), water (2 mL per 1 mmol of boronic ester), microwave irradiation (power max 300 W), 150 °C, 10 min. Conditions B: **7** (1.1 equiv.), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (3 equiv.), toluene/ethanol/water 1:1:1 (3 mL per 1 mmol of boronic ester), microwave irradiation (power max 300 W), 150 ºC, 10 min.

[a] Percentage yields obtained after purification by chromatography. [b] Difficult to separate the expected product from the starting materials which did not react completely (yield calculated by ^{1}H NMR). [c] Yield over 3 steps.

Tetrakis(triphenylphosphine)palladium(0) was a suitable pre-catalyst for the SM coupling reaction of compounds **31**. The corresponding arylethylbiaryls **33** were obtained in very good to quantitative yields. In order to afford more examples of this type of aryethylbiaryl analogues, the nitro group could be reduced and subsequently functionalised.

33h is a very interesting compound since it contains the indole moiety (Figure 5.10, in blue), which is a privileged scaffold in medicinal chemistry. This type of symmetrical compound containing two indole moieties can be seen as an interesting potential ligand for dimeric GPCRs.[157] Moreover, this type of molecule can also be seen as a linker or a stapler thanks to the fixed distance given by the 1,2-diarylethyl moiety (Figure 5.10, in purple).

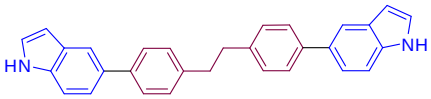


Figure 5.10. Compound **33h**.

Crystals of **33g** were grown and analysed by X-ray crystallography diffraction (Figure 5.11).

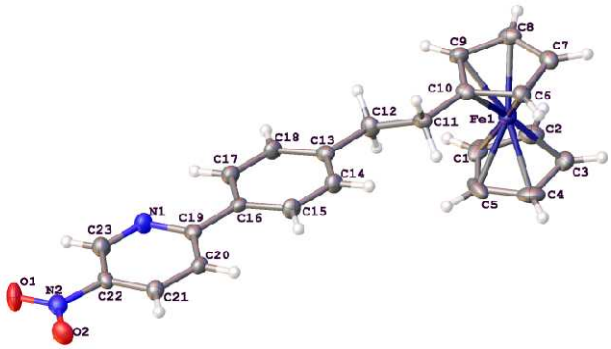
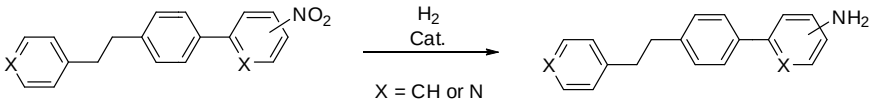


Figure 5.11. Crystal structure of **33g**.

5.6. Other functionalisations

5.6.1. Nitro group reduction

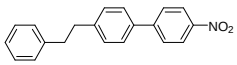
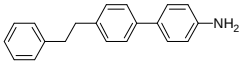
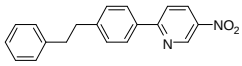
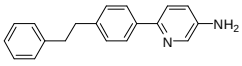
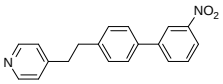
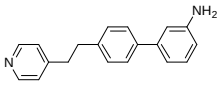
The reduction of (arylethyl)nitrobiaryl derivatives **33a-c** (Scheme 5.25) was first achieved by hydrogenation using an H-Cube and catalysed by Raney Nickel in ethanol/ethyl acetate 1:1 at 65 °C and 1 mL.min^{-1} and in full hydrogen mode. The reduced compound **34a** was obtained in a very poor yield (Table 5.14, entry 1). The reduction was then achieved by hydrogenation catalysed by palladium on activated carbon (Table 5.14).



33 **34**

Scheme 5.25. Nitro group reduction reaction of **33**.

Table 5.14. Nitro group reduction of **33**.

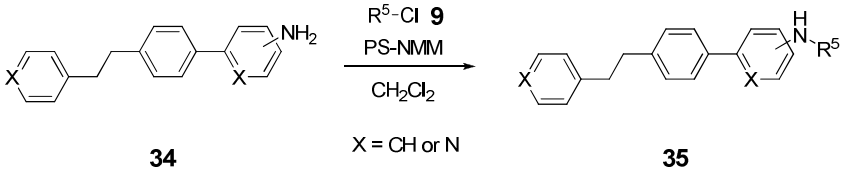
Entry	**33**		conditions	Product (**35**)		Yield (%)[a]
1		**33a**	Ra Ni H-Cube		**34a**	10
2		**33b**	Pd/C Batch reaction		**34b**	72
3		**33c**	Pd/C Batch reaction		**34c**	68

Conditions: 1) Raney Nickel cartridge, H-Cube, EtOH/EtOAc 1:1, 65°C, 0.8 mL.min^{-1}, full H_2 mode. 2) Pd/C (10% wt.), EtOH, rt, 16 h, H_2 atmosphere.
[a] Percentage yields obtained after purification by chromatography.

The expected reduced products **34** were obtained in good yields when the reduction was catalysed by Pd/C.

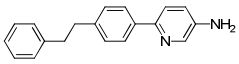
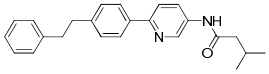
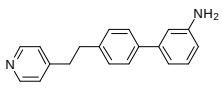
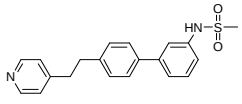
5.6.2. Amine functionalisations

The amine could be then functionalised by reaction with acid or sulphonyl chlorides (Scheme 5.26; Table 5.15).



Scheme 5.26. NH_2 functionalisation reaction on **34**.

Table 5.15. NH_2 functionalisation of **34**.

Entry	**34**		**9**	Time (h)	Product (**35**)		Yield (%)[a]
1		**34b**	**9c**	2		**35a**	47
2		**34c**	**9n**	16		**35b**	82

[a] Percentage yields obtained after purification by chromatography.

After 2 h, the reaction of **34b** with **9a** gave only 47% yield of **35a**. A longer reaction time should be envisaged. Compound **35b** was obtained in good yields after 16 h of reaction time.

5.7. Conclusion

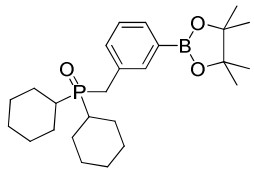
From the S_N2 reaction on (bromomethyl)phenylboronic acid pincol esters with phosphines nucleophiles, a small family of arylethylbiphenyls was synthesised *via* a Wittig, CM, carbon-carbon double bond hydrogenation, SM coupling and other functionalisation reaction sequence. The Wittig and the CM reactions allowed the synthesis of vinylic derivatives but the overall yields were often moderate to poor. Other conditions, reagents or reactions could be attempted in order to improve the yields.

5.8. Experimental procedures and data

Experimental conditions and analytical methods are as for Chapter 2

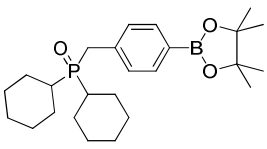
General procedure for the synthesis of *P*-substituted methylphenylboronic acid pinacol esters 4-6:

Dicyclohexyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphine oxide **5o**



2b (2.00 mmol, 54 mg), dicyclohexylphosphine **3s** (10 wt % in hexane) (0.18 mmol, 360 mg), PS-NMM (0.19 mmol, 4 $mmol.g^{-1}$, 48 mg) and THF (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 30 minutes. After cooling, the mixture was filtered. The vial and the supported reagent were washed with some CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 238 mg of a colourless oil which was purified by chromatography on silica gel, CH_2Cl_2/MeOH from 0% to 20% of MeOH, to give 64 mg of the oxidised expected product as a colourless oil in 82% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (2d, 2H, J_{d2} = 7.3 Hz), 7.63 (s, 1H), 7.40 (dd, 1H, *J* = 7.3 Hz), 4.29 (d, 2H, *J* = 14.0 Hz), 1.70-2.10 (m, 14H), 1.10-1.50 (m + s, 20H). ^{13}C NMR ($CDCl_3$) δ (ppm): 136.1, 136.0, 134.6, 133.9, 133.8, 129.0, 84.1 (2C), 30.7, 30.1, 26.4 (2C), 26.3, 26.1, 25.9, 25.6, 25.4, 24.9 (4C), 24.4. ^{31}P NMR ($CDCl_3$) δ (ppm): 28.9.

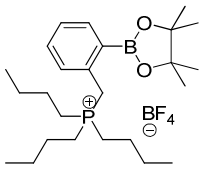
Dicyclohexyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphine oxide **6o**



2c (1 mmol, 297 mg), **3s** (10 wt % in hexane) (1 mmol, 1.98 g), PS-NMM (1.05 mmol, 4 $mmol.g^{-1}$, 260 mg) and THF (1 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 ºC for 20 minutes (15 + 5 minutes) and then cooled to room temperature. The mixture was filtered. The vial and the supported reagent were washed with some DCM. The filtrate was concentrated under reduced pressure to give 416 mg of the

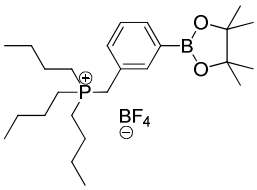
expected product as a yellow oil in > 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.71 (d, 2H, *J* = 7.3 Hz), 7.39 (d, 2H, *J* = 6.2 Hz), 4.29 (d, 2H, *J* = 15.0 Hz), 2.50-3.00 (m, 4H), 1.60-1.90 (m, 12H), 1.28 (s, 12H), 1.20 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.7, 135.6, 132.1, 132.0, 129.8, 129.7, 84.0 (2C), 34.9, 34.0, 30.8, 30.2, 26.5, 26.2, 26.0, 25.9, 25.7, 25.4, 25.2, 24.9 (4C), 24.6. ^{31}P NMR ($CDCl_3$) δ (ppm): 29.3.

Tributyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium **4i**



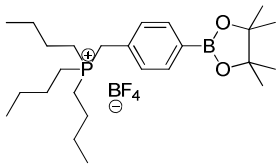
Yellow oil, 282 mg, > 99% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.91 (d, 1H, *J* = 7.3 Hz), 7.47 (m, 1H), 7.30 (m, 2H), 4.10 (d, 2H, *J* = 15.4 Hz), 2.10-2.30 (m, 6H), 1.30-1.50 (m + s, 18H), 1.20-1.30 (m, 6H), 0.80-1.00 (m, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.9, 134.9, 134.8, 132.5, 130.7, 130.0, 129.6, 127.9, 127.8, 84.6 (2C), 27.0, 26.6, 26.3, 25.9, 25.0 (4C), 24.6, 24.1, 24.0, 23.9, 23.8, 23.6, 23.5, 23.4, 18.7, 18.6, 18.3, 18.1, 13.4, 13.3 (coupling with phosphorus and rotamers). ^{31}P NMR ($CDCl_3$) δ (ppm): 32.1. HRMS-ES (m/z) found 418.3279, calcd for $[C_{25}H_{45}O_2{}^{10}BP]^+$ 418.3281.

Tributyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium tetrafluoroborate **5p**



White solid, 260 mg, > 99% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 1H, *J* = 7.0 Hz), 7.44 (s, 1H), 7.45 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 7.39 (dd, 1H, *J* = 7.4 Hz), 3.72 (d, 2H, *J* = 14.7 Hz), 2.16 (m, 6H), 1.46 (m, 12H), 1.31 (s, 12H), 0,92 (m, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.6, 135.5, 134.9, 133.1, 129.2, 127.5, 84.2 (2C), 26.9 and 26.2 (d, 1C), 24.8 (4C), 24.0, 23.7, 23.6 and 23.5 (2d, 6C), 18.7 and 17.9 (d, 3C), 13.3 (3C). ^{31}P NMR ($CDCl_3$) δ (ppm): 32.7.

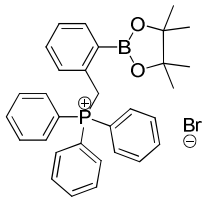
Tributyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium tetrafluoroborate **6p**



Yellow oil, 263 mg, > 99% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.78 (d, 2H, *J* = 7.7 Hz), 7.28 (m, 2H), 3.78 (d, 2H, *J* = 14.7 Hz), 2.17 (m, 6H), 1.43 (m, 12H), 1.33 (s, 12H), 0.91 (m, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.8 (2C), 131.0, 129.9 and 129.5 (d, 1C), 129.3, 129.2, 84.1 (2C), 27.3 and 26.6 (d, 1C), 24.8 (4C), 24.0 and 23.8 (d, 3C), 23.5 and 23.4 (d, 3C), 18.6 and 18.0 (d, 3C), 13.3 (3C). ^{31}P NMR ($CDCl_3$) δ (ppm): 32.5. HRMS-ES (m/z) found 419.3244, calcd for $[C_{25}H_{45}O_2BP]^+$ 419.3245.

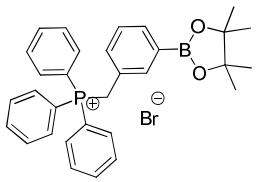
General procedure for the synthesis of phosphonium salts 4j, 5q,r and 6q,r:

Triphenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium bromide **4j**



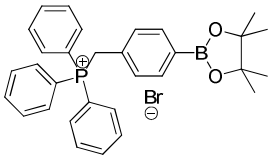
2a (1 mmol, 297 mg), triphenylphosphine **3u** (1 mmol, 263 mg) and THF (4 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 110 ºC for 20 minutes, then cooled to room temperature and concentrated under reduced pressure to give 589 mg of a beige oil which was crystallised in CH_2Cl_2/hexane. The crystals were triturated in diethyl ether to give 560 mg of the pure expected compound as a beige solid in > 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (m, 4H), 7.40-7.70 (m, 12H), 7.20-7.40 (m, 3H), 5.67 (d, 2H, *J* = 15.0 Hz), 1.07 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.2, 134.9, 134.6, 134.5, 134.1, 134.0, 132.2, 132.0, 131.5, 131.4, 130.1, 129.9, 128.4, 127.9, 118.7, 117.5, 84.0 (2C), 30.7 and 30.1 (d, 1C), 24.8 (4C). ^{31}P NMR ($CDCl_3$) δ (ppm): 24.4. HRMS-ES (m/z) found 479.2306, calcd for $[C_{31}H_{33}O_2BP]^+$ 479.2306.

Triphenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium bromide **5q**



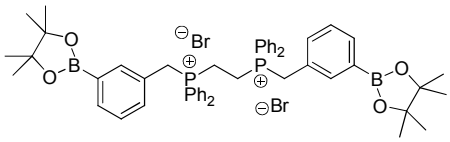
White solid, 243 mg, 87% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 7.50-7.80 (2 m, 17H), 7.20 (dd, 1H, *J* = 7.3 Hz), 7.00 (s, 1H), 5.37 (d, 2H, *J* = 14.3 Hz), 1.24 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.2, 137.2, 134.9, 134.8, 134.5, 134.3, 130.2, 130.0, 128.6, 128.6, 126.3, 126.2, 118.5, 117.2, 83.8 (2C), 31.4 and 30.7 (d, 1C), 24.8 (4C). ^{31}P NMR ($CDCl_3$) δ (ppm): 23.9. MS-ES (m/s) found 479.3 and 397.2 (boronic acid), calcd for $[C_{31}H_{33}O_2BP]^+$ 479.2.

Triphenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium bromide **6q**



White solid, 560 mg, > 99% yield (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ: 7.68-7.78 ppm (2 m, 9H), 7.57-7.65 ppm (3 m, 6H), 7.53 ppm (d, 2H, *J* = 7.3 Hz), 7.04 ppm (dd, 2H, J_1 = 8.1 Hz, J_2 = 2.6 Hz), 5.43 ppm (d, 2H, *J* = 15.0 Hz), 1.30 ppm (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.0, 134.6, 134.5, 132.2, 131.1, 131.0, 130.3, 130.1, 130.0, 128.5, 128.4, 118.5, 117.3, 84.0 (2C), 32.3, 24.8 (4C). ^{31}P NMR ($CDCl_3$) δ (ppm): 23.7. HRMS-ES (m/z) found 479.2306, calcd for $[C_{31}H_{33}O_2BP]^+$ 479.2306. The data are in accordance with the literature.[47a]

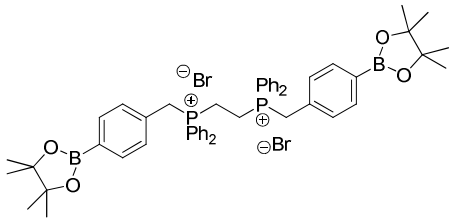
Bis-(diphenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium bromide)ethane **5r**



White solid, 208 mg, 84% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 8.01 (m, 8H), 7.75 (dd, 4H, *J* = 7.3 Hz), 7.64 (dd, 8H, *J* = 8.1 Hz), 7.53 (d, 2H, *J* = 8.1 Hz),

7.47 (d, 2H, *J* = 7.3 Hz), 6.90 (dd, 2H, *J* = 7.7 Hz), 6.55 (s, 2H), 5.00 (m, 4H), 3.49 (m, 4H), 1.19 (s, 24H). ^{13}C NMR ($CDCl_3$) δ (ppm): 136.5, 135.1, 134.5, 133.2, 130.3, 130.2, 128.5, 125.7, 116.7, 116.3, 115.9, 83.8 (4C), 29.6, 29.4, 29.2, 24.8 (8C), 13.9, 13.7, 13.4. ^{31}P NMR ($CDCl_3$) δ (ppm): 29.7.

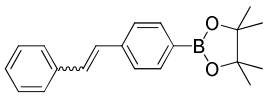
Bis-(diphenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)phosphonium bromide)ethane **6r**



White solid, 227 mg, 92% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.04 (m, 8H), 7.60-7.80 (2m, 12H), 7.29 (d, 4H, *J* = 7.7 Hz), 6.79 (d, 4H, *J* = 4.7 Hz), 5.06 (m, 4H), 3.43 (m, 4H), 1.32 (s, 24H). ^{13}C NMR (DMSO-d_6) δ (ppm): 135.3, 134.7, 133.7 (m), 130.6, 129.9, 129.8, 129.7, 118.8, 117.1, 116.7, 116.1, 115.5, 83.8 (4C), 67.0 (2C), 25.1 (2C), 24.6 (8C). ^{31}P NMR (DMSO-d_6) δ (ppm): 28.8.

General procedure for the synthesis of compounds 23 *via* the Wittig reaction:

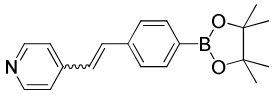
4,4,5,5-Tetramethyl-2-(4-styrylphenyl)-1,3,2-dioxaborolane **23a**



6r (0.4 mmol, 224 mg) was dissolved in DMF (6 mL). Benzaldehyde **22a** (0.4 mmol, 1.045 g.mL^{-1}, 40 µL) was added and then the potassium *tert*-butoxide (1.2 mmol, 135 mg) was added slowly. The mixture was stirred at room temperature for 2 h. The solution was poured in water (20 mL), neutralised with HCl (1M), extracted three times with EtOAc, washed with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 294 mg of a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc 95:5, to give 95 mg of the expected product in mixture with some benzaldehyde. The product was treated with Ps-Ts-$NHNH_2$ (15 mg, 3.05 mmol.g^{-1}, 0.05 mmol) in CH_2Cl_2 overnight then filtered and concentrated under reduced pressure to give 84 mg of the pure expected compound as a colourless oil in 69%

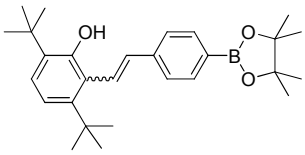
yield which crystallised at room temperature. *E/Z* = 44:56. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (d, 1.6H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.1 Hz), 7.50 (d, 3H, *J* = 8.1 Hz), 7.35 (dd, 1.6H, *J* = 7.0 Hz), 7.28-7.06 ppm (m, ~8H), 6.62 (d, 1H, *J* = 12.1 Hz), 6.57 (d, 1H, *J* = 12.5 Hz), 1.34 and 1.32 (2s, 15H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.2, 140.0, 137.2, 137.1, 135.2, 134.8, 134.6, 130.9, 130.1, 129.6, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.8, 127.2, 126.6, 125.8, 83.7 (2C), 24.9 (4C). Elemental analysis CH (%) found C: 77.7, H: 7.9, calcd for $C_{20}H_{23}O_2B.0.04CH_2Cl_2$ C: 77.7, H: 7.5. The data are in accordance with the literature.[57a]

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)styryl)pyridine **23b**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 1:1, to give 75 mg of the pure expected product as a white solid in 49% yield, *E/Z* = 43:57 (0.50 mmol scale). ^{1}H NMR (*E/Z* = 28:72, $CDCl_3$) δ (ppm): 8.55 (d, 0.7H, *J* = 5.5 Hz), 8.41 (d, 2H, *J* = 5.1 Hz), 7.80 (d, 0.8H, *J* = 7.3 Hz), 7.66 (d, 2H, *J* = 7.3 Hz), 7.51 (d, 0.7H, *J* = 7.7 Hz), 7.34 (m, 0.9H), 7.20 (m + d, 2H, J_d = 7.3 Hz), 7.05 (m, 2H), 6.77 (d, 1H, *J* = 12.1 Hz), 6.49 (d, 1H, *J* = 12.1 Hz), 1.31 (2s, 17H). ^{13}C NMR (*E/Z* = 28:72, $CDCl_3$) δ (ppm): 150.2, 149.8, 144.8, 144.5, 139.0, 138.7, 135.2, 134.8, 134.0, 133.1, 128.1, 128.0, 126.9, 126.2, 123.5, 120.9, 83.9 (2C), 24.8 (4C). HRMS-ES (m/z) found 308.1816, calcd for $[C_{19}H_{22}O_2NB + H]^+$ 308.1816. Elemental analysis CHN (%) found C: 71.7, H: 6.9, N: 4.5, calcd for $C_{19}H_{22}O_2NB.0.16CH_2Cl_2$ C: 71.7, H: 7.0, N: 4.4. The data are in accordance with the literature.[57a]

