Development of New Strategies for the Incorporation of Small Strained Heterocycles.

A thesis submitted in partial fulfillment of the degree of Doctor of Philosophy

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« Seulement ceux qui prendront le risque d'aller trop loin

découvriront jusqu'où on peut aller »

T.S. Elliot

Abstract

The first part of this thesis describes the development of new methods for the introduction of an oxetane and azetidine ring into heterocycles of interest for medicinal chemistry. Small ring heterocycles are of value to medicinal chemists because they have the opportunity to bind to receptor residues whilst contributing relatively little to overall molecular weight.

We have developed a new method for the introduction of an oxetane ring in the C4 position of sydnones and describe their utilization in the development of oxetanyl-substituted pyrazole compounds. In addition, the intramolecular cycloaddition of propargyl ether derivatives allows a small family of spiro-oxetane pyrazoles to be prepared. Finally, the further functionalization of a 3-bromo spiro-oxetane pyrazole can be exploited to provide a range of polycyclic heterocycles.

We have also explored the direct coupling of small ring heterocycles. The synthesis of oxetane and azetidine boronic acids under copper catalysis is first presented. Unfortunately, these substrates were found to be unreactive to Suzuki-Miyaura cross-coupling and conjugate addition to enone derivatives. However, we report the successful preparation of the sodium sulfinate salts of azetidine and oxetane and their introduction in the positions C2 and C3 of indoles. The application of this methodology to the synthesis of analogues of a marketed pharmaceutical is also described.

The second part of this thesis describes the investigation of the scope of a mild cycloaddition of 2-pyrones and potassium alkynyl trifluoroborates in the presence of a Lewis acid.

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Gugu, my little panda, I will miss you and I know you will miss me too. You will need to ask Ben(jina), to replace me for the Bido bido bido. Bababa babanana !!!

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Abbreviations

Å	Angstroms (10^{-10} m)
Ac	Acetyl
Acac	Acetylacetonato
Ad	Adamantyl
Ar	Aryl, Aromatic
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPDS	4,7-diphenyl-1,10-phenanthrolinedisulfonic acid
br	broad
BP	By-Product
BR	Biradical
Bu / ^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
calcd	Calculated
CAN	Ceric Ammonium Nitrate
cat.	Catalytic, catalyst
cat	catechol
CDI	Carbonyldiimidazole
Cod	1,5-Cyclooctadiene
DavePhos	2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
DBH	dibromo-dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	Dichlorobenzene
DCE	Dichloroethane
Δ	chemical shift
DCM	Dichloromethane
DMAc	Dimethylacetamide
DMAD	Dimethylacetylene dicarboxylate
DMAP	4-Dimethylaminopyridine

DME	Dimethoxyethane, dimethyl ether
DMF	Dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpy	2,6-Di-tert-butyl-4-methylpyridine
ee	enantiomeric excess
EI	Electron Impact
equiv.	equivalents
Et	Ethyl
FG	Functional Group
FTIR	Fourier Transform Infrared Spectrometry
g	gram
GC	Gas Chromatography
gem	geminal
hCL_{int}	human intrinsic clearance
Het	Heterocycle
HIV	Human Immunodefiency Virus
HMDS	Bis(trimethylsilyl)amine, hexamethyldisilazane
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectroscopy
Hr(s)	Hour(s)
Hz	Hertz
IAN	Isoamyl nitrite
Ipc	Isopinocampheyl
ISC	Intersystem crossing
J	coupling constant
L	Ligand
log D	distribution coefficient
log P	Partition coefficient
m	milli, medium (FTIR), multiplet (NMR)
m-	meta
mCL_{int}	mouse intrinsic clearance
mCPBA	3-Chloroperoxybenzoic acid

Me	Methyl
Min	minute
MOM	Methoxymethyl acetal
MOP	Methoxypropyl acetal
M.p.	Melting Point
M.S.	Molecular Sieve
Ms	Mesylate, methanesulfonyl
MS	Mass Spectrometry
MVK	Methyl Vinyl Ketone
MW	Microwave irradiation
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NR	No Reaction
o/n	overnight
p-	para
pin	pinacol
Ph	Phenyl
PMP	*para*-methoxyphenyl
ppm	Parts per million
Pr / ^{n}Pr	*normal*-propyl
^{i}Pr	*iso*-propyl
quant.	Quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
RI	Radical ion
RSM	Recovered Starting Material
RT or r.t.	room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	strong (FTIR), singlet (NMR)
SAR	Structure Activity Relationship
SM	Starting material
S_N	Nucleophilic Substitution
Sol.	Intrinsic thermodynamic solubility
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBACl	Tetrabutylammonium chloride

TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TBS / TBDMS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
Thr	Threonine
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	trimethylsilyl
Tol.	Toluene
Ts	4-toluenesulfonyl
UV	Ultra-violet
w	weak
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Part 1

The introduction of an oxetane ring into medicinally important scaffolds

Chapter 1: The oxetane ring in organic chemistry

1. Introduction

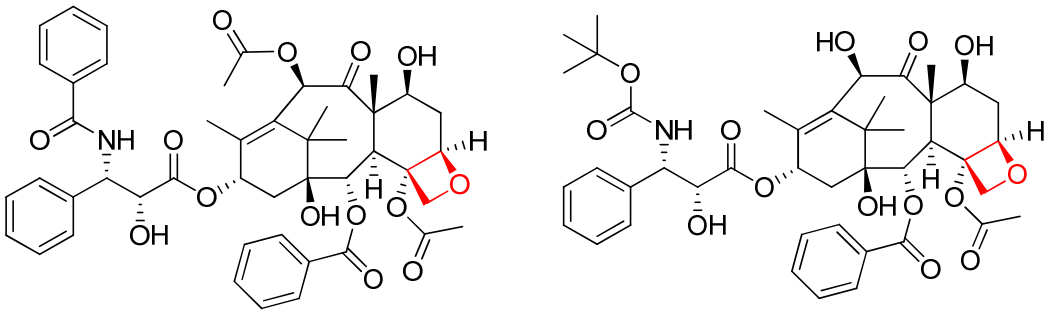
Oxetane was first prepared in 1878 by Reboul, and this fragment is found in numerous compounds that display a wide range of therapeutics activities.[1] For this reason, in the past few years, these small heterocycles have received considerable interest.

In fact, due to its structural relationship with a *gem*-dimethyl or a carbonyl group, its high polarity and its ability to act as a hydrogen bond acceptor, the oxetane ring has become an interesting framework for drug discovery. In this context, the replacement of a carbonyl by an oxetane can increase the bulk of a drug candidate without increasing its lipophilicity. In the case of a *gem*-dimethyl group, which provides steric protection but increases the lipophilicity and is a possible site for metabolic attack, an oxetane can provide more stable and less lipophilic alternative.

2. Oxetanes in nature and on the market

2.1. Marketed products

The oxetane framework is contained in some marketed pharmaceuticals, such as paclitaxel (**1**) (Taxol®) and docetaxel (Taxotere®) (**2**) (Figure 1.1). Both of these compounds are derived from a family of natural products named taxanes and have anticancer properties.



Paclitaxel (Taxol®) (**1**) Docetaxel (Taxotere®) (**2**)

Figure 1.1: Marketed pharmaceuticals containing an oxetane ring

Paclitaxel (**1**) was first isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, by the U.S. National Cancer institute and was then developed commercially by Bristol-Myers-Squibb under the brand name Taxol®.[2] It is used to treat breast, ovarian, leucopenia, liver and lung cancers and Kaposi's sarcoma.[3]

Due to the low natural abundance of paclitaxel (**1**), significant research activity commenced to find a scalable synthesis route and novel analogues with similar activities. These studies delivered the analogue, docetaxel (**2**), found by Pierre Potier and was then commercialized by Sanofi-Aventis under the brand name of Taxotere®.[4] This molecule is a semi-synthetic analogue of paclitaxel (**1**) and an esterified product of 10-deacetyl baccatin III, which is extracted from the renewable and readily available European yew tree. Docetaxel (**2**) is mainly used in the treatment of breast, gastric, prostate and non-small cell lung cancers as well as Squamous cell carcinoma of the head and the neck.[5]

These two compounds stabilise the microtubules of cells and prevent their normal depolymerisation during cell division. Since its discovery, SAR studies have been carried out to determine the role of the oxetane ring in the bonding between paclitaxel and the tubulin dimer.