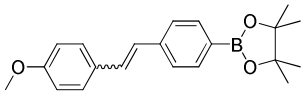
2,4-Di-*tert*-butyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styryl)phenol **23c**



The crude product was purified by column chromatography on silica gel, hexane/CH_2Cl_2 1:1 to give 19 mg of the pure expected product as a colourless oil in 29% yield, *E/Z* = 97:03 (0.15 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (d, 2H, *J* = 8.1 Hz), 7.68 (m, 0.7H), 7.50 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 1H, *J* = 16.5 Hz), 7.26 (m), 7.16 (d, 0.5H, *J* = 8.1 Hz), 7.00 (d, 1H,

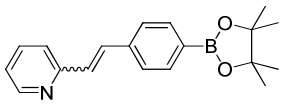
J = 16.5 Hz), 1.43 (s, 8H), 5.13 (s, 1H), 1.34 and 1.31 (2s, 25H). ^{13}C NMR ($CDCl_3$) δ (ppm): 135.2 (2C), 131.9 (2C), 131.7, 127.9 (2C), 125.7 (2C), 124.9, 124.6, 124.0, 122.3, 120.0, 83.8, 38.7, 35.0, 31.3 (3C), 29.3 (3C), 24.9 (4C). The data are in accordance with the literature.[57a]

2-(4-(4-Methoxystyryl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **23d**



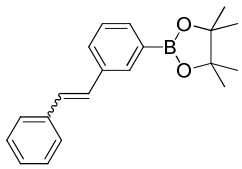
The crude product was purified by chromatography on silica gel, hexane/CH_2Cl_2 1:1, to give 34 mg of the pure expected product as yellow crystals in 68% yield, *E/Z* = 91:9 (0.15 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.8 Hz), 7.12 (d, 0.7H, *J* = 16.1 Hz), 6.96 (d, 0.7H, *J* = 16.1 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 6.72 (m, 0.2H), 6.50 (m, 0.2H), 3.81 (s, 3H), 3.76 (s, 0.3H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.4, 140.4, 137.6, 135.1, 134.6, 130.2, 130.0, 129.2, 128.6, 128.2, 128.1, 127.8 (2C), 127.7, 126.5, 126.2, 125.5 (2C), 114.1 (2C), 113.6, 83.7 (2C), 55.2, 24.9 (4C). Elemental analysis CH (%) found C: 75.5, H: 7.7, calcd for $C_{21}H_{25}O_3B$ C: 75.0, H: 7.5. The data are in accordance with the literature.[57a]

2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)styryl)pyridine **23e**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc from 0% to 50% of EtOAc to give 24 mg of the pure expected product as a beige solid/oil in 50% yield, *E/Z* = 28:72 (0.15 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.56 (d, 1.2H, *J* = 4.8 Hz), 7.79 (d, 0.6H, *J* = 8.1 Hz), 7.67 (d, 2H, *J* = 7.7 Hz), 7.63-7.52 (m, 1H), 7.50-7.35 (m, 1.4H), 7.28-7.20 (m), 7.20-7.02 (m, 2H), 6.82 (d, 1H, *J* = 12.5 Hz), 6.70 (d, 1H, *J* = 12.5 Hz), 1.32 (s, 15H). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.2, 155.1, 149.7, 149.3, 139.5, 139.3, 136.6, 135.8, 135.2, 134.7, 133.3, 132.8, 131.0, 128.8, 128.7, 128.1, 126.4, 124.0, 122.2, 121.9, 121.6, 115.9, 83.8 (2C), 24.9 (4C). HRMS-ES (m/z) found 308.1820, calcd for $[C_{19}H_{22}O_2NB + H]^+$ 308.1816.

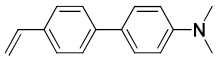
4,4,5,5-Tetramethyl-2-(3-styrylphenyl)-1,3,2-dioxaborolane **23f**



The crude product was purified by chromatography on silica gel, hexane/EtOAc from 0% to 50% of EtOAc, to give 86 mg of the pure expected product as a colourless oil in 74% yield, *E/Z* = 40:60 (0.38 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.96 (s, 0.7H), 7.69 (m, 1.2H), 7.65-7.56 (m, 3H), 7.50 (d, 1.3H, *J* = 7.0 Hz), 7.40-7.28 (m, 2.4H), 7.28-7.07 (m, 8H), 6.61 (d, 1H, *J* = 12.5 Hz), 6.56 (d, 1H, *J* = 12.1 Hz), 1.33 (2s, 19H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.4, 137.2, 137.1, 136.6, 135.5, 135.3, 134.0, 133.4, 132.8, 132.0, 131.8, 131.4, 130.2 (2C), 129.3, 128.9, 128.7, 128.6, 128.1, 127.7, 127.5, 127.4, 127.0, 126.5, 83.8 (2C), 24.8 (4C).

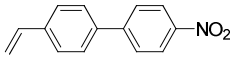
General procedure for the SM coupling on compound 24:

N,*N*-Dimethyl-4'-vinylbiphenyl-4-amine **25a**



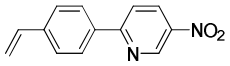
24 (0.50 mmol, 75 mg), **7l** (0.50 mmol, 100 mg), bis[1,2-bis(diphenylphosphino)ethane]palladium(0) (0.005 mmol, 5 mg), potassium carbonate (1.20 mmol, 166 mg), THF (5 mL) and water (5 mL) were placed in a microwave vial, purged with nitrogen, sealed and stirred under microwave irradiation (power 100 W) at 100 ºC for 30 min. The mixture was cooled to rt, diluted with EtOAc (20 mL) and filtered on Celite®. The filtrate was washed with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give 139 mg of a yellow solid. The crude product was purified by chromatography on silica gel, hexane/EtOAc 9:1, to give 70 mg of the pure expected product as a yellow solid in 63% yield. Yellow solid, 70 mg, 63% yield (0.5 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.56-7.50 (m, 4H), 7.44 (d, 2H, *J* = 8.2 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 6.74 (dd, 1H, J_1 = 17.6 Hz, J_2 = 10.9 Hz), 5.75 (d, 1H, *J* = 17.2 Hz), 5.22 (d, 1H, *J* = 10.9 Hz), 3.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.0, 140.6, 136.6, 135.3, 128.7, 127.5 (2C), 126.6 (2C), 126.2 (2C), 113.1, 112.8 (2C), 40.6 (2C). HRMS-ES (m/z) found 224.1433, calcd for $[C_{16}H_{17}N + H]^+$ 224.1434. Elemental analysis CHN (%) found C: 83.0, H: 7.23, N: 5.4, calcd for $C_{16}H_{17}N$.0.27EtOAc C: 83.0, H: 7.8, N: 5.7. The data are in accordance with the literature.[142b]

4-Nitro-4'-vinylbiphenyl **25b**



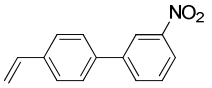
Yellow solid, 221 mg, 98% yield, (1 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.30 (d, 2H, *J* = 8.6 Hz), 7.74 (d, 2H, *J* = 9.0 Hz), 7.61 (d, 2H, *J* = 8.2 Hz), 7.54 (d, 2H, *J* = 8.2 Hz), 6.77 (dd, 1H, J_1 = 17.6 Hz, J_2 = 10.9 Hz), 5.85 (d, 1H, *J* = 17.6 Hz), 5.35 (d, 1H, *J* = 10.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.1 (2C), 138.3, 138.0, 136.0, 127.5 (4C), 127.0 (2C), 124.2 (2C), 115.1. Elemental analysis CHN (%) found C: 73.9, H: 5.1, N: 6.2, calcd for $C_{14}H_{11}O_2N$.0.1EtOAc C: 73.9, H: 5.1, N: 6.0.

5-Nitro-2-(4-vinylphenyl)pyridine **25c**



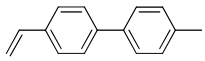
Yellow solid, 301 mg, 67% yield, (2.2 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.49 (d, 1H, *J* = 2.7 Hz), 8.52 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.6 Hz), 8.08 (d, 2H, *J* = 8.2 Hz), 7.91 (d, 1H, *J* = 9.0 Hz), 7.56 (d, 2H, *J* = 8.2 Hz), 6.79 (dd, 1H, J_1 = 10.5 Hz, J_2 = 17.6 Hz), 5.89 (d, 1H, *J* = 17.6 Hz), 5.39 (d, 1H, *J* = 10.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.0, 145.4, 142.9, 140.2, 136.3, 136.1, 132.0, 128.0 (2C), 127.0 (2C), 119.9, 116.0. HRMS-ES (m/z) found 227.0813, calcd for $[C_{13}H_{10}O_2N_2 + H]^+$ 227.0815. Elemental analysis CHN (%) found C: 69.2, H: 4.6, N: 12.3, calcd for $C_{13}H_{10}O_2N_2$ C: 69.0, H: 4.5, N: 12.4.

3-Nitro-4'-vinylbiphenyl **25d**



Off-white solid, 282 mg, 63% yield, (2 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.46 (m, 1H), 8.19 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 7.92 (d, 1H, *J* = 7.7 Hz), 7.64-7.57 (2d, 3H, J_{d1} = 7.7 Hz, J_{d2} = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 6.78 (dd, 1H, J_1 = 17.6 Hz, J_2 = 11.0 Hz), 5.84 (d, 1H, *J* = 17.6 Hz), 5.33 (d, 1H, *J* = 11.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.2, 148.8, 142.4, 137.9, 136.1, 132.8, 129.7, 127.3 (2C), 127.0 (2C), 122.0, 121.8, 114.9. Elemental analysis CHN (%) found C: 73.6, H: 4.8, N: 6.1, calcd for $C_{14}H_{11}O_2N$.0.14EtOAc C: 73.6, H: 5.1, N: 5.9.

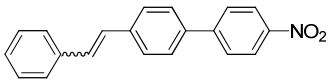
4-Methyl-4'-vinylbiphenyl **25f**



White solid, 259 mg, 67% yield, (2.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.58-7.44 (3d, 6H, J_{d1} = 8.4 Hz, J_{d2} = 8.8 Hz, J_{d3} = 8.4 Hz), 7.24 (d, 2H), 6.75 (dd, 1H, J_1 = 17.6 Hz, J_2 = 11.0 Hz), 5.78 (d, 1H, J = 17.6 Hz), 5.26 (d, 1H, J = 11.0 Hz), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.6, 137.9, 137.1, 136.5, 131.4, 129.5 (2C), 127.0 (2C), 126.8 (2C), 126.6 (2C), 113.7, 21.1. Elemental analysis CH (%) found C: 91.2, H: 7.4, calcd for $C_{15}H_{14}$.0.09EtOAc C: 91.2, H: 7.3.

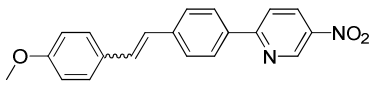
General procedure for the CM reaction on compounds 25:

4-Nitro-4'-styrylbiphenyl **28a**



25b (0.50 mmol, 113 mg), **26a** (1.50 mmol, 172 µL, 0.909 g.mL^{-1}), **27c** (0.015 mmol, 9 mg), and CH_2Cl_2 (5 mL) were mixed and stirred under reflux (~ 45 °C) and nitrogen atmosphere for 6 hours. The mixture was cooled to rt, the volatiles were removed under reduced pressure and the crude product purified by chromatography on silica gel, hexane/CH_2Cl_2 6:4, to give 93 mg of the pure expected product as a yellow solid in 62% yield, *E/Z* = 95:5. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.30 (d, 2H, J = 8.6 Hz), 7.76 (d, 2H, J = 8.8 Hz), 7.64 (s, 4H), 7.54 (d, 2H, J = 7.2 Hz), 7.38 (dd, 2H, J = 7.5 Hz), 7.29 (dd, 1H, J = 7.5 Hz), 7.20 and 7.15 (2d, AB system, 2H, J = 16.4 Hz), 6.69 and 6.62 (2d, AB system, 0.01H, J = 12.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.1 (2C), 138.1, 137.6, 137.0, 130.0, 128.8 (2C), 128.0, 127.7 (2C), 127.6, 127.5 (2C), 127.2 (2C), 126.7 (2C), 124.2 (2C). Elemental analysis CHN (%) found C: 79.0, H: 5.5, N: 4.5, calcd for $C_{20}H_{15}O_2N$.0.04CH_2Cl_2 C: 79.0, H: 5.0, N: 4.6.

2-(4-(4-Methoxystyryl)phenyl)-5-nitropyridine **28b**

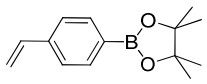


Yellow solid, 164 mg, 75% yield, isomer E only (0.66 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.49 (d, 1H, J = 2.3 Hz), 8.51 (dd, 1H, J_1 = 2.7 Hz, J_2 = 9.0 Hz), 8.10 (d, 2H, J = 8.6 Hz), 7.91 (d, 1H, J = 9.0 Hz), 7.63 (d, 2H, J = 8.6 Hz), 7.49 (d, 2H, J = 9.0 Hz), 7.19 (d, 1H,

J = 16.0 Hz), 7.03 (d, 1H *J* = 16.4 Hz), 6.92 (d, 2H, *J* = 8.6 Hz), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.9, 159.7, 145.3, 142.6, 140.4, 135.5, 131.9, 130.2, 129.7, 128.0 (4C), 126.9 (2C), 125.4, 119.6, 114.2 (2C), 55.4. HRMS-ES (m/z) found 333.1231, calcd for $[C_{20}H_{16}O_3N_2 + H]^+$ 333.1234. Elemental analysis CHN (%) found C: 71.8, H: 5.0, N: 7.9, calcd for $C_{20}H_{16}O_3N_2$.0.1EtOAc C: 71.8, H: 5.0, N: 8.2.

General procedure for the synthesis of compound 29:

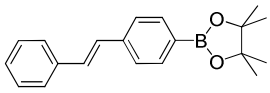
4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **29**



24 (6.76 mmol, 1.00 g), pinacol (6.80 mmol, 802 mg) and two spatula tip of magnesium sulphate were combined in anhydrous THF (55 mL) and left to stir at room temperature for 2 h. The mixture was filtered and concentrated under reduced pressure to afford 1.55 g of the pure expected product as a colourless liquid in quantitative yield (> 99%). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 6.72 (dd, 1H, J_1 = 11.0 Hz and J_2 = 17.6 Hz), 5.81 (d, 1H, *J* = 17.6 Hz), 5.29 (d, 1H, *J* = 11.0 Hz), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.2, 136.9 (2C), 135.0 (2C), 125.5 (2C), 114.9, 83.8 (2C), 24.9 (4C).

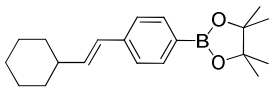
The CM reactions on compound **29** were achieved following the same procedure than for the CM reaction on compounds **25**.

(*E*)-4,4,5,5-Tetramethyl-2-(4-styrylphenyl)-1,3,2-dioxaborolane **23a**



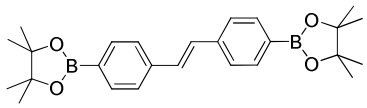
White solid, 97 mg, 65% yield (0.49 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (d, 2H, *J* = 8.0 Hz), 7.52 (dd, 4H, J_1 = 8.0 Hz, J_2 = 2.7 Hz), 7.36 (dd, 2H, *J* = 7.5 Hz), 7.26 (dd, 1H, *J* = 7.5 Hz), 7.18 and 7.11 (2d, AB system, 2H, *J* = 16.0 Hz), 1.35 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.0, 137.2, 135.2 (2C), 135.0, 129.7, 128.7 (2C), 127.8, 127.6, 126.6, 126.5, 125.8 (2C), 83.8 (2C), 24.9 (4C). Elemental analysis CH (%) found C: 78.0, H: 7.6, calcd for $C_{20}H_{23}O_2B$.0.02CH_2Cl_2 C: 78.1, H: 7.5.

(*E*)-2-(4-(2-Cyclohexylvinyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **23h**



White solid, 183 mg, 58% yield (1.02 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 6.34 (d, 1H, *J* = 16.0 Hz), 6.24 (dd, 1H, J_1 = 16.0 Hz, J_2 = 6.7 Hz), 2.18-2.08 (m, 1H), 1.83-1.64 (m, 5H), 1.33 (s, 12H), 1.31-1.12 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.9, 138.0 (2C), 135.0 (2C), 127.3, 125.3 (2C), 83.7 (2C), 41.2, 32.9 (2C), 26.2, 26.0 (2C), 24.9 (4C). Elemental analysis CH (%) found C: 76.9, H: 9.6, calcd for $C_{20}H_{29}O_2B$ C: 76.9, H: 9.4.

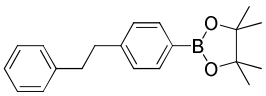
(*E*)-1,2-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane **30**



Off white solid, 214 mg, 89% yield (1.01 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (d, 4H, *J* = 8.0 Hz), 7.52 (d, 4H, *J* = 8.3 Hz), 7.18 (s, 2H), 1.33 (s, 24H). ^{13}C NMR ($CDCl_3$) δ (ppm): 139.9 (2C), 135.2 (4C), 129.6 (2C), 125.9 (6C), 83.8 (4C), 24.9 (8C). Elemental analysis CH (%) found C: 72.2, H: 8.7, calcd for $C_{26}H_{34}O_4B_2$ C: 72.3, H: 7.9.

General procedure for the hydrogenation reaction on compouds 23 using the H-Cube:

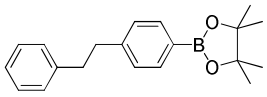
4,4,5,5-Tetramethyl-2-(4-phenethylphenyl)-1,3,2-dioxaborolane **31a**



23a (0.07 mmol, 21 mg) was dissolved in EtOH/EtOAc 1:1 mixture (20 mL) and reduced by hydrogenation in a H-Cube catalysed by platinum oxide at 80 ºC, 1 mL.min^{-1}. The solution obtained was concentrated under reduced pressure to give 17 mg of the expected product as a yellow oil, which crystallised at room temperature, in 77% yield.

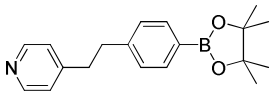
General procedure for the hydrogenation reaction on compounds 23, 26 and 30 in batch reaction:

4,4,5,5-Tetramethyl-2-(4-phenethylphenyl)-1,3,2-dioxaborolane **31a**



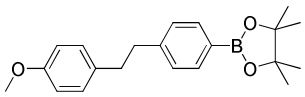
23a (0.72 mmol, 219 mg) was dissolved in EtOH (20 mL) and palladium on activated carbon (22 mg) was added and the mixture was stirred overnight at room temperature under hydrogen atmosphere. The mixture was filtered on Celite® and the filtrate was concentrated to give 220 mg of the expected product as a yellow solid in > 99% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73 (d, 2H, *J* = 8.1 Hz), 7.31-7.24 (m, 2H), 7.22-7.15 (m, 5H), 2.92 (s, 4H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.1, 141.7, 134.9 (2C), 134.8, 128.4 (2C), 128.3 (2C), 127.9 (2C), 125.9, 83.6 (2C), 38.1, 37.7, 24.9 (4C). Elemental analysis CH (%) found C: 77.1, H: 8.1, calcd for $C_{20}H_{25}O_2B.0.04CH_2Cl_2$ C: 77.2, H: 8.1.

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)pyridine **31b**



Beige solid, 245 mg, > 99% yield (0.79 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.47 (d, 2H, *J* = 5.9 Hz), 7.73 (d, 2H, *J* = 8.1 Hz), 7.16 (d, 2H, *J* = 8.7 Hz), 7.07 (d, 2H, *J* = 6.2 Hz), 2.93 (s, 4H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.4, 149.7 (2C), 144.0, 135.0 (2C), 128.4, 127.9 (2C), 123.9 (2C), 83.7 (2C), 36.8 (2C), 24.9 (4C). HRMS-ES (m/z) found 310.1981, calcd for $[C_{19}H_{24}O_2NB + H]^+$ 310.1973. Elemental analysis CHN (%) found C: 73.8, H: 7.6, N: 4.4, calcd for $C_{19}H_{24}O_2NB$ C: 73.8, H: 7.8, N: 4.5.

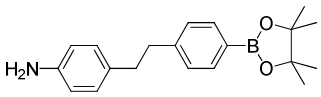
2-(4-(4-Methoxyphenethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **31c**



Off white solid, 144 mg, 95% yield (0.45 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (d, 2H, *J* = 8.1 Hz), 7.19 (d, 2H, *J* = 8.1 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 6.81 (d, 2H, *J* = 8.8 Hz), 3.79 (s, 3H), 2.88 (m, 4H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.8, 145.3, 134.8

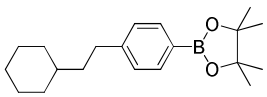
(2C), 133.8, 129.3 (2C), 128.4, 128.0 (2C), 113.7 (2C), 83.7 (2C), 55.3, 38.4, 36.8, 24.9 (4C). Elemental analysis CH (%) found C: 74.7, H: 8.0, calcd for $C_{21}H_{27}O_3B$ C: 74.6, H: 8.1.

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)aniline **31d**



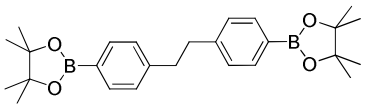
Off white solid, 111 mg, 34% yield over 2 steps (1.00 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (d, 2H, *J* = 7.8 Hz), 7.19 (d, 2H, *J* = 7.8 Hz), 6.96 (d, 2H, *J* = 8.2 Hz), 6.62 (d, 2H, *J* = 8.6 Hz), 3.55 (m, 2H), 2.90-2.75 (m, 4H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.5, 144.3, 134.8 (2C), 131.8, 129.2 (3C), 128.0 (2C), 115.2 (2C), 83.6 (2C), 38.5, 36.9, 24.9 (4C). HRMS-ES (m/z) found 323.2172, calcd for $[C_{20}H_{26}O_2N^{10}B + H]^+$ 323.2166. Elemental analysis CHN (%) found C: 74.1, H: 8.5, calcd for $C_{20}H_{26}O_2NB$ C: 74.3, H: 8.1.

2-(4-(2-Cyclohexylethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **31e**



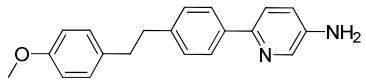
White solid, 268 mg, 94% yield (0.91 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (d, 2H, *J* = 7.9 Hz), 7.19 (d, 2H, *J* = 8.3 Hz), 2.62 (dd, 2H, *J* = 8.1 Hz), 1.80-1.60 (m, 5H), 1.56-1.45 (m, 2H), 1.33 (s, 12H), 1.30-1.10 (m, 4H), 0.98-0.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 146.8, 134.8 (3C), 127.9 (2C), 83.6 (2C), 39.2, 37.3, 33.5, 33.3 (2C), 26.7, 26.3 (2C), 24.9 (4C). Elemental analysis (%) found C: 76.3, H: 10.0, calcd for $C_{20}H_{31}O_2B$ C: 76.4, H: 9.9.

1,2-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane **31g**



White solid, 231 mg, 99% yield (0.54 mmol scale), crystallisation in CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (d, 4H, *J* = 8.3 Hz), 7.18 (d, 4H, *J* = 8.3 Hz), 2.92 (s, 4H), 1.34 (s, 24H). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.0 (2C), 134.9 (6C), 127.9 (4C), 83.7 (4C), 38.0 (2C), 24.9 (8C). Elemental analysis CHN (%) found C: 71.1, H: 8.3, calcd for $C_{26}H_{36}O_4B_2.0.07CH_2Cl_2$ C: 71.1, H: 8.3.

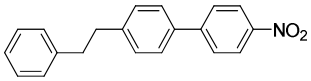
6-(4-(4-Methoxyphenethyl)phenyl)pyridin-3-amine **32b**



Beige solid, 30 mg, 75% yield (0.13 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.17 (d, 1H, *J* = 3.1 Hz), 7.80 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 1H, *J* = 8.6 Hz), 7.21 (d, 2H, *J* = 8.20 Hz), 7.09 (d, 2H, *J* = 9.0 Hz), 7.04 (dd, 1H, J_1 = 3.1 Hz, J_2 = 8.2 Hz), 6.81 (d, 2H, *J* = 9.0 Hz), 3.78 (s, 3H), 3.71 (m, 2H), 2.94-2.85 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.8, 148.2, 141.5, 141.2, 137.2, 137.1, 133.9, 129.4 (2C), 128.8 (2C), 125.9 (2C), 122.4, 120.5, 113.7 (2C), 55.3, 37.9, 36.9. HRMS-ES (m/z) found 305.1642, calcd for $[C_{20}H_{20}ON_2 + H]^+$ 305.1648. Elemental analysis CHN (%) found C: 78.3, H: 6.6, N: 8.9, calcd for $C_{20}H_{20}ON_2.0.04CH_2Cl_2$ C: 78.2, H: 6.6, N: 9.1.

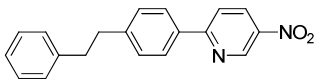
Compounds **31** were coupled in SM coupling reactions as for **8l** in Chapter 2.

4-Nitro-4'-phenethylbiphenyl **33a**



The crude product was purified by chromatography on silica gel, hexane/CH_2Cl_2 1:1, to give 55 mg of the pure expected product as a yellow solid in quantitative yield (> 99%) (0.17 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, *J* = 9.2 Hz), 7.73 (d, 2H, *J* = 8.8 Hz), 7.55 (d, 2H, *J* = 8.1 Hz), 7.15-35 (m, 7H), 2.97 ppm (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.8 (2C), 141.3, 136.7, 132.8 (2C), 129.7, 129.3 (2C), 128.4, 127.2 (2C), 123.9 (2C), 121.9 (2C), 121.8 (2C), 36.9, 36.2. Elemental analysis CHN (%) found C: 79.0, H: 5.8, N: 4.6, calcd for $C_{20}H_{17}O_2N$ C: 79.2, H: 5.7, N: 4.6.

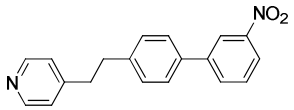
5-Nitro-2-(4-phenethylphenyl)pyridine **33b**



Yellow solid, 94 mg, 89% yield (0.35 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.48 (d, 1H, *J* = 2.6 Hz), 8.51 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.6 Hz), 8.02 (d, 2H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 8.8 Hz), 7.15-35 (2m, 7H), 3.00 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.4, 145.3 (2C),

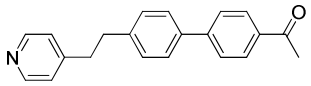
145.1, 141.2, 134.8, 131.9, 129.4 (2C), 128.5 (2C), 128.4 (2C), 127.7 (2C), 126.1, 119.7, 37.7, 37.6. Used as such for the next step.

4-(2-(3'-Nitrobiphenyl-4-yl)ethyl)pyridine **33c**



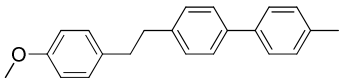
The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 8:2, to give 82 mg of the expected product as an off white solid in 82 % yield (0.33 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.51 (d, 2H, *J* = 5.9 Hz), 8.45 (m, 1H), 8.19 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz), 7.90 (d, 1H, *J* = 7.0 Hz), 7.60 (dd, 1H, *J* = 7.7 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.11 (d, 2H, *J* = 5.9 Hz), 3.00 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.8 (2C), 142.6, 141.3, 132.9 (2C), 129.7 (2C), 129.3 (2C), 128.4, 127.2 (2C), 123.9 (2C), 121.9, 121.8, 36.9, 36.2. MS-ES (m/z) found 305.4, calcd for $[C_{19}H_{16}O_2N_2 + H]^+$ 305.1. Elemental analysis CHN (%) found C: 74.8, H: 5.5, N: 8.9, calcd for $C_{19}H_{16}O_2N_2$ C: 75.0, H: 5.3, N: 9.2.

1-(4'-(2-(Pyridin-4-yl)ethyl)biphenyl-4-yl)ethanone **33d**



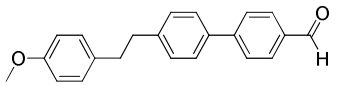
The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 6:4, to give 88 mg of the expected product as an off white solid in 86% yield (0.34 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.50 (d, 2H, *J* = 5.9 Hz), 8.03 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.56 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.4 Hz), 7.11 (d, 2H, *J* = 5.9 Hz), 2.98 (m, 4H), 2.64 (s, 3H).^{13}C NMR ($CDCl_3$) δ (ppm): 150.2, 149.8 (2C), 145.4, 140.9, 135.8, 132.2, 129.1 (2C), 128.9 (2C), 128.6, 128.4, 127.3 (2C), 127.0 (2C), 124.0, 36.9, 36.2, 26.7. HRMS-ES (m/z) found 302.1541, calcd for $[C_{21}H_{19}ON + H]^+$ 302.1539. Elemental analysis CHN (%) found C: 82.1, H: 6.3, N: 4.0, calcd for $C_{21}H_{19}ON$.0.2EtOAc C: 82.1, H: 6.5, N: 4.4.

4-(4-Methoxyphenethyl)-4'-methylbiphenyl **33e**



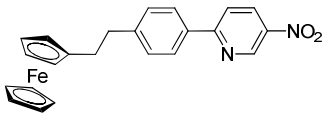
The crude product was purified by chromatography on silica gel, hexane/CH_2Cl_2 from 0% to 40% of CH_2Cl_2, to give 43 mg of the expected product as a white solid in 75% yield. (0.19 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.49 (d, 2H, *J* = 8.1 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.23 (m, 4H), 7.12 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 3.79 (s, 3H), 2.90 (m, 4H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.8, 140.7, 138.7, 138.2, 136.8, 133.8, 129.4 (2C), 129.3 (2C), 128.8 (2C), 126.8 (4C), 113.7 (2C), 55.2, 37.8, 37.0, 21.1. Elemental analysis CH (%) found C: 87.3, H: 7.6, calcd for $C_{22}H_{22}O$ C: 87.4, H: 7.3.

1-(4'-(4-Methoxyphenethyl)biphenyl-4-yl)ethanone **33f**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 95:5-9:1, to give 31 mg of the expected product as a white solid in 54% yield (0.18 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.05 (s, 1H), 7.95 (d, 2H, *J* = 8.4 Hz), 7.75 (d, 2H, *J* = 8.1 Hz), 7.57 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H), 7.12 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 3.80 (s, 3H), 2.93 (m, 4H).^{13}C NMR ($CDCl_3$) δ (ppm): 192.0, 157.9, 147.1, 142.4, 137.2, 135.0, 133.6, 130.3 (2C), 129.4 (2C), 129.2 (2C), 127.4 (2C), 127.3 (2C), 113.8 (2C), 55.3, 37.8, 36.9. Elemental analysis CH (%) found C: 84.3, H: 6.7, calcd for $C_{22}H_{20}O_2$ C: 83.5, H: 6.4.

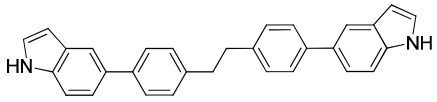
2-(4-(2-Ferrocenylethyl)phenyl)-5-nitropyridine **33g**



Red solid, 167 mg, 41% yield over 3 steps (1 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.49 (d, 1H, *J* = 2.3 Hz), 8.51 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.7 Hz), 8.03 (d, 2H, *J* = 8.2 Hz), 7.90 (d, 1H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 8.6 Hz), 4.12 (s, 5H), 4.06 (s, 4H), 2.90 (dd, 2H, J_1 = 7.4 Hz, J_2 = 5.9 Hz), 2.70 (dd, 2H, J_1 = 7.4 Hz, J_2 = 5.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.4, 145.5, 145.3, 142.7, 134.7, 131.9, 129.3 (2C), 127.7 (2C), 119.7, 88.1, 68.5 (5C), 68.1 (2C), 67.3 (2C), 37.5, 31.5. HRMS-ES (m/z) found 411.0996, calcd for $[C_{23}H_{20}O_2N_2{}^{54}Fe + H]^+$

411.0994. Elemental analysis CHN (%) found C: 66.9, H: 4.9, N: 6.8, calcd for $C_{23}H_{20}O_2N_2Fe$ C: 67.0, H: 4.9, N: 6.8.

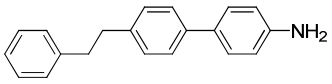
1,2-Bis(4-(*1H*-indol-5-yl)phenyl)ethane **33h**



Beige solid, 63 mg, 77% yield (0.20 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.17 (m, 2H), 7.86 (s, 2H), 7.60 (d, 4H, *J* = 8.2 Hz), 7.46 (s, 4H), 7.31 (d, 4H, *J* = 8.2 Hz), 7.25 (m, 2H), 6.61 (m, 2H), 3.02 (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 140.2 (2C), 140.0 (2C), 135.2 (2C), 133.3 (2C), 128.8 (4C), 128.4 (2C), 127.3 (4C), 124.7 (2C), 121.9 (2C), 119.1 (2C), 111.2 (2C), 103.0 (2C), 37.6 (2C).

34a was synthesised following the general procedure for the hydrogenation reaction on compouds **23** using the H-Cube.

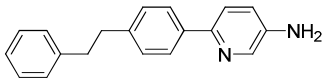
4'-Phenethylbiphenyl-4-amine **34a**



The crude product was purified by chromatography on silica gel, hexane/EtOAc from 0% to 30% of EtOAc, to give 7 mg of the expected product as a yellow oil/solid in 10% yield (0.26 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.46 (d, 2H, *J* = 8.1 Hz), 7.41 (d, 2H, *J* = 8.4 Hz), 7.33-7.17 (m, 7H), 6.75 (d, 2H, *J* = 8.4 Hz), 3.73 (m, 2H), 2.94 (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.7, 141.9, 139.6, 139.0, 130.0, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.8 (2C), 126.2 (2C), 125.9, 113.0 (2C), 38.5, 38.0. Used as such for the next step.

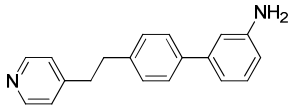
34b,**c** were synthesised following the general procedure for the hydrogenation reaction on compounds **23**, **26** and **30** in batch reaction.

6-(4-Phenethylphenyl)pyridin-3-amine **34b**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 8:2, to give 51 mg of the pure expected product as an orange solid in 72% yield (0.26 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.18 (d, 1H, *J* = 2.6 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 8.4 Hz), 7.32-7.16 (m, 7H), 7.05 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 3.73 (m, 2H), 2.95 (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 141.7, 141.5, 141.2, 136.8 (2C), 128.8 (3C), 128.5 (2C), 128.3 (2C), 126.0 (2C), 125.9, 122.6, 120.6, 37.8, 37.6. HRMS-ES (m/z) found 275.1541, calcd for $[C_{19}H_{38}N_2 + H]^+$ 275.1543. Elemental analysis CH (%) found C: 82.4, H: 6.9, calcd for $C_{19}H_{38}N_2$.0.08EtOAc C: 82.5, H: 6.7.

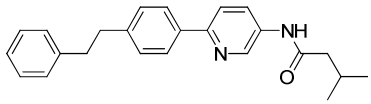
4'-(2-(Pyridin-4-yl)ethyl)biphenyl-3-amine **34c**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc from 50% to 80% of EtOAc, to give 47 mg of the pure expected product as a white solid in 68% yield (0.25 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.49 (d, 2H, *J* = 6.2 Hz), 7.49 (d, 2H, *J* = 8.1 Hz), 7.21 (m, 3H), 7.11 (d, 2H, *J* = 6.2 Hz), 6.98 (d, 1H, *J* = 7.7 Hz), 6.90 (m, 1H), 6.67 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 2.5 Hz, J_3 = 1.1 Hz), 3.73 (m, 2H), 2.96 (s, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.6, 149.6 (2C), 146.7, 142.1, 139.7, 139.4, 129.7, 128.7 (2C), 127.1 (2C), 124.0 (2C), 117.5, 114.0, 113.7, 37.0, 36.2. HRMS-ES (m/z) found 275.1546, calcd for $[C_{19}H_{18}N_2 + H]^+$ 275.1543. Elemental analysis CH (%) found C: 83.1, H: 6.8, calcd for $C_{19}H_{18}N_2$ C: 83.2, H: 6.6.

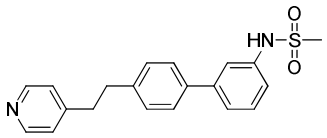
The functionalisation reaction of compounds **34** was performed as for **12a** in Chapter 3.

3-Methyl-*N*-(6-(4-phenethylphenyl)pyridin-3-yl)butanamide **35a**



The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 8:2, to give 32 mg of the pure expected product as a beige solid in 47% yield (0.19 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.55 (s, 1H), 8.30 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.1 Hz), 7.68 (d, 1H, *J* = 8.8 Hz), 7.53 (s, 1H), 7.30-7.10 (m, 7H), 2.98 (s, 4H), 2.26 (m, 3H), 1.02 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.2, 153.1, 142.5, 141.6, 140.6, 136.6, 133.3, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.0, 126.5 (2C), 125.9, 120.3, 46.9, 37.8, 37.6, 26.3, 22.5 (2C). HRMS-ES (m/z) found 359.2109, calcd for $[C_{24}H_{26}ON_2 + H]^+$ 359.2118. Elemental analysis CHN (%) found C: 80.4, H: 7.4, N: 7.6, calcd for $C_{24}H_{26}ON_2$ C: 80.4, H: 7.3, N: 7.8.

N-(4'-(2-(Pyridin-4-yl)ethyl)biphenyl-3-yl)methanesulphonamide **35b**

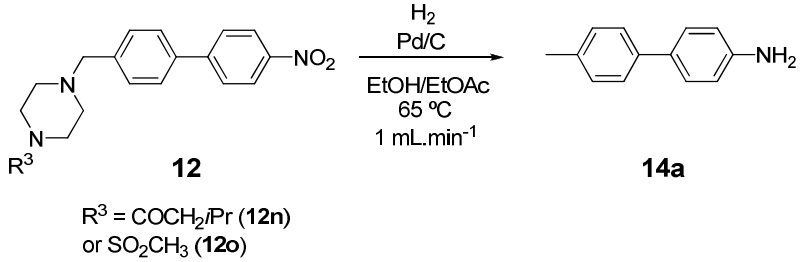


The crude product was purified by chromatography on silica gel, CH_2Cl_2/MeOH 95:5, to give 40 mg of the pure expected product as a beige solid in 82% yield (0.14 mmol scale). ^{1}H NMR (dmso-d_6) δ (ppm): 9.80 (m, 1H), 8.45 (d, 2H, *J* = 5.9 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.46-7.36 (m, 3H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 6.2 Hz), 7.19 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.2 Hz), 3.02 (s, 3H), 2.95 (s, 4H).). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.5, 149.6 (2C), 142.7, 140.4, 138.0, 137.2, 130.1, 129.0 (2C), 127.2 (2C), 124.1 (3C), 119.2 (2C), 39.5, 36.9, 36.1. HRMS-ES (m/z) found 353.1323, calcd for $[C_{20}H_{20}O_2N_2S + H]^+$ 353.1318. Elemental analysis CH (%) found C: 65.8, H: 5.7, calcd for $C_{20}H_{20}O_2N_2S.0.18CH_2Cl_2$ C: 65.9, H: 5.6.

Chapter 6: Synthesis and solid state study of methylbiphenylamides

6.1. Introduction

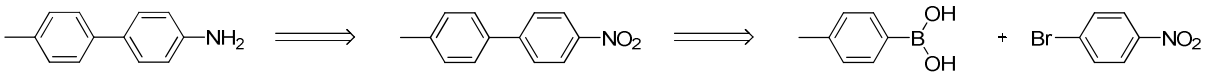
We previously observed that the reduction of the nitro group in compounds **12** catalysed by palladium on activated carbon gave the reduced and debenzylated product: 4'-methylbiphenyl-4-amine **14a** (Scheme 6.1; see Chapter 3.5).



Scheme 6.1. Nitro group reduction catalysed with Pd/C of compounds **12n** and **12o**.

As this product was not initially isolated in pure form, it was in some cases difficult to calculate the yields for the aniline functionalisation which took place afterwards. Hence, it was decided to synthesise **14a** by an unambiguous route in order to form biphenyl products (amides, sulphonamides) for solid state investigation (see later).

We opted for the reaction of 4-methylphenylboronic acid with 1-bromo-4-nitrobenzene in a SM coupling reaction to give 4'-methyl-4-nitrobiphenyl. The 4-tolylnitrobenzene could then be reduced to give the expected 4'-methylbiphenyl-4-amine (Scheme 6.2). This chemistry would, in principle, be applicable to regioisomeric bromonitrobenzenes, bromonitropyridine and tolylboronic acids.

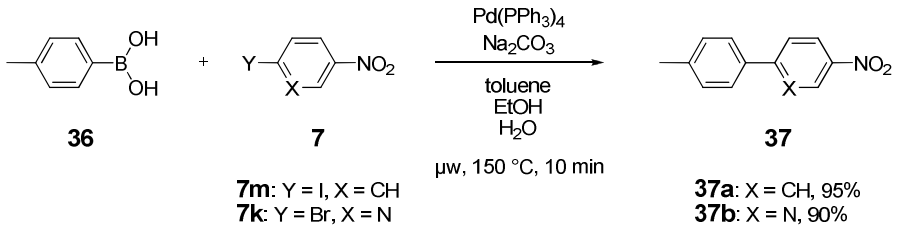


Scheme 6.2. Retrosynthetic analysis of 4'-methylbiphenyl-4-amine.

6.2. Synthesis of 4'-methylbiaryls

6.2.1. SM coupling reaction

The SM coupling reaction between 4-methylphenylboronic acid (**36**) and 1-iodo-4-nitrobenzene (**7m**) or 2-bromo-5-nitropyridine (**7k**) (Scheme 6.3) and was achieved using tetrakis(triphenylphosphine)palladium(0) as precatalyst using the conditions previously used (see Chapter 2).



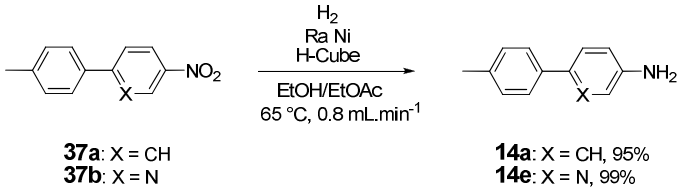
Conditions: Aryl halide (1.1 equiv.), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (3 equiv.), toluene/ethanol/water 1:1:1, microwave (power max. 300 W). Percentage yields given after purification by chromatography.