For this purpose, paclitaxel (**1**) and its analogue D-secopaclitaxel, where D-secopaclitaxel is the oxetane-ring opened analogue of paclitaxel, were subjected to *in silico* biological studies. In these investigations, it was shown that the oxetane framework influences the rigidity of the overall scaffold of paclitaxel (**1**), and, orientates favorably the side chain in the C13 and the benzoyl group into the tubulin

pocket.[6] Because of its conformational properties, the oxetane ring is essential for paclitaxel's biological activity. The oxetane framework acts also as a hydrogen-bond acceptor with the alcohol group of the Thr276 of the tubulin protein.[7] In addition to this bonding, the polarity and the direction of the C-O bond in the oxetane ring results in favorable electrostatic interactions with the surrounding protein. Other studies concerning the replacement of the oxygen on the oxetane ring by a nitrogen, sulfur and selenium produced analogues with no or lower biological activity.[8,9] Even if the role of this 4-membered ring in paclitaxel remains unclear, it appears to be very important to its biological activity.

2.2. Other oxetane-based natural products

The oxetane moiety has also been found in numerous biologically active natural products (Figure 1.2). All of these compounds have different activities, but many of them come from the family of terpernoids. For example, the sesquiterpene merrilactone A (**3**) is isolated from the fruit of *Illicium merrilianum*. It displays neurotrophic activity in fetal rat cortical neuron cultures and has the potential to be used in the treatment of neurodegenerative diseases.[10] The antimetabolite compound oxetin (**4**) was isolated from the fermentation broth of *Streptomyces sp. OM-2317* in 1984 by Omura *et al.* This amino-acid presents herbicidal and antibacteriologic effects.[11] The diterpene dictyoxetane (**5**) was isolated from the brown algae *Dictyoata dichotoma*. It is a natural product related to the class of dolabellanes which present a wide spectrum of biological activities.[12] Bradyoxetin (**6**) was found to be in the bacteria *Bradyrhizobium japonicum* involved in the synthesis of nodules in soybean.[13]