Scheme 6.3. SM coupling reaction of **36**.

The expected products **37** were obtained in very good yield after purification by chromatography.

6.2.2. Nitro group reduction

The products **37** were then reduced in order to obtain the amino derivatives **14** (Scheme 6.4).

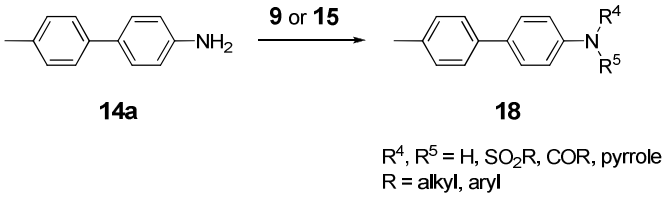


Scheme 6.4. Nitro group reduction of **37**.

The expected products were obtained in very good yield after purification by chromatography.

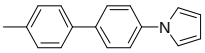
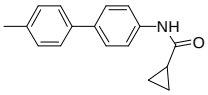
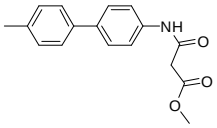
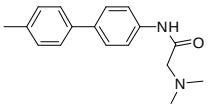
6.2.3. Amine functionalisations

14a was reacted with different acid, or sulphonyl, chlorides (**9**) in order to obtain the corresponding amide or sulphonamide. It also reacted with 2,5-dimethoxytetrahydrofuran (**15**) to yield pyrrole derivatives (Scheme 6.5; Table 6.1).



Scheme 6.5. NH_2 functionalisation reaction of **14a**.

Table 6.1. NH_2 functionalisation of **14a**.

Entry	Reagent	Conditions	Products (**18**)		Yield (%)[a]
1	**15**	acetic acid µw, 115 ºC, 15 min		**18b**	86
2	**9d**	PS-NMM, CH_2Cl_2 rt, 1 h		**18a**	71[b]
3	**9f**	PS-NMM, CH_2Cl_2 rt, 16 h		**18c**	97
4	**9g**	PS-NMM, CH_2Cl_2 rt, 16 h		**18d**	81

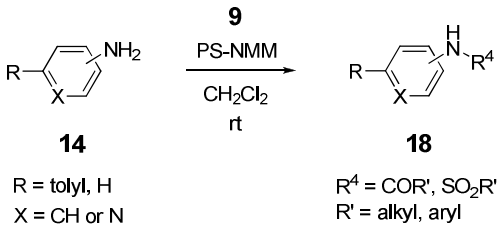
[a] Isolated yields after purification by chromatography on silica gel. [b] As seen in Chapter 3.

Compounds **18a-d** were now synthesised and unequivocally obtained in very good yields.

6.3. Crystallographic studies

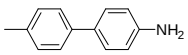
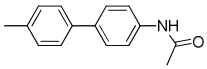
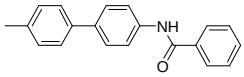
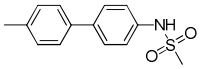
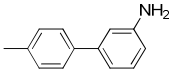
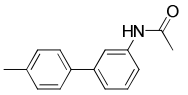
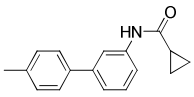
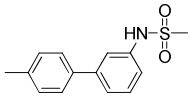
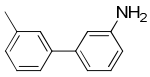
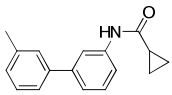
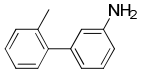
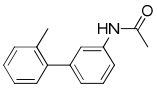
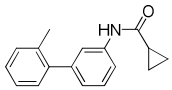
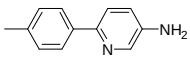
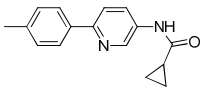
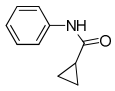
6.3.1. Synthesis

The crystal structure obtained for the compound **18a** (see Chapter 3, Figure 3.5) was found to be very interesting with three molecules in the asymmetric unit (Z' = 3) and chains formed by intermolecular N–H···O hydrogen bonds. Therefore, a library of similar compounds was synthesised in order to compare their crystal structures with that of **18a**, to look at the influence of variation around the biphenyl unit on the final crystal structure (Scheme 6.6; Table 6.2). The variation of the substituents on the nitrogen (e.g. **18a** vs **18e**), the regiochemistry on the biphenyl unit (e.g. **18e** vs **18h**) and the replacement of the biphenyl unit by an aryl pyridinyl unit (e.g. **18a** vs **18n**) were investigated. Not only were the amides or related substituents varied around the biphenyl unit but also the methyl group in the 2' and 3' position of the biphenyl (e.g. **18k** vs **18l**).



Scheme 6.6. NH_2 functionalisation reaction of **14**.

Table 6.2. NH_2 functionalisations of **14**.

Entry	**14**		**9**	Time (h)	Product (**18**)		Yield (%)[a]
1		**14a**	**9b**	48		**18e**	> 99
2		**14a**	**9h**	24		**18f**	91
3		**14a**	**9n**	24		**18g**	82
4		**14b**	**9b**	16		**18h**	89
5		**14b**	**9d**	16		**18i**	74
		14b	**9n**	16		**18j**	40
6		**14c**	**9d**	16		**18k**	[b]
7		**14d**	**9b**	16		**18l**	46
8		**14d**	**9d**	16		**18m**	52
9		**14e**	**9d**	16		**18n**	34
10		**14f**	**9d**	16		**18o**	90

[a] Isolated yields after purification by chromatography. [b] Not determined.

14b-d and **14f** were commercially available as amines or as the corresponding HCl salts.

Different amides and sulphonamides **18e-g** were synthesised in order to study the resulting compounds in the solid state. Some positional isomers were synthesised, **18h-m**. The position of the amide group on the phenyl ring was changed from *para*- to *meta*- and the methyl group from *para*- to *meta*- and *ortho*- in order to ascertain if the solid state structure would be influenced by these changes.

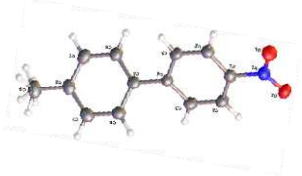
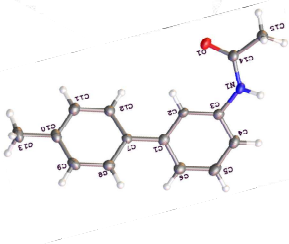
One of the phenyl rings was replaced by a pyridine, **18n**, which adds one more hydrogen bond acceptor to the molecule. A phenylamide, **18o**, was synthesised to see if the biphenyl unit was necessary for a high Z' value.

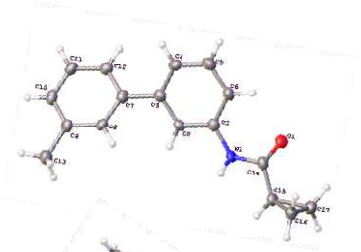
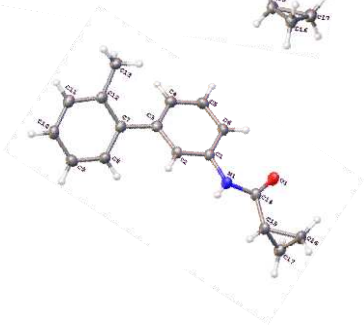
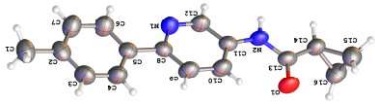
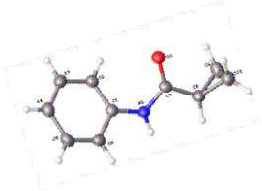
The biphenylamides and sulphonamides **18** were obtained in very good yields and, for some of them, crystals were grown in order to study them by single crystal X-ray crystallography.

6.3.2. X-Ray diffraction analysis for crystal structure determination

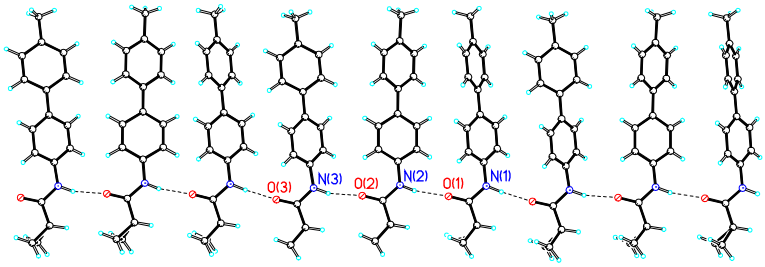
Not all of the compounds **18** were able to crystallise properly to give crystals good enough for structure determination (Table 6.3; Figure 6.1).

Table 6.3. Crystallographic data of compounds **37a** and **18**.

Entry	**37a** or **18**	Data	Crystal structure
1	**37a**	Orthorhombic *Fdd*2 Z = 8	
2	**18a**	Monoclinic P21/c Z = 12	See below
3	**18e**	Monoclinic P21/c Z = 24	See below
4	**18g**	Orthorhombic Pbca Z = 8	
5	**18h**	Orthorhombic P212121 Z = 4	

Entry	**37a** or **18**	Data	Crystal structure
6	**18k**	Orthorhombic Pbca Z = 8	
7	**18m**	Monoclinic P21/c Z = 4	
8	**18n**	Orthorhombic Pbca Z = 8	
9	**18o**	Monoclinic P21/c Z = 4	

a)



b)

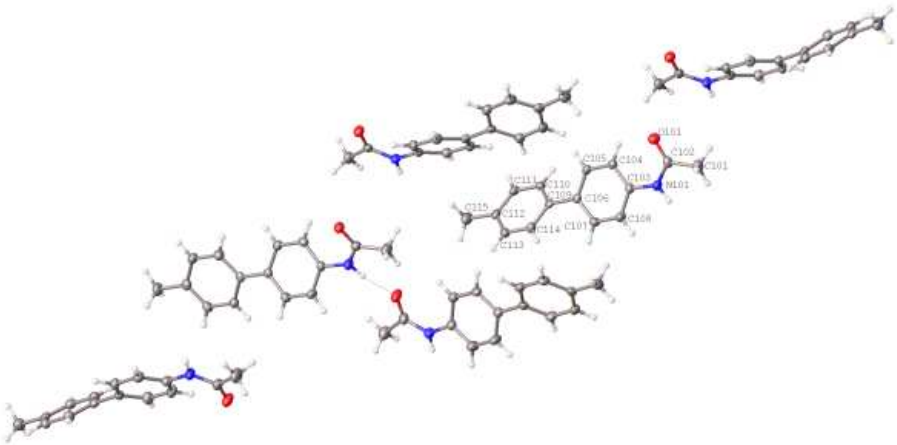


Figure 6.1. Crystal structure of **18a** (a) and **18e** (b).

37a is a simple nitrobiphenyl and was studied by X-ray crystallography as a comparator. In its crystal structure, the molecule lies on a 2-fold axis in the crystal, thus 2 asymmetric units of atoms are shown, hence the repeat of atom label numbers.

The crystal structure of **18e** was found to be very interesting. The molecules are linked *via* NH···O hydrogen bonds and the asymmetric unit consists of six independent molecules (Z' = 6), which is twice that of **18a**.

The structure determination of **18l** was not fully completed because of the poor quality of the data obtained. However, preliminary data collection seemed promising with 8 molecules in the asymmetric unit (Z' = 8). **18l** will be recrystallised in order to obtain better crystals and data.

The other compounds gave interesting crystal structures where Z' = 1, which were less remarkable than those of **18a** and **18e**. The biphenyl unit seems to be necessary to form an interesting lattice. The introduction of a pyridine unit did not lead to more hydrogen bonds and larger Z' values. The position of the methyl and the amide groups appears to influence the solid state structure of the biphenylamides. However, the crystallisation process has a large influence on crystal formation, including temperature, solvent(s) and concentration.

6.4. Conclusion

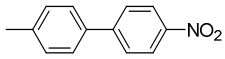
An unambiguous synthesis of 4'-methylbiphenyl-4-amine has been achieved and it has been found to be a useful synthon the synthesis of functionalised biphenyls. Compounds **18a-d** were obtained in very good yields. The synthesis of a methylbiarylamide derivatives library was successful and led to the determination of nine crystal structures, of which two were noteworthy from a crystallographic point of view in terms of their high Z' values. The solid state study of the influence of the functionality and regiochemistry in hydrogen bonded biphenyls is not an easy process and further investigations should be undertaken for interpretations and conclusions to be given, including thermogravimetric and calorimetric studies.

6.5. Experimental procedures and data

Experimental conditions and analytical methods are as for Chapter 2

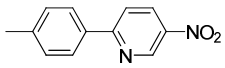
The SM couplings were achieved with the same procedure as in Chapter 2 for **8l**.

4'-Methyl-4-nitrobiphenyl **37a**



The crude product was purified by chromatography on silica gel, hexane/EtOAc 9:1-8:2, to give 203 mg of the pure expected product as an off white solid in 95% yield (1.00 mmol scale). The product was crystallised from CH_2Cl_2 and gave beige crystals. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, *J* = 8.8 Hz), 7.72 (d, 2H, *J* = 8.8 Hz), 7.53 (d, 2H, *J* = 8.1 Hz), 7.31 (d, 2H, *J* = 8.1 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.6, 146.6, 139.1, 135.1, 129.9 (2C), 127.5 (2C), 127.2 (2C), 124.1 (2C), 21.2. Elemental analysis CHN (%) found C: 72.9, H: 5.2, N: 6.3, calcd for $C_{13}H_{11}O_2N$ C: 73.2, H: 5.2, N: 6.6. The data are in accordance with the literature.[158]

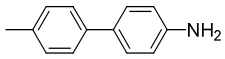
5-Nitro-2-*p*-tolylpyridine **37b**



Yellow solid, 96 mg, 90% yield (0.50 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.47 (d, 1H, *J* = 2.0 Hz), 8.50 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9.0 Hz), 8.00 (d, 2H, *J* = 8.2 Hz), 7.88 (d, 1H, *J* = 9.4 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.5, 145.2, 142.6, 141.4, 134.3, 131.9, 129.9 (2C), 127.6 (2C), 119.6, 21.4. HRMS-ES (m/z) found 215.0812, calcd for $[C_{12}H_{10}O_2N_2 + H]^+$ 215.0815. Elemental analysis CHN (%) found C: 67.4, H: 4.7, N: 13.2, calcd for $C_{12}H_{10}O_2N_2$ C: 67.3, H: 4.7, N: 13.1.

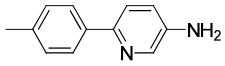
The nitro group reductions were achieved with the same procedure as in Chapter 3 for **13a**.

4'-Methylbiphenyl-4-amine **14a**



Off-white solid, 144 mg, 95% yield (2.54 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.41 (d, 2H, *J* = 8.8 Hz), 7.37 (d, 2H, *J* = 8.8), 7.18 (d, 2H, *J* = 8.1 Hz), 6.73 (d, 2H, *J* = 8.4 Hz), 3.68 (m, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.5, 138.3, 135.9, 131.6, 129.4 (2C), 127.8 (2C), 126.3 (2C), 115.4 (2C), 21.0. HRMS-ES (m/z) found 184.1117, calcd for $[C_{13}H_{13}N + H]^+$ 184.1121. Elemental analysis CHN (%) found C: 85.4, H: 7.2, N: 7.6, calcd for $C_{13}H_{13}N$ C: 85.2, H: 7.2, N: 7.6.

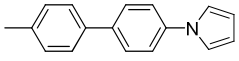
6-*p*-Tolylpyridin-3-amine **14e**



Off-white solid, 80 mg, 99% yield (0.44 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.16 (d, 1H, *J* = 2.7 Hz), 7.78 (d, 2H, *J* = 8.2 Hz), 7.51 (d, 1H, *J* = 8.7 Hz), 7.22 (d, 2H, *J* = 8.2 Hz), 7.03 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.7 Hz), 3.70 (m, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.1, 141.1, 137.6, 136.9, 136.6, 129.4 (2C), 125.9 (2C), 122.5, 120.5, 21.2. HRMS-ES (m/z) found 185.1071, calcd for $[C_{12}H_{12}N_2 + H]^+$ 185.1073. Elemental analysis CHN (%) found C: 78.0, H: 6.6, N: 15.0, calcd for $C_{12}H_{12}N_2$ C: 78.2, H: 6.6, N: 15.2.

The pyrrole synthesis was achieved with the same procedure as in Chapter 3.

1-(4'-Methylbiphenyl-4-yl)-*1H*-pyrrole **18b**

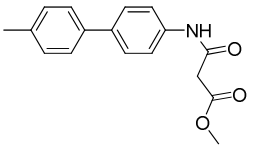


The crude product was purified by chromatography on silica gel, hexane/CH_2Cl_2 1:1, to give 54 mg of the pure expected product as a beige solid in 86% yield (0.27 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.63 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 8.1 Hz), 7.45 (d, 2H, *J* = 8.8 Hz), 7.27 (d, 2H), 7.13 (m, 2H), 6.37 (m, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 139.7, 138.5, 137.3, 137.2, 129.6 (2C), 128.0 (2C), 126.8 (2C), 120.7 (2C), 119.3 (2C), 110.4 (2C),

21.1. Elemental analysis CHN (%) found C: 86.3, H: 6.6, N: 5.7, calcd for $C_{17}H_{15}N.0.05CH_2Cl_2$ C: 86.2, H: 6.4, N: 5.9.

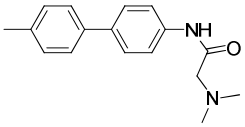
The amide couplings were achieved with the same procedure as in Chapter 3.

Methyl 3-(4'-methylbiphenyl-4-ylamino)-3-oxopropanoate **18c**



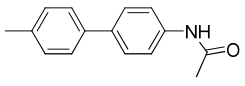
White solid, 123 mg, 97% yield (0.45 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.13 (m, 1H), 7.55 (d, 2H, *J* = 9.0 Hz), 7.48 (d, 2H, *J* = 9.0 Hz), 7.40 (d, 2H, *J* = 8.2 Hz), 7.17 (d, 2H, *J* = 7.8 Hz), 3.75 (s, 3H), 3.44 (s, 2H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.5, 162.6, 137.6, 137.4, 136.9, 136.4, 129.5 (2C), 127.4 (2C), 126.7 (2C), 120.4 (2C), 52.7, 41.2, 21.1. HRMS-ES (m/z) found 284.1280, calcd for $[C_{17}H_{17}O_3N + H]^+$ 284.1281. Elemental analysis CHN (%) found C: 71.9, H: 6.2, N: 4.7, calcd for $C_{17}H_{17}O_3N$ C: 72.1, H: 6.1, N: 4.9.

2-(Dimethylamino)-*N*-(4'-methylbiphenyl-4-yl)acetamide **18d**



White solid, 95 mg, 81% yield (0.44 mmol scale). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.14 (m, 1H), 7.65 (d, 2H, *J* = 8.6 Hz), 7.55 (d, 2H, *J* = 8.6 Hz), 7.47 (d, 2H, *J* = 8.2 Hz), 7.23 (d, 2H, *J* = 7.8 Hz), 3.09 (s, 2H), 2.39 (m, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.7, 137.7, 136.9, 136.8, 136.7, 129.5 (2C), 127.4 (2C), 126.7 (2C), 119.7 (2C), 63.7, 46.0 (2C), 21.1. HRMS-ES (m/z) found 269.1651, calcd for $[C_{17}H_{20}ON_2 + H]^+$ 269.1648. Elemental analysis CHN (%) found C: 76.0, H: 7.5, N: 10.2, calcd for $C_{17}H_{20}ON_2$ C: 76.1, H: 7.5, N: 10.4.

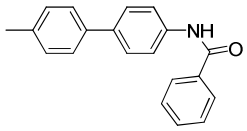
N-(4'-Methylbiphenyl-4-yl)acetamide **18e**



White solid, 77 mg, 100% yield (0.33 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.54 (m, 4H), 7.46 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.1 Hz),

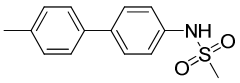
7.19 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.2, 137.6, 137.2, 136.9 (2C), 129.5 (2C), 127.4 (2C), 126.7 (2C), 120.1 (2C), 24.6, 21.1. HRMS-ES (m/z) found 226.1220, calcd for $[C_{15}H_{15}ON + H]^+$ 226.1226. Elemental analysis CHN (%) found C: 80.0, H: 6.8, N: 6.6, calcd for $C_{15}H_{15}ON$ C: 80.0, H: 6.7, N: 6.2.

N-(4'-Methylbiphenyl-4-yl)benzamide **18f**



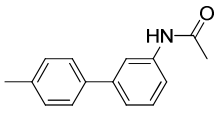
White solid, 115 mg, 91% yield (0.44 mmol scale). ^{1}H NMR (DMSO-d_6) δ (ppm): 10.33 (m, 1H), 7.97 (d, 2H, *J* = 8.6 Hz), 7.87 (d, 2H, *J* = 8.6 Hz), 7.65 (d, 2H, *J* = 9.0 Hz), 7.61-7.51 (m, 5H), 7.26 (d, 2H, *J* = 8.2 Hz), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6) δ (ppm): 165.5, 138.4, 136.8, 136.3, 135.2, 134.9, 131.6, 129.5 (2C), 128.4 (2C), 127.7 (2C), 126.5 (2C), 126.1 (2C), 120.6 (2C), 20.7. HRMS-ES (m/z) found 288.1384, calcd for $[C_{20}H_{17}ON + H]^+$ 288.1383. Elemental analysis CHN (%) found C: 83.2, H: 6.0, N: 4.7, calcd for $C_{20}H_{17}ON.0.07CH_3OH$ C: 83.2, H: 6.0, N: 4.8.

N-(4'-Methylbiphenyl-4-yl)methanesulphonamide **18g**



White solid, 94 mg, 82% yield (0.44 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.55 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 2H, *J* = 8.4 Hz), 7.28-7.21 (m, 4H), 6.33 (m, 1H), 3.03 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 138.6, 137.3, 137.1, 135.5, 129.6 (2C), 128.2 (2C), 126.7 (2C), 121.3 (2C), 39.5, 21.1. Elemental analysis CHN (%) found C: 63.7, H: 5.9, N: 5.3, calcd for $C_{14}H_{15}O_2NS.0.19CH_3OH$ C: 63.7, H: 5.9, N: 5.2.

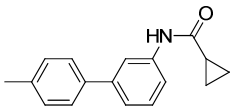
N-(4'-Methylbiphenyl-3-yl)acetamide **18h**



White solid, 164 mg, 89% yield (0.82 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.69 (m, 1H), 7.48 (m + d, 3H, *Jd* = 8.0 Hz), 7.37 (dd, 1H, *J* = 8.0

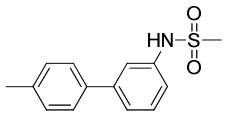
Hz), 7.32 (d, 1H, *J* = 7.6 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.21 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.3, 142.2, 138.3, 137.9, 137.4, 129.6 (2C), 129.4, 127.1 (2C), 123.1, 118.6, 118.5, 24.8, 21.2. HRMS-ES (*m/z*) found 226.1227, calcd for $[C_{15}H_{15}ON + H]^+$, 226.1226. Elemental analysis CHN (%) found C: 79.8, H: 6.6, N: 6.1, calcd for $C_{15}H_{15}ON$ C: 78.0, H: 6.7, N: 6.2.

N-(4'-Methylbiphenyl-3-yl)cyclopropanecarboxamide **18i**



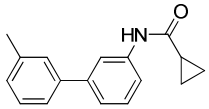
White solid, 186 mg, 74% yield (1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (m, 1H), 7.50-7.42 (d + m, 3H, *Jd* = 8.2 Hz), 3.39 (m, 1H), 7.36 (dd, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 7.8 Hz), 7.22 (d, 2H, *J* = 8.2 Hz), 2.38 (s, 3H), 1.50 (m, 1H), 1.11 (m, 2H), 0.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 142.1, 138.6, 137.9, 137.4, 129.5 (2C), 129.4, 127.1 (2C), 122.7, 118.3 (2C), 21.2, 15.9, 8.1 (2C). Elemental analysis CHN (%) found C: 81.1, H: 6.6, N: 5.3, calcd for $C_{17}H_{17}ON$ C: 81.2, H: 6.8, N: 5.6.

N-(4'-Methylbiphenyl-3-yl)methanesulphonamide **18j**



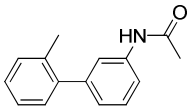
White solid, 103 mg, 40% yield (1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.47 (d, 2H, *J* = 8.0 Hz), 7.43-7.39 (m, 3H), 7.26 (d, 2H, *J* = 8.0 Hz), 7.20-7.16 (m, 1H), 6.36 (m, 1H), 3.04 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 143.0, 137.8, 137.1, 137.0, 130.1, 129.6 (2C), 127.0 (2C), 124.1, 119.2, 119.1, 39.5, 21.1. Elemental analysis CHN (%) found C: 64.2, H: 6.0, N: 5.6, calcd for $C_{14}H_{15}O_2NS$ C: 64.3, H: 5.8, N: 5.4.

N-(3'-Methylbiphenyl-3-yl)cyclopropanecarboxamide **18k**



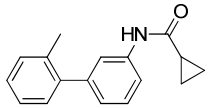
Beige solid (1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (m, 1H), 7.51-7.26 (m, 7H), 7.16 (d, 1H, *J* = 7.4 Hz), 2.40 (s, 3H), 1.52 (m, 1H), 1.11 (m, 2H), 0.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 142.3, 140.7, 138.5, 138.3, 129.3, 128.6, 128.2, 128.0, 124.3, 122.9, 118.4 (2C), 21.5, 15.9, 8.0 (2C). Elemental analysis CHN (%) found C: 80.6, H: 6.8, N: 5.5, calcd for $C_{17}H_{17}ON.0.12CH_3OH$ C: 80.6, H: 6.9, N: 5.5.

N-(2'-Methylbiphenyl-3-yl)acetamide **18l**



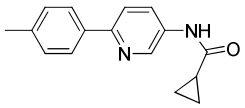
White solid, 103 mg, 46% yield (1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73-7.68 (m, 1H), 7.56-7.50 (m, 2H), 7.42 (s, 1H), 7.35 (dd, 1H, *J* = 7.8 Hz), 7.30-7.17 (m, 3H), 7.07 (d, 1H, *J* = 7.4 Hz), 2.27 (s, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.2, 142.8, 141.4, 137.6, 135.3, 130.3, 129.7, 128.7, 127.4, 125.7, 125.3, 120.6, 118.3, 24.7, 20.4. Elemental analysis CHN (%) found C: 79.2, H: 6.8, N: 6.2, calcd for $C_{15}H_{15}ON.0.13CH_3OH$ C: 79.2, H: 6.8, N: 6.1.

N-(2'-Methylbiphenyl-3-yl)cyclopropanecarboxamide **18m**



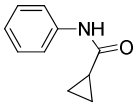
White solid, 131 mg, 52% yield (1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.52 (d, 1H, *J* = 7.8 Hz), 7.45 (s, 1H), 7.40 (m, 1H), 7.35 (dd, 1H, *J* = 7.8 Hz), 7.26-7.20 (m, 4H), 7.06 (d, 1H, *J* = 7.4 Hz), 2.28 (s, 3H), 1.51 (m, 1H), 1.12-1.07 (m, 2H), 0.88-0.82 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.8, 142.8, 141.4, 137.8, 135.3, 130.3, 129.7, 128.7, 127.4, 125.7, 125.0, 120.5, 118.1, 20.5, 15.8, 8.0 (2C). Elemental analysis CHN (%) found C: 81.0, H: 6.9, N: 5.6, calcd for $C_{17}H_{17}ON$ C: 81.2, H: 6.8, N: 5.6.

N-(6-*p*-Tolylpyridin-3-yl)cyclopropanecarboxamide **18n**



White solid, 26 mg, 34% yield (0.30 mmol scale). Crystallisation from CH_2Cl_2/MeOH. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.57 (m, 1H), 8.25 (d, 1H, *J* = 8.7 Hz), 7.85 (d, 2H, *J* = 7.9 Hz), 7.68 (d, 1H, *J* = 8.7 Hz), 7.47 (m, 1H), 7.26 (d, 2H, *J* = 7.9 Hz), 2.40 (s, 3H), 1.59-1.52 (m, 1H), 1.16-1.11 (m, 2H), 0.93-0.88 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.3, 140.4, 138.6, 136.1, 133.4, 129.5 (3C), 127.8, 126.4 (2C), 120.2, 21.4, 15.8, 8.3 (2C). HRMS-ES (m/z) found 253.1332, calcd for $[C_{16}H_{16}ON_2 + H]^+$ 253.1335. Elemental analysis CHN (%) found C: 75.8, H: 6.4, N: 11.0, calcd for $C_{16}H_{16}ON_2.0.08CH_3OH$ C: 75.8, H: 6.5, N: 11.0.

N-Phenylcyclopropanecarboxamide **18o**

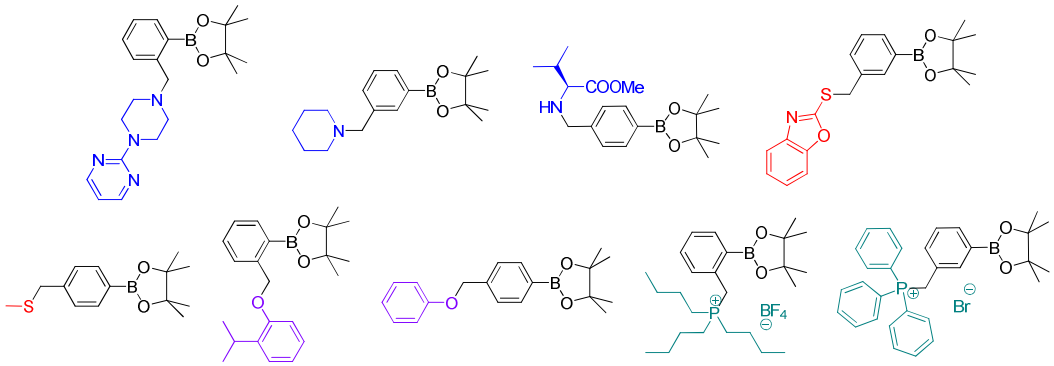


White solid, 87 mg, 90% yield (0.60 mmol scale). Crystallisation from CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.50 (d, 2H, *J* = 7.8 Hz), 7.43-7.26 (m, 1H), 7.31 (dd, 2H, *J* = 7.8 Hz), 7.09 (dd, 1H, *J* = 7.3 Hz), 1.49 (m, 1H), 1.09 (m, 2H), 0.84 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 138.2, 129.1 (2C), 124.1, 119.8 (2C), 15.9, 8.0 (2C). HRMS-ES (m/z) found 162.0911, calcd for $[C_{10}H_{11}ON + H]^+$ 162.0913. Elemental analysis CHN (%) found C: 74.3, H: 6.9, N: 8.6, calcd for $C_{10}H_{11}ON$ C: 74.5, H: 6.9, N: 8.7.

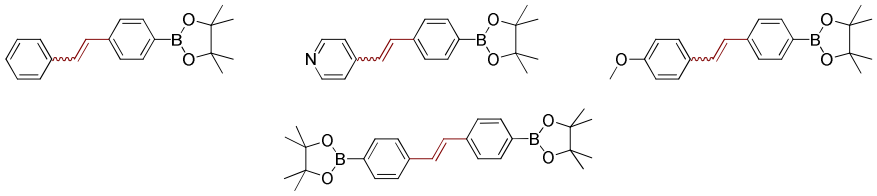
CONCLUSION

Boronates are important synthons in organic synthesis and they can lead, *via* the Suzuki-Miyaura (SM) coupling reaction, to interesting biphenyl derivatives with potential interest in medicinal chemistry and a host of other fields.

Arylboronic acid pinacol esters are extremely versatile tools for the synthesis of functionalised boronates and biaryls. A varied and interesting library of arylboronic acid pinacol ester derivatives was synthesised *via* microwave-mediated S_N2 reactions, Wittig and cross-metathesis (CM) reactions. Microwave-mediated S_N2 reactions on (bromomethyl)phenylboronic acid pinacol ester isomers led to amino-, mercapto-, alkoxy-, phenoxy- and phosphinomethylphenylboronic acid pinacol esters, as shown below.



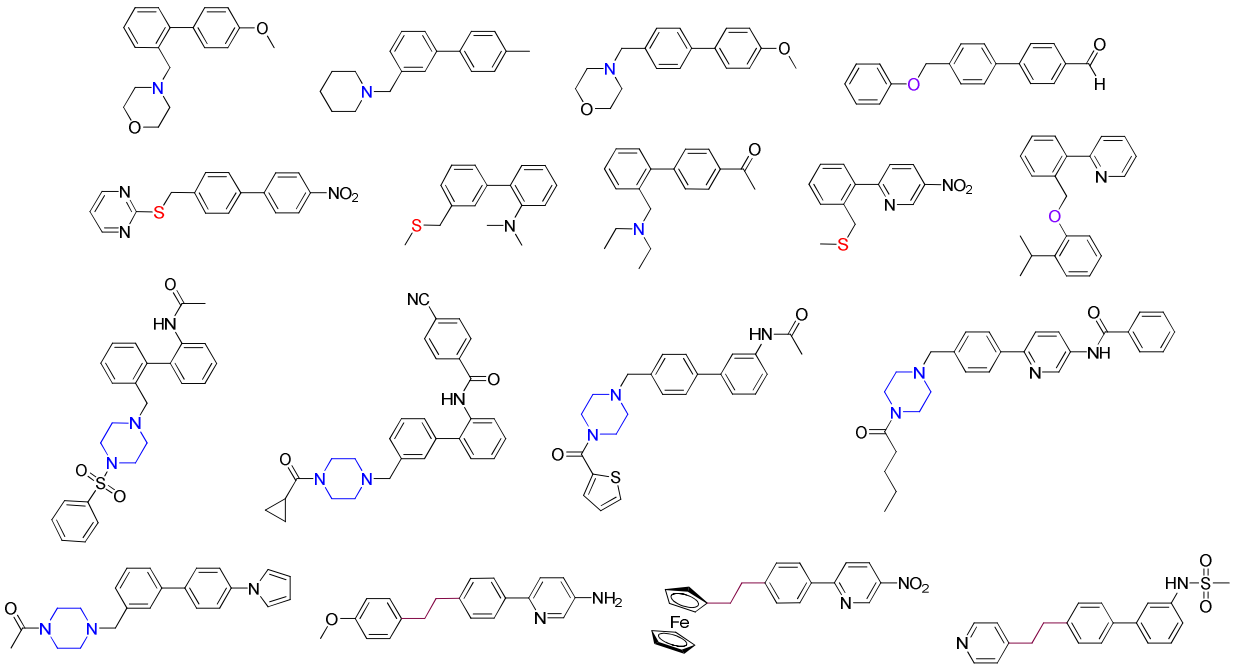
Wittig and CM reactions led to the synthesis of arylvinylphenylboronic acid pinacol esters, as shown below.



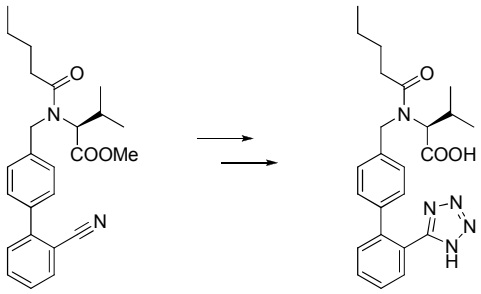
The aim of this project was to synthesise a library of biphenyl compounds mediated by the SM coupling reaction. The facile SM coupling reactions of *N*- and *O*-substituted arylboronic acid pinacol esters with aryl bromides has led to a small library of biphenyls. The optimisation of the conditions for the SM coupling of *S*-substituted and *o*-substituted arylboronates with aryl halides allowed the synthesis of interesting *S*-substituted and *o*-substituted biaryls. (Piperazin-1-ylmethyl)biaryl compounds represent a remarkable drug-like

library of compounds. The arylethylbiaryl derivatives obtained by the SM coupling of arylvinylboronates add a significant value to the biphenyl library.

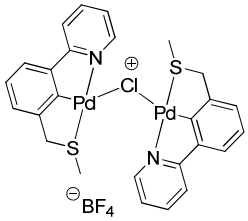
A library of approximately one hundred and thirty biphenyl compounds, including sixty functionalised, elaborated, biphenyl compounds, has been synthesised and analysed thanks to a multistep synthesis procedure using parallel synthesis, representative examples of which are shown below.

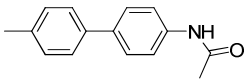


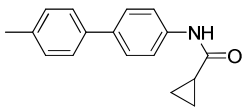
The chemistry used for the synthesis of this biphenyl library is easily applicable to the synthesis of drug-like molecules. Hence, a precursor of a well-known drug, valsartan, was also synthesised, as shown below.



Crystallographic analysis of some compounds gave some unexpected results such as the chloride-bridged *S*-substituted biphenyl palladacycle, the 4'-methyl-4-methylamide biphenyl and the 4'-methyl-4-cyclopropylamide biphenyl shown below.



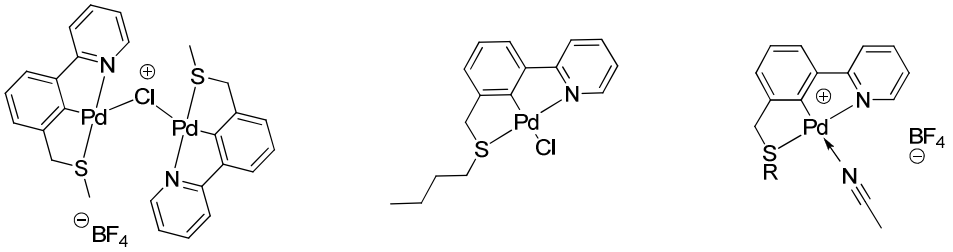




FUTURE WORK

- A study on the conditions for the preparation of unsymmetrical biaryl palladacycles.

Since the two reactions attempted led to a mixture of the expected product with chlorido-bridged biaryl palladacycle or chloro-biaryl palladacycle (Chapter 4), optimistation studies should be attempted in order to understand the reaction and to selectively obtain the desired products, especially the monomeric pincer, for catalytic studies (see below).

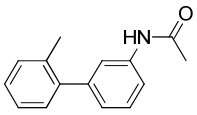


- The synthesis of more arylethylbiaryl derivatives.

The synthesis of the arylethylbiaryl library (Chapter 5) was achieved towards the end of the project and some of the intermediates were not transformed into final compounds, due to lack of time. Some CM reaction on vinylbiphenyls should be undertaken followed by hydrogenation of the carbon-carbon double bond. More CM reactions on vinylphenylboronic acid pinacol ester should be carried out in order to broaden the scope of the arylethylbiaryl library.

- Crystallographic study of biphenylamides.

The biphenylamide **18l** should be recrystallised in order to obtain good quality crystals for a full structure determination by X-ray analysis, since a preliminary structure revealed a Z' = 8 for this compound.



18l

Some biphenylamides did not crystallise in the different conditions used. An investigation could be done on the different way of crystallising these compounds. Moreover, all the results obtained should be discussed closely with crystallography collaborators (in Southampton University) and material science experts to draw conclusions and maybe synthesise more derivatives as well as delve into the application of high Z' molecules. Moreover, polymorph analysis *via* DSC and TGA is currently underway and will inform us of the thermodynamic stability of the crystals.

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APPENDIX

Publications:

1. Microwave-Mediated Synthesis of an Arylboronate Library. Spencer, J.; Baltus, C. B.; Patel, H.; Press, N. J.; Callear, S. K.; Male, L.; Coles, S. J. *ACS Comb. Sci.* **2011**, *13*, 24–31.

2. Synthesis of a (piperazin-1-ylmethyl)biaryl library via microwave-mediated Suzuki-Miyaura cross-couplings. Spencer, J.; Baltus, C. B.; Press, N. J.; Harrington, R. W.; Clegg, W. *Tetrahedron Lett.* **2011**, *52*, 3963–3968.

3. Suzuki-Miyaura coupling on *S*- and *ortho*-substituted phenylboronic esters. Publication in progress (*Synthesis*).

4. Synthesis of an arylethylbiaryl library. Publication in progress (*Adv. Synth. Catal.*).

5. Synthesis and solid state study of methylbiphenylamides. Publication in progress (*Cryst. Eng. Comm.*).

6. Suzuki-Miyaura Mediated Biphenyl Synthesis: A Spotlight on the Boronate Coupling Partner. Publication in progress (review).

Poster presentation:

Suzuki-Miyaura Mediated Biphenyl Synthesis: A Spotlight on the Boronate Coupling Partner, 18-ICOS 2010, Bergen, Norway, August 2010.

School seminar presentations:

9th December 2009 and 1st June 2011 on Suzuki-Miyaura Mediated Biphenyl Synthesis: A Spotlight on the Boronate Coupling Partner.

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Microwave-Mediated Synthesis of an Arylboronate Library

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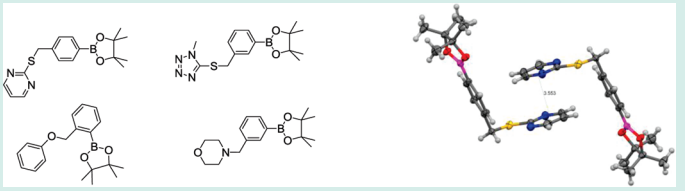
Supporting Information

ABSTRACT: A series of arylboronates has been synthesized from the reaction of 2-(2-, (3-, or (4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1**{*1*−*3*} respectively with a range of N-, S-, and O-nucleophiles, using microwave-mediated chemistry. For the synthesis of N- and S-substituted boronates, a supported base, PS-NMM, was employed, and many reactions were complete within 15 min. With O-nucleophiles, a mixture of tetrabutylammonium bromide, potassium carbonate, and sodium hydroxide was employed. The resulting aminomethyl, mercaptomethyl, or alkoxy-/phenoxymethyl-arylboronates were subjected to microwave-mediated Suzuki Miyaura coupling reactions to afford a range of biaryls in moderate to good yields. The X-ray structures of five boronates were determined.