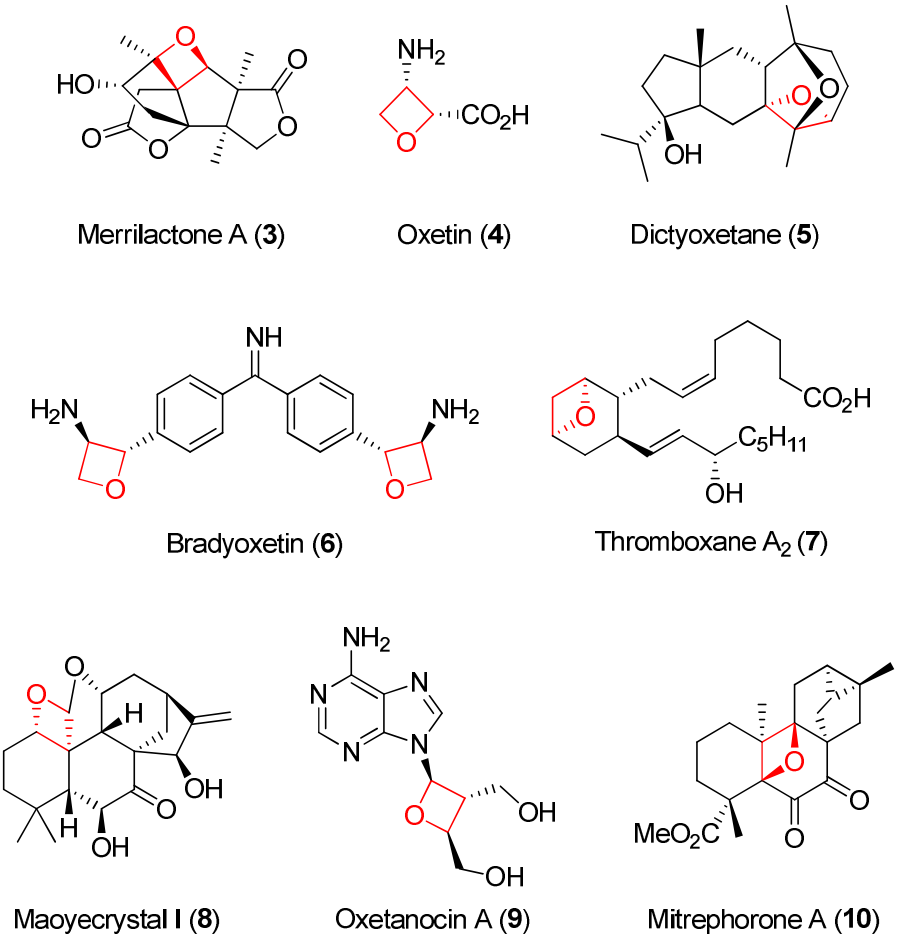


Figure 1.2: Other oxetane-based natural products

Thromboxane A2 (**7**) is produced by activated platelets and has vasoconstriction, platelet aggregation, and bronchoconstriction activities. [14] The diterpenoid maoyecrystal I (**8**) was isolated from *Isidon japonicas* and displays cytotoxic activity. [15] Oxetanocin A (**9**) was isolated from a culture filtrate from bacterium *Bacillus*. It has shown inhibition activities against the reverse transcriptase protein of HIV by mimicking adenosine.[16] The diterpenoid mitrephorone A (**10**) was isolated from *Mitrephora glabra*, and has cytotoxic activity against a broad panel of cancer cells.[17]

3. Importance of the oxetane ring in medicinal chemistry

The oxetane moiety in medicinal chemistry can play an important role to improve the physicochemical properties of a drug candidate. In fact, the oxetane framework can change the steric hindrance, the metabolic liabilities, the lipophilicity, the basicity, and the solubility of a scaffold of interest.

3.1. Oxetanes as potential surrogates of gem-dimethyl and carbonyl groups

Methylene groups are prone to metabolic derivatisation.[18] Therefore, in the context of drug design, a *gem*-dimethyl moiety is often introduced as a surrogate to block metabolic and chemical attack by increasing steric hindrance. However, this replacement often increases the lipophilicity of the molecule. This in turn affects the pharmacological and physicochemical properties of the compound. In principle, a carbonyl group could be introduced to avoid this increase of lipophilicity. Unfortunately however, the carbonyl group is also prone to metabolism.[19]

Due to its analogous properties, the oxetane ring can be considered as a potential surrogate for the *gem*-dimethyl and carbonyl groups. In fact, the oxetane framework occupies a similar volume to a *gem*-dimethyl by comparison of the partial molar volumes of oxetane and propane in water, but, it is liponeutral.[20] Moreover, oxetane and carbonyl groups have structural similarities (Figure 1.3). In fact, an oxetane ring is essentially planar with a weak puckering (Figure 1.4). In addition, thanks to its electron lone pairs on the oxygen atoms, the oxetane ring displays comparable spatial arrangements, polarizes similarly to the carbonyl group and acts as a hydrogen bonding acceptor.[21] This character comes from the inherent angle strain which has the effect of decreasing the endocyclic C-O-C angle, thereby effectively exposing the oxygen atom to donors of hydrogen-bonds. It was also shown that the oxetane unit had a greater tendency to form hydrogen bonds than carbonyl groups such as aliphatic aldehydes, ketones, and esters, but not amide groups. Oxetane rings can

also be an alternative of carboxylic acid derivatives, like esters and amides, which are potential targets of enzymatic cleavage in an organism.

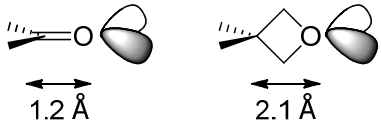


Figure 1.3: Structural similarities of carbonyl and oxetane groups

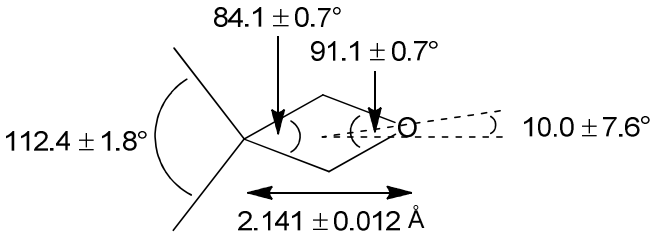
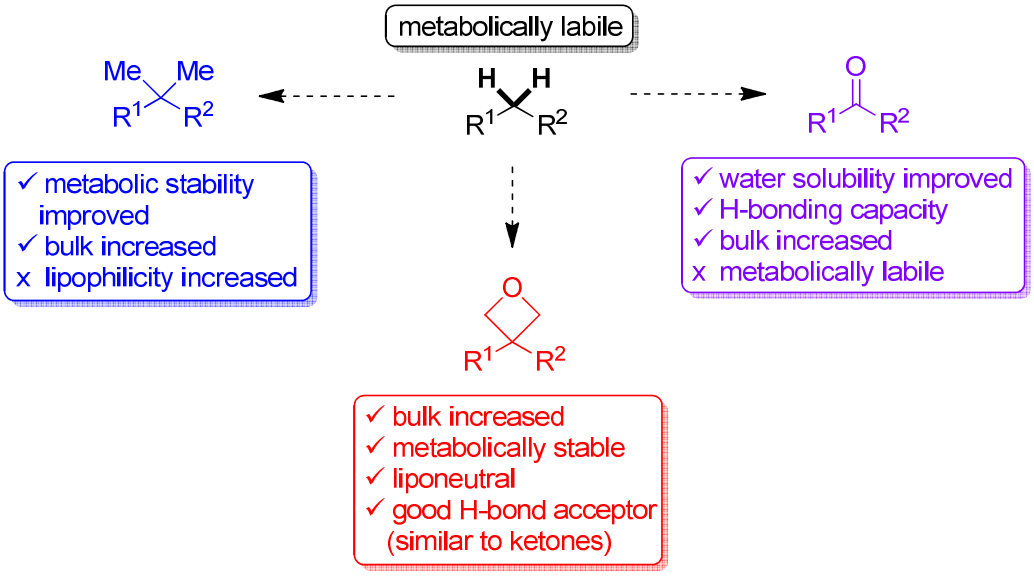


Figure 1.4: Structural properties of oxetanes

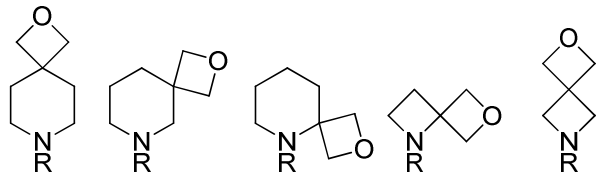
Overall therefore, the oxetane unit has the characteristics of a good surrogate for the methylene, *gem*-dimethyl and carbonyl groups to reduce lipophilicity and metabolic liability (Scheme 1.1).



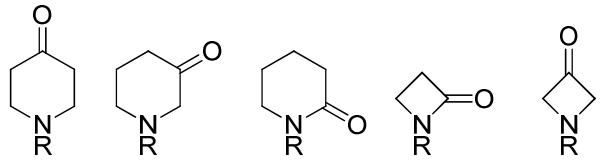
Scheme 1.1: Comparison of methylene, *gem*-dimethyl and oxetane frameworks

3.2. Influence of oxetane on the lipophilicity, solubility, metabolic stability and basicity

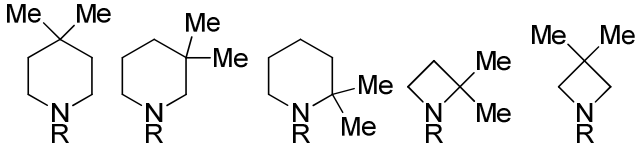
As discussed earlier, the replacement of a *gem*-dimethyl group by an oxetane moiety decreases the lipophilicity and compound clearance, while increasing solubility. However, oxetanes are not unique in providing druggable fragments. Indeed, amino-ketones have traditionally been exploited in drug design as these show good lipophilicity and solubility profiles. However, these compounds do possess a metabolically labile carbonyl group. In this context, Carreira *et al.* undertook a systematic study of the physiochemical properties of amino ketones whereby the carbonyl unit was replaced by *gem*-dimethyl group and oxetane groups (Figure 1.5).



log P	2.0	2.3	2.4	1.3	1.2
Sol.	5400	7700	2900	6000	100000
hCL$_{int}$	6	16	19	21	3



		80			
log P	1.6	0.5	1.6	1.1	unstable
Sol.	17000	9000	27000	10000	
hCL$_{int}$	120	120	8	5	



log P	4.4	4.3	3.9	2.8	3.1
Sol.	890	53	120	1700	1700
hCL$_{int}$	23	31	0	7	0

log P = intrinsic lipophilicity of the neutral base
Sol. = intrinsic thermodynamic solubility (mg.mL^{-1}) in 50 mM phosphate buffer (at pH = 9.9)
hCL$_{int}$ = intrinsic clearance [min^{-1}/mg$_{protein}$mL^{-1}]