KEYWORDS: Suzuki coupling, microwave, boronic acid, nucleophilic substitution, biaryls, supported reagents

INTRODUCTION

The biaryl motif is found in many natural and synthetic products and as a privileged scaffold in medicinal chemistry, notably in a variety of inhibitors of enzymes, transporter proteins, and GPCR ligands as well as in herbicides,[1] fungicides,[2] chiral ligands in catalysis,[3] liquid crystals,[4] and novel materials (organic conductors, organic electric wires) (Figure 1).[5−7]

The palladium-catalyzed Suzuki−Miyaura (SM) coupling reaction is one of the most important and efficient strategies for the construction of biaryls. This reaction involves the coupling of organic halides, typically a bromide with organoboron compounds, in the presence of a base and a catalytic amount of palladium complex.[8] Arylboronic acids are often synthesized by a low-temperature transmetalation reaction and can be difficult to modify or isolate. They are often purchased (many are expensive) for use in SM couplings, which limits the scope of the parallel synthetic process.[8]

We[9a,b] and others[9c] have advocated the deployment of pinacol-ester-protected arylboronic acids (ArBPin) **1** in biaryl synthesis, given their ease of synthesis, purification, and stability compared with their acid precursors. Moreover, **1** can be functionalized, in parallel, by the use of a simple S_N2 reaction with S- and N-nucleophiles, which can lead to a variety of analogs **3**. By introducing a high degree of diversity on the ArBPin coupling partner at an early stage,[9a,10] not only is the scope of the synthetic process increased and the range of biphenyls **5** to be synthesized widened, but also the ArBPin compounds may have interesting structural properties in their own right or applications such as enzyme inhibitors or in molecular recognition (Scheme 1).[8,11]

Our previously published preliminary attempted SM coupling reactions on a few analogs **3** were unsuccessful, yielding protodeboronated species,[9a] although we have recently found that the use of MAOS (microwave assisted organic synthesis) can lead to biaryl compounds,[12d] notably employing literature conditions.[12] The aim of the current study was to extend the synthetic scope of the S_N2 reaction leading to a library of ArBPin using a variety of N-, S-, and O-nucleophiles and to investigate SM couplings to afford biphenyl products.

RESULTS AND DISCUSSION

The S_N2 reaction of the pinacol ester **1**{*1*} with a piperazine derivative **2**{*1*} was initially investigated with a view to reducing the reaction time to minutes for it to be amenable to parallel synthesis: previously, **1**{*1*} was found to react at room temperature overnight with S-nucleophiles or at reflux for several hours with N-nucleophiles.[9a] For this to be feasible, we attempted microwave-mediated reactions, and using a rapid screen, the best results were obtained when a supported base was employed as base (PS-NMM) as opposed to potassium carbonate or excess nucleophile. When required, supported scavengers, PS-trisamine and PS-isocyanate, were used to remove unreacted bromide or amine, respectively, and in general, yields of product

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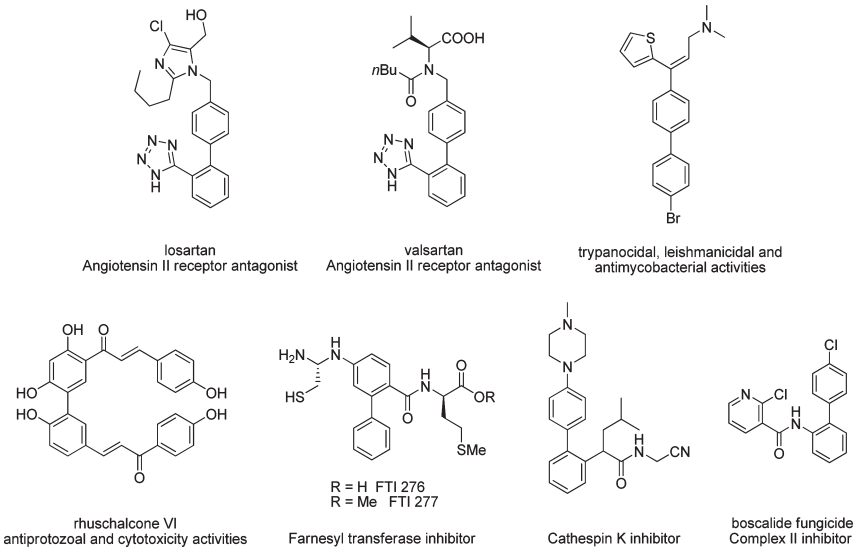
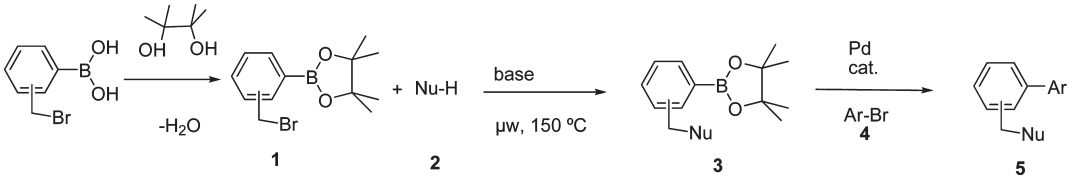


Figure 1. Examples of important biologically active biphenyls.

Scheme 1. Boronate and Biaryl Synthesis



were good to excellent (Table 1, Figure 2). In one case, we were able to react a protected valine analogue (Table 1, entry 15) to yield a precursor to valsartan (vide supra). The reaction of other primary amines, including benzylamine as well as tautomerizable heterocycles such as imidazoles, often led to a mixture of products, presumed to result from mono- or disubstitution reactions, and these were not investigated further in the present study.

Next, we focused our attention to thiols as nucleophiles. Hence, heteroaromatic thiols, such as 2-mercaptopyrimidine, afforded the thioether derivatives **3**{*2,8*} and **3**{*3,8*} in excellent yields using the standard conditions, although in some cases, reaction times were slightly longer; cooled reaction mixtures were assessed by TLC after 15 or 30 min reaction time, and if incomplete, the reaction was extended an additional 15−30 min (see Table 1). Aliphatic thiols were found to be unreactive when employing a supported base; however, when treated with sodium hydride prior to the microwave mediated reaction, an excellent yield of thioether **3**{*2,13*} was recorded (Figure 3). Sodium thiomethoxide proved to be an effective nucleophile in the synthesis of **3**{*1,12*} and **3**{*3,12*}.

The use of modified literature conditions enabled us to synthesize ether containing boronates.[13] Sodium hydride was effective as base, although a combination of potassium carbonate, sodium hydroxide, and tetrabutylammonium bromide gave moderate to good yields; for example, **3**{*3,16*} and **3**{*3,14*}. Limited success was achieved with an aliphatic alcohol as nucleophile **3**{*3,17*}.

To investigate the structures of the arylboronates in the solid state, X-ray structure determinations on compounds **1**{*2*}, **3**{*2,10*}, **3**{*3,8*}, **3**{*1,6*}, and **3**{*3,3*} were carried out and are shown in Figure 4 and in Figure S1 in the Supporting Information.

The geometry of the arylboronate rings in all five molecules is very similar (Table S2 of the Supporting Information). The rings are twisted in every case, with the angle between the least-squares planes drawn through atoms B1, O2, and O3 and those drawn through atoms O2, C3 and C4 ranging from 21.4° to 24.5° (Table S2). In three out of five cases, **1**{*2*}, **3**{*2,10*}, and **3**{*3,3*}, the least-squares plane drawn through atoms B1, O2, O3, and C10 is almost parallel to the plane of the phenyl ring C10−C15, with the angle between the least-squares planes ranging from 4.2° to 5.0° (Table S2). This angle is larger in structures **3**{*1,6*} and **3**{*3,8*}: 21.3° and 16.3°, respectively.

Structure **3**{*1,6*} has two substituents of the phenyl ring that are in ortho positions, and it is thought that the steric hindrance caused by this configuration is the reason for the twisting of the plane of the phenyl ring away from the B1, O2, O3, C10 plane. Structure **3**{*3,8*} is the only one of the five structures in which a $\pi-\pi$ stacking interaction is formed, with the distance between the least-squares planes drawn through the two pyrimidine rings (C18, C20−C22, N19, N23) involved being 3.6 Å (see Figure S1, Supporting Information).

SUZUKI COUPLINGS

Selected members of the arylboronate library were subjected to SM couplings under microwave conditions. Good to excellent yields were obtained for the coupling of *meta*-and *para*-ArBPin derivatives. Excellent yields were observed for aryl halide coupling

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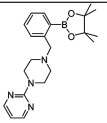
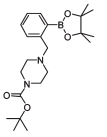
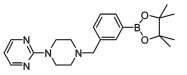
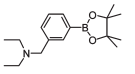
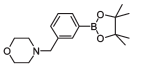
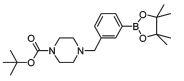
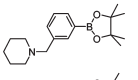
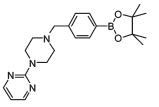
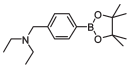
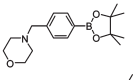
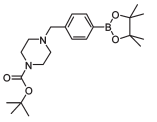
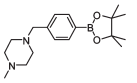
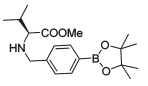
Table 1. Amine-Substituted Arylboronates

Entry	NuH **2**	Time (min)	Product **3**	IsolatedYield (%)
1	*{1}*	15		100
2	*{2}*	15		63
3	*{3}*	15		100
4	*{6}*	15		100
5	*{1}*	15		100
6	*{2}*	15		100
7	*{3}*	15		98
8	*{6}*	15		75
9	*{4}*	30		100
10	*{1}*	30		93
11	*{2}*	15		100
12	*{3}*	40		99
13	*{6}*	45		95
14	*{5}*	35		100
15[b]	*{7}*	120		72

[a] Microwave, PS- NMM base. [b] Two equivalents of (L)-Val(OMe), 140 °C.

partners substituted with electron-withdrawing groups (e.g. **5**{*2,3,4*}), as opposed to moderate yields for aryl halides substituted with electron-rich groups (e.g. 37% yield obtained for **5**{*2,4,5*}). Tetrakis(triphenylphosphine)palladium(0) is a very efficient precatalyst for the SM cross-coupling process[8] and was effective in the presence of sodium carbonate as base, a toluene/ethanol/water solvent system, under microwave conditions[9b] to afford, for example, **5**{*3,1,14*} in good yields (Figure 5).

These coupling conditions do not appear to be appropriate for either S- or ortho-substituted arylboronic acid pinacol ester coupling partners. In these two cases, protodeborylation products, starting materials, or both were observed. An O-substituted compound gave a moderate yield of 38% of the expected biphenyl **5**{*3,14,3*}.

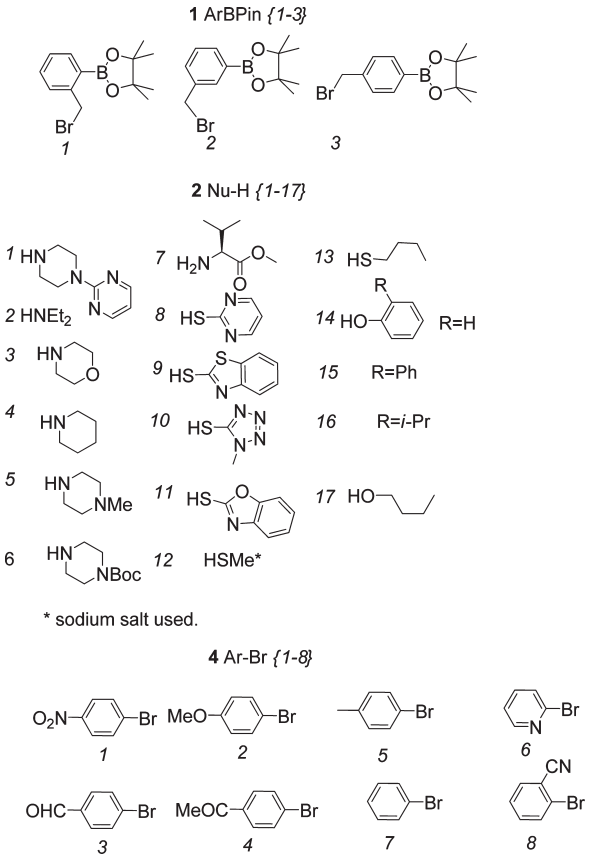


Figure 2. Building blocks used.

Finally, we investigated the coupling reaction in the synthesis of a precursor to valsartan, an antihypertensive.[14,15] The known compound **7**{*3,7,1*},[14d] synthesized from **3**{*3,7*}, was coupled with both bromobenzene and 2-bromobenzonitrile in acceptable yields (Scheme 2). The biphenyl derivative **8**{*3,7,1,8*} is a known intermediate in the synthesis of valsartan.[14e,15] The ^{1}H NMR spectra of the compounds showed the presence of rotamers as noted in other publications; for **7**{*3,7,1*}, increasing the temperature (and changing the solvent to DMSO-d_6) led to coalescence (see Experimental Procedures).

A previous synthesis of **8**{*3,7,1,8*} employed a reductive amination of 2-cyano-4′-formylbiphenyl (formed from a decarboxylative coupling in 80% yield) with a protected valine derivative followed by treatment with valeroyl chloride, in an overall yield of around 70%.[14e] Analog **7**{*3,7,1*} has been shown to undergo direct SM couplings with phenyltetrazole halides under thermal conditions. Our attempts using protected and unprotected phenyltetrazole chlorides or bromides under microwave conditions gave unsatisfactory yields.

Current studies are aimed at expanding the scope of the SM coupling reaction involving the arylboronate library as coupling partners, especially in regard to the use of thioether or ortho-substituted ArBPin, and will be reported in due course.

CONCLUSION

A library of N- and S-substituted arylboronates can be synthesized using MAOS coupled with supported reagents to ease workup.

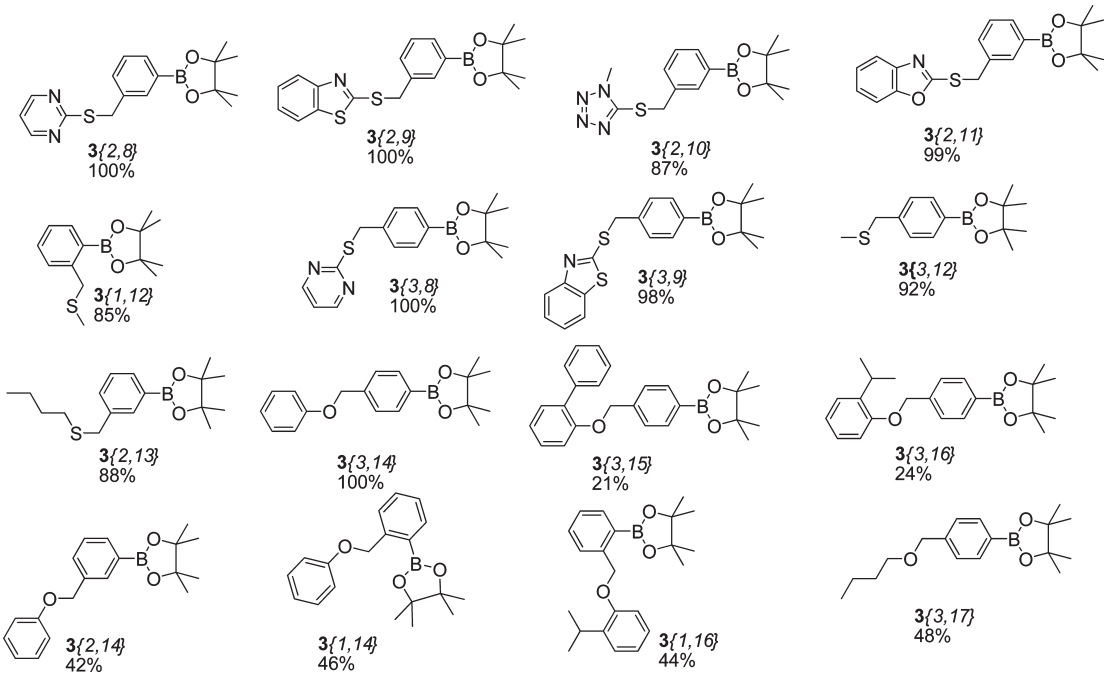


Figure 3. *S*- and *O*-boronate library.

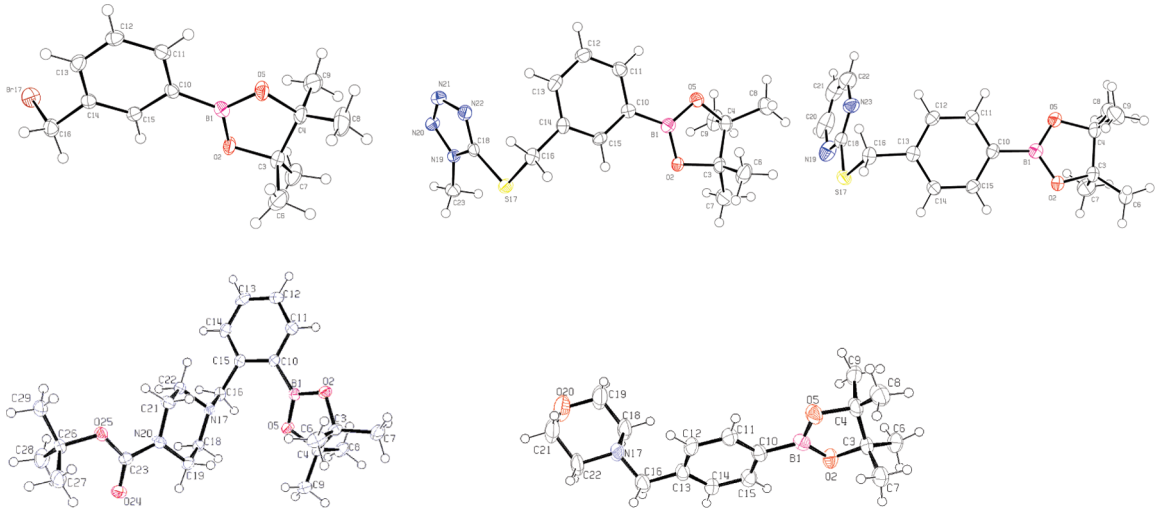


Figure 4. Solid state structure of ArBPin analogs.

O-substituted analogues were formed under solventless conditions. SM coupling reactions of the arylboronates with aryl halides led to a library of biphenyls.

EXPERIMENTAL PROCEDURES

All reactions were carried out in air, and commercial grade solvents and materials were used except where specified. Supported reagents PS-NMM, -trisamine, and -isocyanate were purchased from Biotage or Novabiochem. NMR spectra were measured on a Jeol EX270 spectrometer at 270 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$. Microwave reactions were performed in a CEM Discover unit. Elemental analyses were performed on a CE Instruments apparatus. Chromatographic purification was carried out on an ISCO purification unit using Redisep silica gel columns. Purities of compounds were assessed by inspection of their NMR spectra, and a large number of solid compounds were analyzed by combustion analysis. General procedures are given below, and analytical data for compounds can be found in the Supporting Information.

General Procedure for the Synthesis of 3 . *2-(4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazin-1-yl) Pyrimidine, 3{1,1}.* Compound **1**{*1*} (0.5 mmol, 149 mg), 1-(2-pyrimidyl)piperazine **2**{*1*} (0.7 mmol, 0.1 mL), PS-NMM (0.75 mmol, 2.28 mmol g^{-1}, 329 mg), and THF (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 20 min. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under

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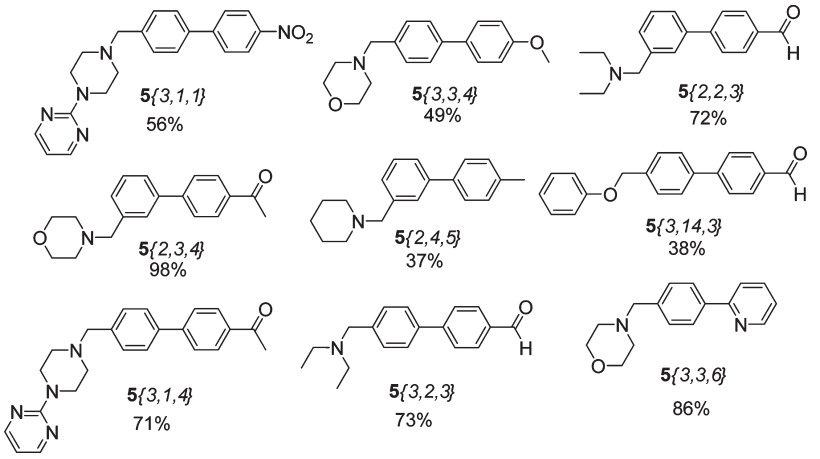
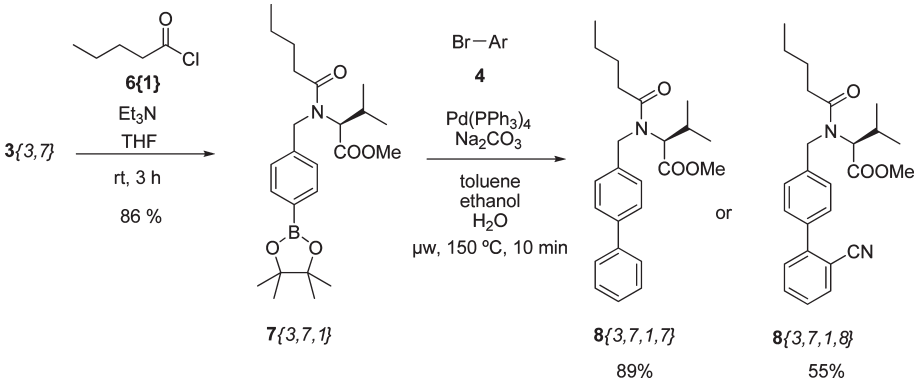


Figure 5. Biphenyls synthesized.

Scheme 2. Synthesis of a Precursor to Valsartan



reduced pressure to afford 229 mg of a yellow oil, which contained unreacted **2**{*1*}, observed by TLC and ^{1}H NMR analysis. The oil was treated with PS-trisamine (0.1 mmol, 3.34 mmol g^{-1}, 30 mg) and PS-isocyanate (0.2 mmol, 1.58 mmol g^{-1}, 127 mg) in THF under microwave irradiation at 150 °C for 5 min, cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure to give 210 mg of the expected product as a beige solid in 100% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22 (d, 2H, J = 4.8 Hz), 7.65 (d, 1H, J = 7.3 Hz), 7.20−7.35 (m, 3H), 6.40 (dd, 1H, J = 4.8 Hz), 3.68 (m, 6H), 2.42 (m, 4H), 1.28 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.7 (2C), 135.1, 130.9, 130.0, 129.3, 128.8, 126.5, 125.5, 109.7, 83.4 (2C), 62.1, 52.8 (2C), 43.5 (2C), 25.1 (4C). HRMS-ES (m/z) found, 381.2462; calcd for $[C_{21}H_{29}O_2N_4B + H]^+$, 381.2456. Elemental analysis CHN (%) found: C, 66.0, H, 7.7, N, 14.3. Calcd for $C_{21}H_{29}O_2N_4B$: C, 66.3; H, 7.7; N, 14.7.

(S)-Methyl-3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylamino) Butanoate 3{3,7}. [Note: Stench for thiols and thiomethoxides.] Compound **1**{3} (0.89 mmol, 264 mg), L-valine methyl ester (1.79 mmol, 234 mg), PS-NMM (1 mmol, 250 mg), and THF (3 mL) were mixed in a microwave vial and stirred under microwave irradiation at 130 °C for 2 h. The mixture was cooled to room temperature, filtered, and concentrated to give 417 mg of a yellow oil, which was purified by chromatography on silica gel, hexane/EtOAc from 0% to 20% of EtOAc, to give 222 mg of the expected product as a pale yellow oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.76 (d, 2H, J = 7.7 Hz), 7.35 (d, 2H, J = 8.1 Hz), 3.86 (d, 1H, J = 13.2 Hz), 3.72 (s, 3H), 3.58 (d, 1H, J = 13.2 Hz), 2.99 (d, 1H, J = 6.2 Hz), 1.90 (sex, 1H, J = 7.0 Hz), 1.80 (m, 1H, NH), 1.34 (s, 12H), 0.93 (2d, 6H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.8, 143.3, 134.8 (3C), 127.6 (2C), 83.7 (2C), 66.4, 52.5, 51.4, 31.7, 24.8 (4C), 19.3, 18.6. HRMS-ES (m/z) found, 347.2378; calcd for $[C_{19}H_{30}O_4NB + H]^+$, 347.2377.

4,4,5,5-Tetramethyl-2-(2-(methylthiomethyl)phenyl)-1,3,2-dioxaborolane 3{1,12}. Compound **1**{*1*} (1 mmol, 297 mg), sodium thiomethoxide (1 mmol, 70 mg), and THF (3 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 20 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 225 mg of the expected product as a pale yellow oil in 85% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 1H, J = 7.3 Hz), 7.34 (dd, 1H, J = 8.4 Hz), 7.18−7.30 (m, 2H), 3.97 (s, 2H), 1.93 (s, 3H), 1.34 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.4, 145.3, 136.1, 130.5, 129.4, 126.1, 83.6 (2C), 37.4, 24.9 (4C), 14.7.

2-(3-(Butylthiomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3{2,13}. n-Butylthiol (1 mmol, 107 μL, 0.842 g mL^{-1}), sodium hydride (1 mmol, 40 mg), and THF (2 mL) were mixed in a microwave vial and stirred at room temperature for

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15 min, then a solution of **1**{*2*} (1 mmol, 297 mg) in THF (2 mL) was added. The mixture was stirred under microwave irradiation at 150 °C for 15 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 270 mg of the expected product as a pale yellow liquid in 88% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H), 7.65 (d, 1H, J = 7.3 Hz), 7.42 (d, 1H, J = 7.7 Hz), 7.30 (dd, 1H, J = 7.3 Hz), 3.69 (s, 2H), 2.39 (t, 2H, J = 7.3 Hz), 1.53 (m, 2H), 1.36 (m, 5H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 137.9, 135.1 (2C), 133.3, 131.7, 127.9, 83.8 (2C), 36.2, 31.3, 31.1, 24.9 (4C), 22.0, 13.6.

General Procedure for O-Nucleophiles. *4,4,5,5-Tetramethyl-2-(2-(phenoxymethyl)phenyl)-1,3,2-dioxaborolane 3{1,14}.* Compound **1**{*1*} (1.00 mmol, 298 mg), phenol (1.03 mmol, 97 mg), sodium hydroxide (1.13 mmol, 45 mg), potassium carbonate (4.00 mmol, 552 mg), and tetrabutylammonium bromide (0.10 mmol, 32 mg) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 110 °C for 5 min. The mixture was cooled to room temperature, diluted with EtOAc and water, extracted with EtOAc, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 269 mg of a brown oil. The crude product was purified by chromatography on silica gel, hexane/EtOAc 9:1, to give 144 mg of the expected product as a yellow oil in 46% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (d, 1H, J = 7.3 Hz), 7.53 (d, 1H, J = 7.7 Hz), 7.44 (dd, 1H, J_1 = 1.5 Hz, J_2 = 7.3 Hz), 7.34−7.23 (m, 3H), 6.97 (d, 2H, J = 8.8 Hz), 6.91 (d, 1H, J = 7.3 Hz), 5.34 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.1, 143.4, 136.4, 135.9, 131.1, 129.3 (2C), 127.4, 127.0, 120.5, 114.8 (2C), 83.7 (2C), 69.4, 24.8 (4C).

2-(4-(Butoxymethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3{3,17}. *n*-Butanol (1 mmol, 91 μL, 0.811 g.mL^{-1}), sodium hydride (2 mmol, 80 mg), and THF (3 mL) were mixed in a microwave vial and stirred at room temperature for 15 min, then **1**{*3*} (1 mmol, 297 mg) was added, and the mixture was stirred under microwave irradiation at 150 °C for 15 min. THF was removed under reduced pressure. The product was diluted in water and CH_2Cl_2, extracted by CH_2Cl_2, washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 247 mg of a colorless oil. The product was purified by chromatography on silica gel, CH_2Cl_2, to give 139 mg of the expected product as a colorless oil in 48% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.50 (s, 2H), 3.43 (t, 2H, J = 6.6 Hz), 1.60 (m, 2H), 1.35 (m, 2H), 1.32 (s, 12H), 0.89 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 142.0, 134.8 (3C), 126.7 (2C), 83.7 (2C), 72.7, 70.2, 31.8, 24.9 (4C), 19.4, 13.9.

General Procedure for $Pd(OAc)_2$ Mediated SM Couplings. *2-(4-((4′-Nitrobiphenyl-4-yl)methyl)piperazin-1-yl)pyrimidine 5{3,1,1}.* 2-[4-(1-(4-(2-Pyrimidyl)piperazine)methyl)phenyl]-4,4,5,5-tetramethyl-1,3-dioxaborolane **3**{*1,1*} (0.5 mmol, 190 mg), 1-bromo-4-nitrobenzene **4**{*1*} (0.5 mmol, 101 mg), palladium-(II) acetate (0.005 mmol, 1 mg), sodium carbonate (1 mmol, 106 mg), tetrabutylammonium bromide (0.5 mmol, 161 mg), and water (2 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 10 min. The mixture was cooled and diluted with EtOAc and water. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give 105 mg of the expected product as a brown solid in 56% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (2d, 4H), 7.73 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 6.46 (dd, 1H, J = 4.8 Hz), 3.83 (m, 4H), 3.59 (s, 2H), 2.52 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 161.7, 157.7 (2C), 147.4, 147.0, 139.2 (2C), 129.8 (2C), 127.6 (2C), 127.3 (2C), 124.1 (2C), 109.8, 62.6, 53.0 (2C), 43.6 (2C). HRMS-ES (m/z) found, 376.1770; calcd for $[C_{21}H_{21}O_2N_5 + H]^+$, 376.1768. Elemental analysis CH (%) found: C, 65.2; H, 5.7. Calcd for $C_{21}H_{21}O_2N_5 \cdot 0.17CH_2Cl_2$: C, 65.2; H, 5.5.

General Procedure for $Pd(PPh_3)_4$-Mediated SM Couplings. *1-[4′-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-biphenyl-4-yl]-ethanone 5{3,1,4}.* 2-{4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-piperazin-1-yl}-pyrimidine **3**{*3,1*} (0.3 mmol, 115 mg), 4-bromobenzophenone (0.35 mmol, 70 mg), tetrakis-(triphenylphosphine)palladium(0) (0.01 mmol, 12 mg), sodium carbonate (0.9 mmol, 95 mg), toluene (1 mL), ethanol (1 mL), and water (1 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 10 min then cooled to room temperature, diluted with EtOAc and water, and extracted with EtOAc. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a crude product, which was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 1:1, to give 79 mg of the expected product as a white solid in 71% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.31 (d, 2H, J = 4.8 Hz), 8.04 (d, 2H, J = 8.8 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.61 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.4 Hz), 6.48 (dd, 1H, J = 4.8 Hz), 3.85 (m, 4H), 3.61 (s, 2H), 2.65 (s, 3H), 2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 197.7, 161.7, 157.7 (2C), 145.5, 138.8, 138.2, 135.8, 129.8 (2C), 128.9 (2C), 127.2 (2C), 127.1 (2C), 109.8, 62.7, 53.0 (2C), 43.7 (2C), 26.6. HRMS-ES (m/z) found, 373.2023; calcd for $[C_{23}H_{24}ON_4 + H]^+$, 373.2023. Elemental analysis CHN (%) found: C, 73.6; H, 6.4; N, 14.2. Calcd for $C_{23}H_{24}O_1N_4 \cdot 0.34$EtOAc: C, 73.6; H, 6.7; N, 14.3.

(S)-Methyl-3-methyl-2-(N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-l)benzyl) Pentanamido)butanoate 7{3,7,1}. Compound **3**{*3,7*} (2.06 mmol, 714 mg), valeroyl chloride (4.12 mmol, 0.995 g mL^{-1}, 0.50 mL), triethylamine (2.10 mmol, 0.726 g mL^{-1}, 0.31 mL), and THF (10 mL) were mixed and stirred at room temperature for 3 h. THF was removed, and the mixture was diluted with EtOAc, washed with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 1.006 g of a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc from 0 to 20% of EtOAc to give 763 mg of the expected product as a yellow oil in 86% yield. ^{1}H NMR mixture of rotamers ($CDCl_3$) δ (ppm): 7.76 and 7.69 (2d, 2H, J = 8.1 Hz), 7.17 and 7.14 (2d, 2H, J = 8.1 Hz), 5.00 and 4.91 (2d, 1H, J_{d1} = 10.4 Hz, J_{d2} = 15.3 Hz), 4.63 (s, 1.5H), 4.32 (d, 0.25H, J = 15.4 Hz), 4.03 (d, 0.25H, J = 10.6), 3.44 and 3.37 (2s, 3H), 2.65−2.11 (m, 3H), 1.79−1.53 (m, 2H), 1.49−1.17 (m + s, 14H), 0.96 (d, 3H, J = 6.2 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.84 (t, 3H, J = 7.3 Hz). ^{13}C NMR mixture of rotamers ($CDCl_3$) δ (ppm): 174.7, 174.1, 171.0, 170.3, 141.3, 140.5, 135.1, 134.6 (2C), 126.8, 125.0 (2C), 83.8 (2C), 66.0, 61.6, 51.7, 51.6, 48.3, 45.8, 33.3, 27.8, 27.6, 27.4, 24.8 (4C), 22.4, 19.8, 18.7, 13.8. HRMS-ES (m/z) found, 431.2947; calcd for $[C_{24}H_{38}O_5N^{10}B + H]^+$, 431.2952.

Coalescence was observed at higher temperature ^{1}H NMR (DMSO-d_6, 400 MHz, 373 K) δ (ppm): 7.63 (d, 2H, J = 7.4 Hz),

7.19 (d, 2H, J = 7.5 Hz), 4.69 (m, 1H), 4.60−4.30 (m, 2H), 3.44 (s, 3H), 2.45−2.15 (m, 3H), 1.60−1.40 (m, 2H), 1.31 (s, 12H), 1.40−1.20 (m, 2H), 0.94 (d, 3H, J = 6.5 Hz), 0.89 (t, 3H, J = 7.4 Hz), 0.82 (d, 3H, J = 6.9 Hz).

(S)-Methyl-2-(N-(biphenyl-4-ylmethyl)pentanamido)-3-methylbutanoate 8{3,7,1,7}. Compound 7{3,7,1} (0.37 mmol, 160 mg), bromobenzene (0.44 mmol, 1.491 g mL^{-1}, 46 μL), sodium carbonate (1.11 mmol, 118 mg), tetrakis(triphenylphosphine)-palladium(0) (0.01 mmol, 12 mg), toluene (1 mL), EtOH (1 mL), and water (0.5 mL) were mixed in a microwave vial and stirred under microwave irradiation at 150 °C for 10 min. The mixture was cooled to room temperature, diluted with EtOAc and water, and extracted three times with EtOAc. The separated organic layer was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica gel, hexane/EtOAc 8:2, to give 126 mg of the expected product as a pale yellow oil in 89% yield. ^{1}H NMR mixture of rotamers ($CDCl_3$) δ (ppm): 7.61−7.52 (m, 3H), 7.52−7.30 (m, 4H), 7.30−7.18 (m, 2H), 4.97 (2d, 1H, J = 10.3 Hz), 4.66 (s, 1.3H), 4.29 (d, 0.3H, J = 15.3 Hz), 4.05 (d, 0.3H, J = 10.9 Hz), 3.45 and 3.36 (2s, 3H), 2.67−2.20 (m, 3H), 1.82−1.54 (m, 2H), 1.50−1.20 (m, 2H), 0.99 (d, 3H, J = 6.5 Hz), 0.95−0.80 (d + t, 6H, J_d = 7.0 Hz, J_t = 7.3 Hz). ^{13}C NMR mixture of rotamers ($CDCl_3$) δ (ppm): 174.6, 171.2, 140.5, 140.2, 136.4, 128.8, 128.7, 128.1, 127.4, 127.3, 127.0 (2C), 126.8, 126.4, 65.9, 61.8, 51.6, 48.2, 45.4, 33.4, 27.9, 27.4, 22.5, 19.9, 18.8, 13.8. HRMS-ES (m/z) found, 382.2375; calcd for $[C_{24}H_{31}O_3N_1 + H]^+$, 382.2377.

■ ASSOCIATED CONTENT

Supporting Information. Analytical data (^{1}H, ^{13}C spectra, MS, elemental analysis) for compounds are provided, as well as X-ray crystallography experimental details for **1**{*2*}, **3**{*1,6*}, **3**{*2,10*}, **3**{*3,3*}, and **3**{*3,8*}.This material is available free of charge via the Internet at http://pubs.acs.org.

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Synthesis of a (piperazin-1-ylmethyl)biaryl library via microwave-mediated Suzuki–Miyaura cross-couplings

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ABSTRACT

Boc-protected (piperazin-1-ylmethyl)biaryls have been synthesised from (Boc-piperazin-1-ylmethyl) phenylboronic acid pinacol esters via a microwave-mediated Suzuki–Miyaura coupling with aryl bromides viz. 1-bromo-, 2-, 3- or 4-nitrobenzene or 2-bromo-5-nitropyridine. Judicial removal of the protecting group on the piperazine, or facile reduction of the nitro group on the biaryl system enabled the manipulation of two points of functionality in order to diversify the scope of the resulting biaryl library.

The biaryl unit is found in many natural and synthetic products and as a privileged scaffold in medicinal chemistry. Undoubtedly, the most important and efficient strategy for its construction is the palladium-catalyzed Suzuki–Miyaura (SM) coupling reaction.[1]

The incorporation of a piperazine motif into a molecule is interesting from a medicinal chemistry point of view since it produces analogues that have a lower lipophilicity and enhances aqueous solubility.[2] Hence, piperazine units are found in many drugs with a broad scope of actions such as antidepressants,[3] antihistamines,[4] antiretrovirals,[5] anti-Parkinson's,[6] antianginals[7] and antipsychotics[8] amongst others (Fig. 1).[9–11]

Recently, we reported the synthesis of an arylboronate library using microwave-mediated S_N2 reactions of (bromomethyl)phenylboronic acid pinacol esters with a range of *N*-, *S*- and *O*-nucleophiles.[12] These were further reacted to afford a library of biaryls. In certain instances, Boc-piperazine was used as an *N*-nucleophile and the arylboronic esters obtained were found to be interesting because the protecting group on the piperazine could be easily removed to liberate an amine, allowing further functionalisation prior to, or following, a Suzuki–Miyaura cross-coupling with various aryl halides.

Herein, we describe the use of protected *m*- or *p*-substituted (piperazin-1-ylmethyl)phenylboronic acid pinacol esters **1** as useful synthons for the synthesis of a wide range of biaryls. As a starting point, we have repeated or elaborated upon our previous findings, in order to increase the scope of the SM coupling reaction

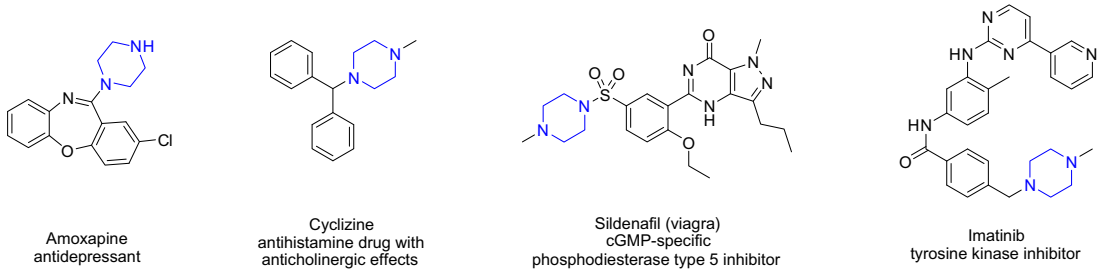

Figure 1. Examples of drugs containing the piperazine motif (in blue).

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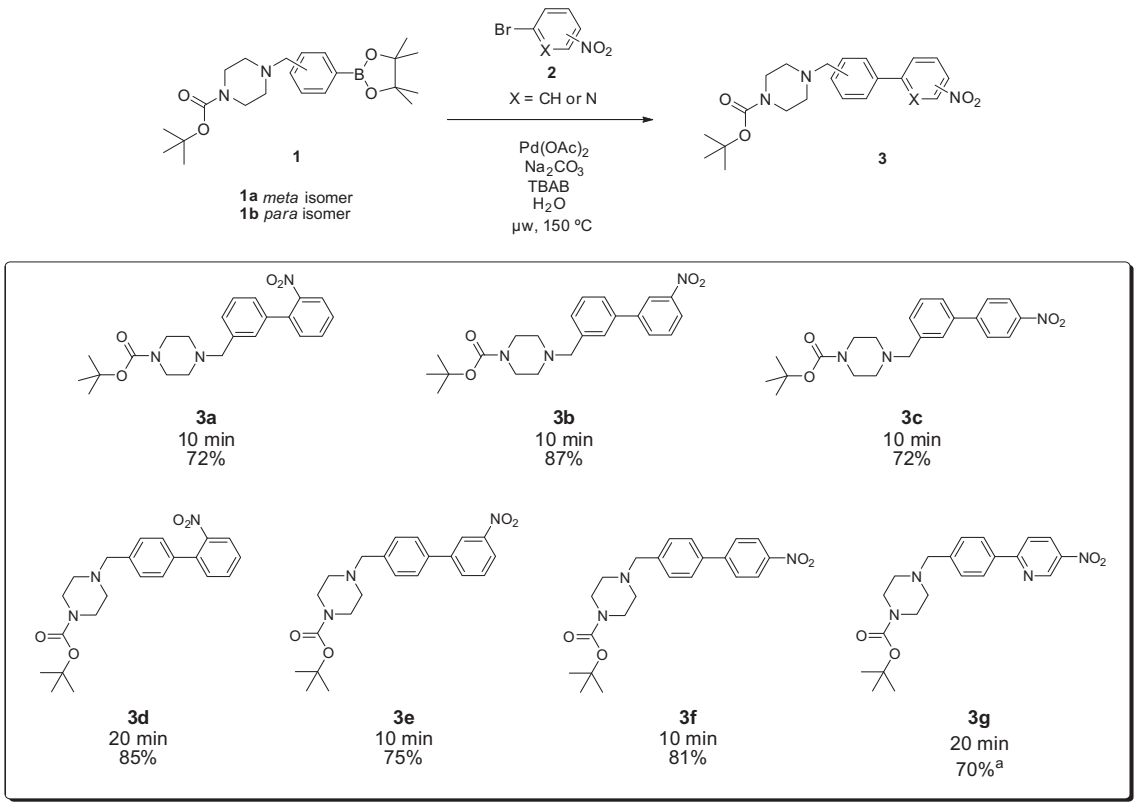
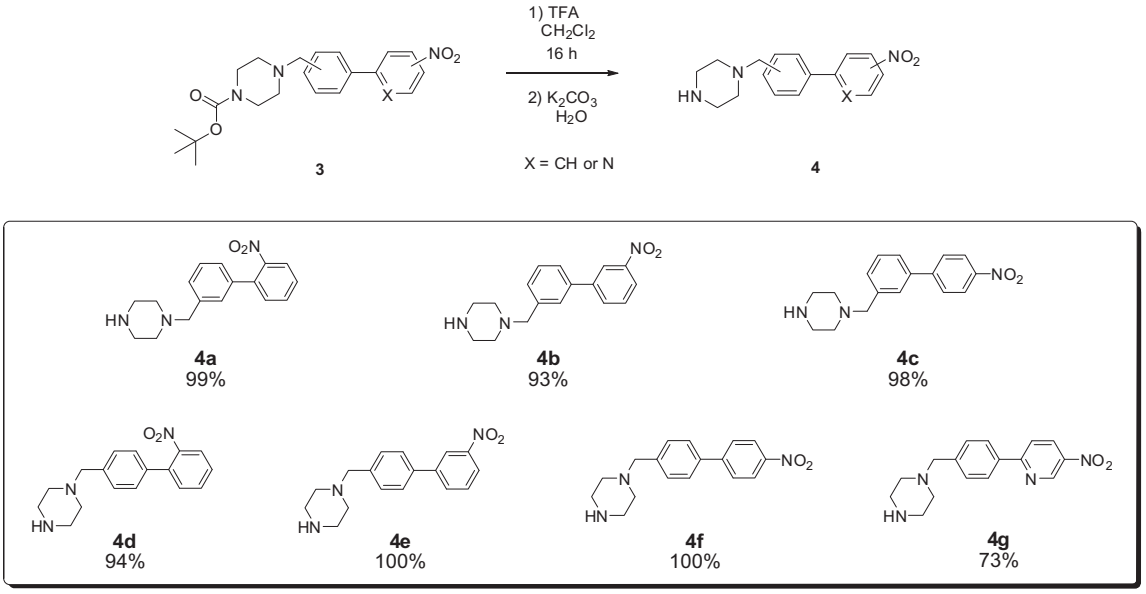


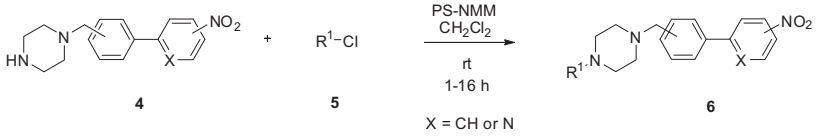
Scheme 1. SM reactions on compounds **1**. Reaction yields given after purification by chromatography. Reaction times given in minutes (min). [a]$Pd(PPh_3)_4$ used as precatalyst (3 mol %), Na_2CO_3 (3 equiv) in toluene/EtOH/H_2O (1:1:1), 150 °C, microwave irradiation (maximum power 300 W).

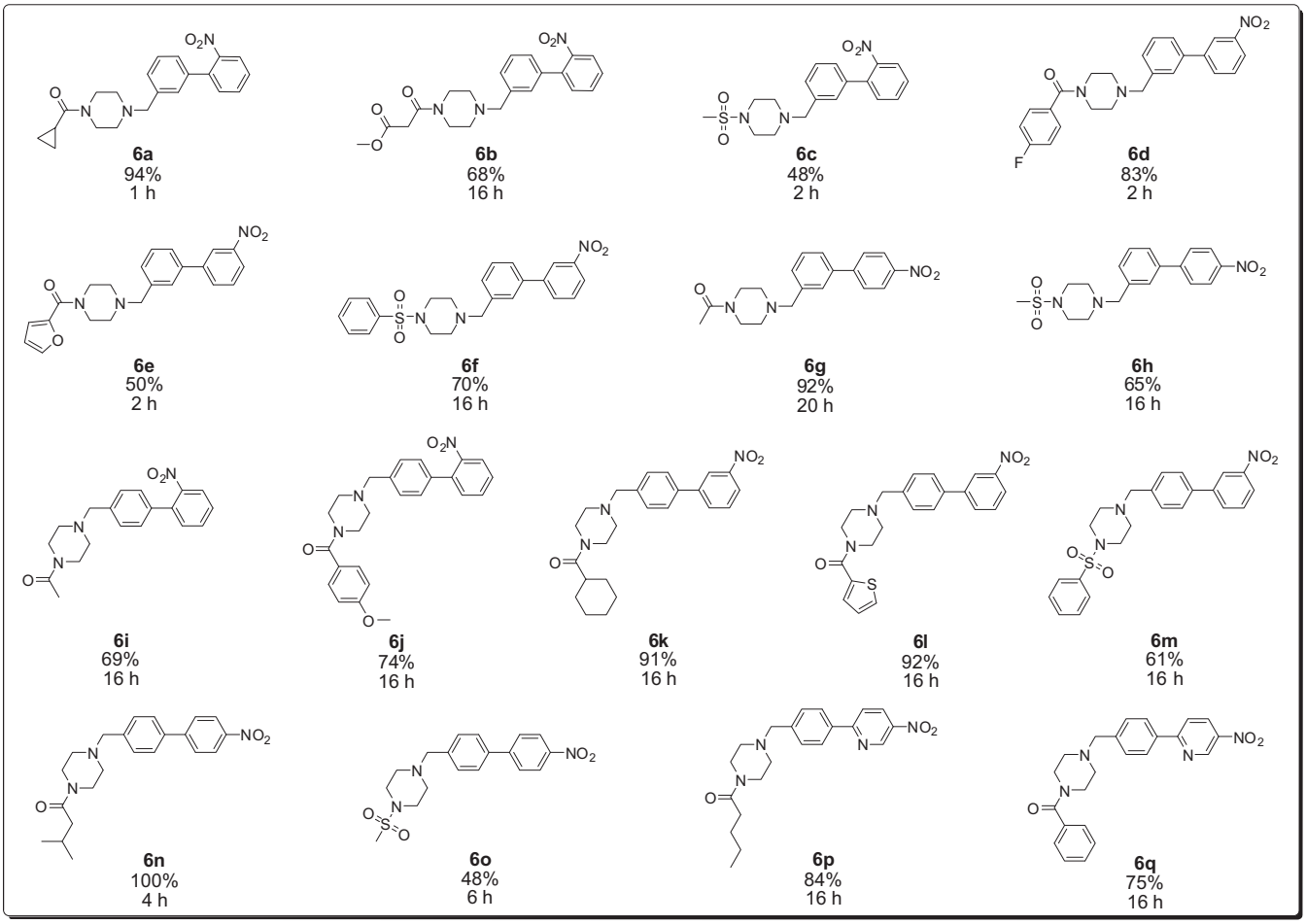


Scheme 2. Cleavage of the Boc group in **3**. Crude reaction yields given as the products were used without further purification.

of **1**. The isomeric 2-methylphenylboronic acid pinacol esters were previously shown to deprotodeborylate in SM reactions and so were not selected.[13] We also found that *N*-substituted 3- and 4-methylphenylboronic acid pinacol esters could react with different aryl bromides in a Suzuki–Miyaura cross-coupling using microwave-assisted organic synthesis (MAOS) to afford the corresponding biphenyl compounds. 2-, 3- and 4-bromo-nitrobenzenes and 2-bromo-5-nitropyridine **2** were used as aryl halides partly due to their facile coupling in the SM process, but also because the nitro groups can be reduced at a later stage to anilines, which can be functionalised leading to diversity in the final library.

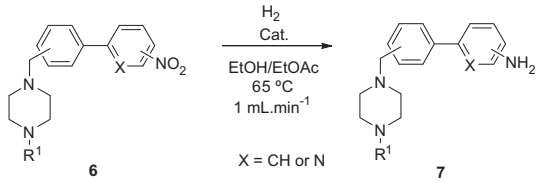
The SM coupling was achieved employing Leadbeater's conditions[14] with palladium(II) acetate as the precatalyst and **2** as aryl bromides under microwave irradiation (μw) on compounds **1a** and **1b**. The expected biphenyls were obtained in good yields, within 10–20 min (Scheme 1).

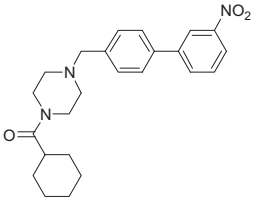
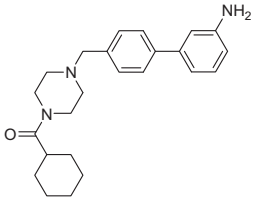




Scheme 3. Functionalisation of compounds **4** to afford **6**. Reaction yields given after purification by chromatography. Reaction times given in hours (h).

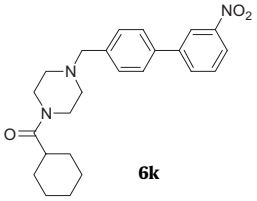
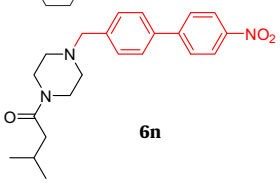
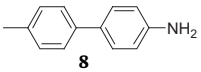
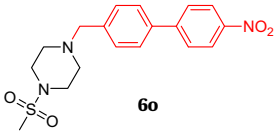
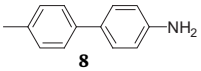
Table 1
Optimisation of the nitro group reduction of **6**



Entry	**6**	Conditions	Product	Yield (%)
1	 **6k**	Raney Ni/H_2	 **7a**	94

(*continued on next page*)

Table 1 (*continued*)

Entry	6	Conditions	Product	Yield (%)
2	 **6k**	$SnCl_2 \cdot 2H_2O$	**7a**	67[a]
3	 **6n**	$Pd/C/H_2$	 **8**	97
4	 **6o**	$Pd/C/H_2$	 **8**	94

[a] Microwave irradiation (maximum power 300 W), EtOH, 130 °C, 30 min.

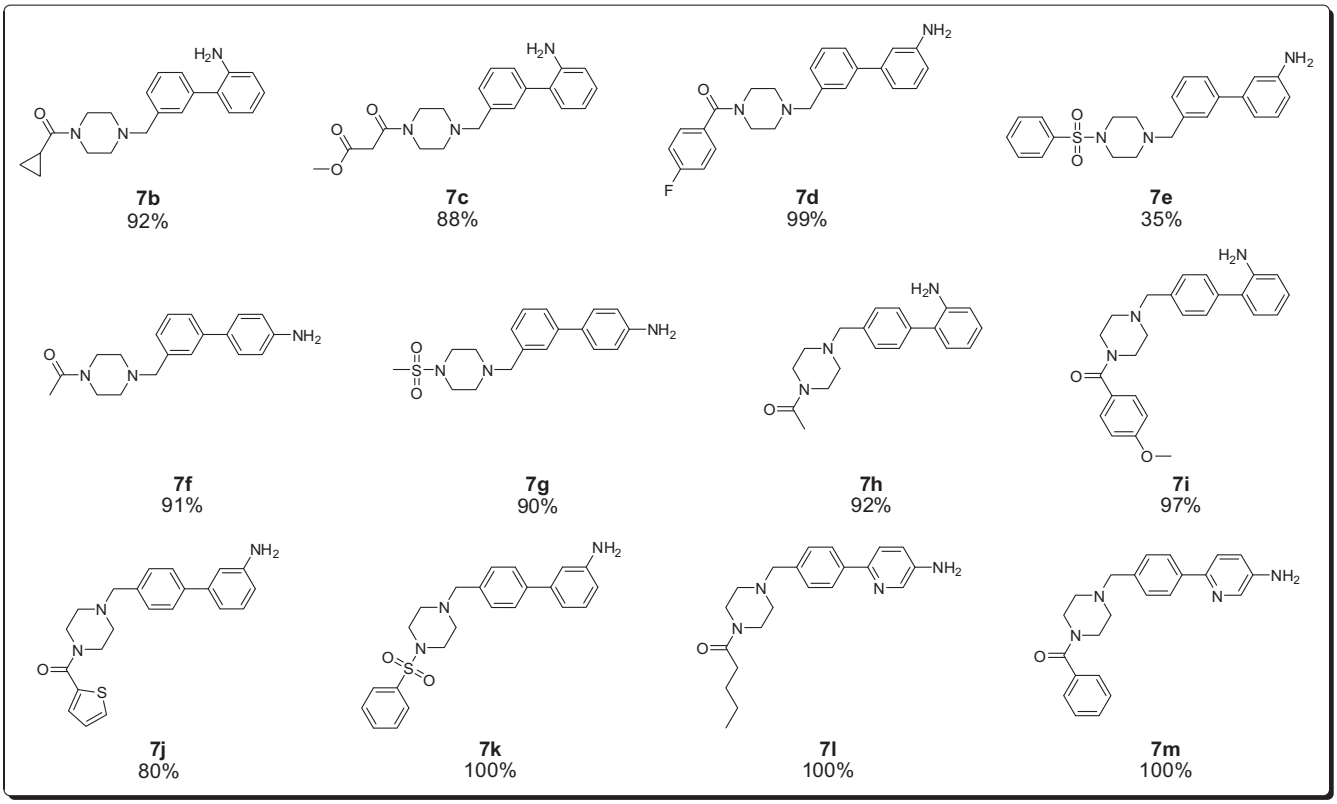
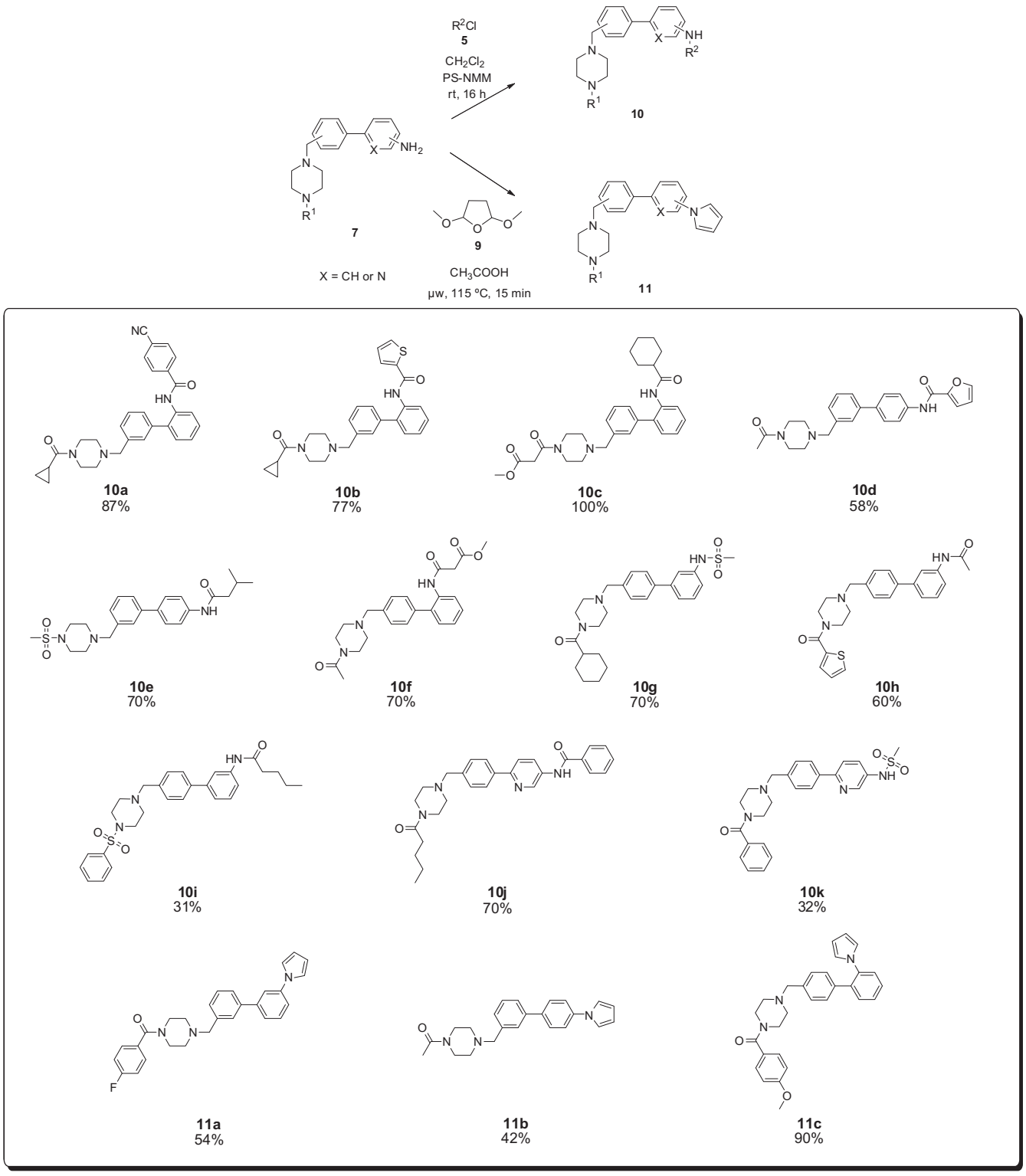


Figure 2. Amines **7** synthesised using Raney Nickel/H-Cube conditions. Crude reaction yield given as the products were used without further purification.

Once the biphenyl unit had been synthesised, the functionalisation reactions could be initiated. Boc group cleavage was achieved with trifluoroacetic acid (TFA) in dichloromethane at room temperature within 2 h or overnight, followed by a basic work-up to liberate the free amine (Scheme 2).[15]

Compounds **4** were functionalised by reaction with acid or sulfonyl chlorides **5** in dichloromethane at room temperature in the presence of a supported base (PS-NMM: polystyrene *N*-methylmorpholine) (Scheme 3).[16] The amidation reaction gave the expected products in good yields (e.g., **6a** in 94% yield) while the sulfonylation process afforded the corresponding products in moderate yields (e.g., **6c** in 48% yield). Most reactions with acid chlorides worked very well in a few hours (e.g., **6a** in 94% yield in 1 h, **6d** in 83% yield in 2 h and **6n** in 100% yield in 4 h), whereas some required an overnight reaction to give the expected products in moderate yields (e.g., **6i** in 69% yield and **6m** in 61% yield).

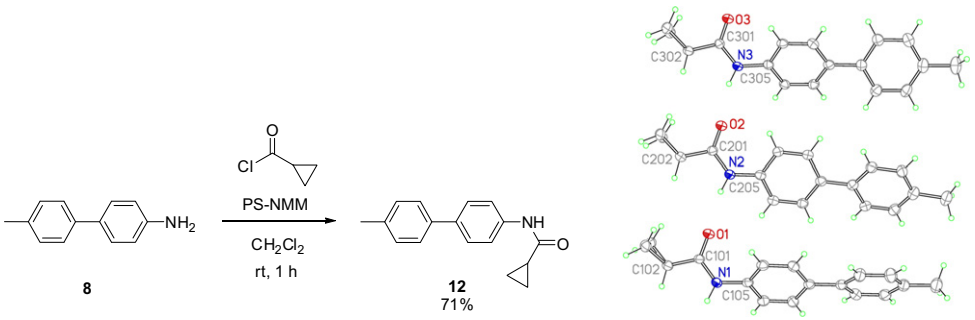
We next intended to reduce the nitro group in compounds **6** in order to produce amines for further functionalisation reactions. Nitro group reduction can be performed by thermal, microwave or flow chemistry (H-Cube)[17] routes. We found the latter to be



Scheme 4. Amine functionalisation reactions of compounds **7**. Reaction yields given after purification by chromatography.

the most straightforward option since it generally obviated a purification or work-up step. The attempted reduction of nitro-biphenyl derivatives was mainly investigated in an H-Cube, in ethanol/ethyl acetate (1:1), at 65 °C, with a flow rate of 1 mL min^{-1} and in full hydrogen mode, as outlined in Table 1.

When Raney Nickel was used as the catalyst, the expected product **7a** was obtained in very good yield (Table 1, entry 1). A microwave-mediated nitro reduction was attempted using tin chloride dihydrate (entry 2), but gave an inferior yield and a more complicated work-up, compared with the former reduction. However, unexpected hydrogenolysis of the benzylic-like unit in **6n** and **6o** led to the corresponding 4-tolylaniline **8** when Pd/C and H_2 were used (Table 1, entries 3 and 4). This is akin to a standard debenzylation reaction in organic synthesis.[15] Thereafter, the Raney Nickel/



Scheme 5. Amine functionalisation reaction of compound **8** and the asymmetric unit of the crystal structure of **12**. Reaction yield given after purification by chromatography.

H-cube conditions were used to reduce the other (piperazin-1-ylmethyl)nitrobiphenyl derivatives (Fig. 2). Many of the products **7** were obtained in very good yields without any further purification.

The amine group could next be functionalised by amidation and sulfonylation reactions with the corresponding acid or sulfonyl chlorides **5** in the presence of a supported base (PS-NMM). Pyrrole derivatives were synthesised by reaction of **7** with 2,5-dimethoxytetrahydrofuran (**9**) in acetic acid (Scheme 4)[18]

The elaborated biaryl products were obtained in moderate to good yields after purification by chromatography on silica gel. An amide coupling of **8** led to an interesting biphenyl derivative **12** in good yield (Scheme 5). Very small crystals of **12** were grown and analysed by a synchrotron X-ray diffraction crystal structure determination which shows a very interesting structure with a Z' value of 3 (Supplementary data, S19).

In summary, a (piperazin-1-ylmethyl)biaryl library has been synthesised over a few steps using, inter alia, the MAOS-mediated Suzuki-Miyaura coupling reaction. This library is composed of a number of very interesting drug-like molecules. The crystal structure of **12** has stimulated our interest into examining analogues in the solid state and results will be disclosed in due course.

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Supplementary data

Supplementary data (general procedures, analytical data for compounds and crystallography data (CCDC 810173)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.025.

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