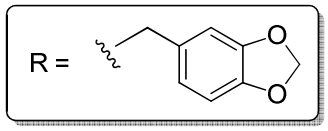


Figure 1.5: Intrinsic lipophilicity, solubility and clearance of *gem*-dimethyl, carbonyl, and oxetane analogues

The presence of an oxetane framework instead of a carbonyl or a dimethyl group at the β or γ position of the amine was found to offer better metabolic stability (Figure 1.5).[19] On the other hand, when the oxetane unit was introduced at the α position of the amine, the oxetane counterpart of the ketone and dimethyl compound showed greater metabolic liability due to the decrease of basicity of the compound which in turn increased the overall lipophilicity. This had the effect of enhancing exposure to cytochrome P450 on the membrane.

Many drug molecule candidates have basic sites that are important for drug transport around the body. It is therefore important to realize that the incorporation of an oxetane moiety has an effect on the basicity of a proximal amine (Scheme 1.2).[19] This effect is dependent of the distance between the two functional groups. Moreover, the influence of the oxetane group on the pKa of cyclic amines is stronger than acyclic ones. The incorporation of an oxetane moiety instead of a carbonyl, a *gem*-dimethyl or hydrogen atoms in different positions of an acyclic amine was studied by Carreira, Rogers-Evans, and Müller (Figure 1.6).[19,20]

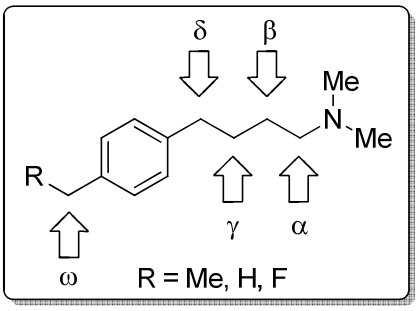
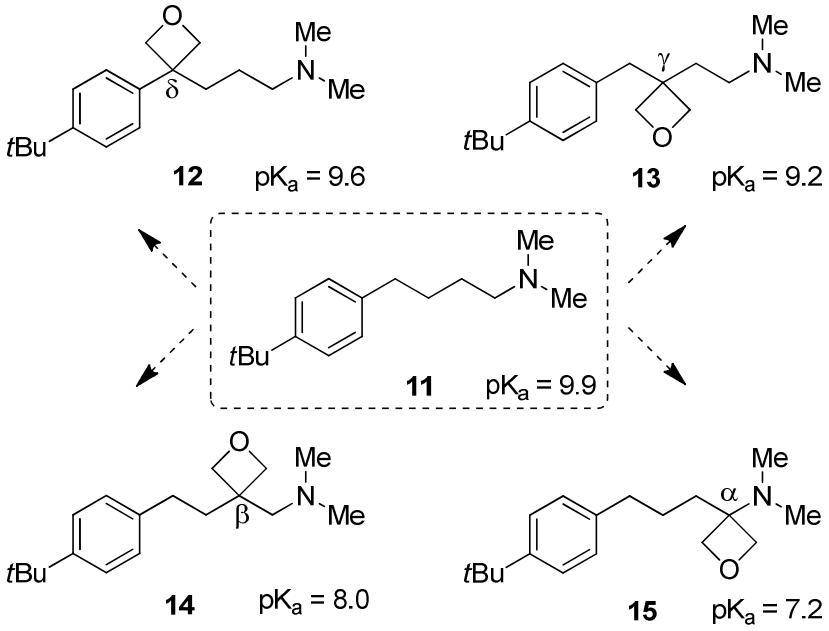


Figure 1.6:

The incorporation of an oxetane ring at the ω-position renders the oxetane derivatives highly soluble at basic pH, provides lower lipophilicity and offers lower clearance rates from human and mouse microsomes relative to their *gem*-dimethyl analogues (Scheme 1.2 and Table 1.1). The introduction of an oxetane ring at the position δ (**12**) and γ (**13**) also increases the solubility of the compounds and decreases clearance rates, but has no effect on the lipophilicity and on the basicity. In contrast, the incorporation of the oxetane unit in the α (**15**) and β (**14**) positions results in a slight augmentation of the solubility, and a large increase of the

lipophilicity. These phenomena are the result of a reduction of the basicity, and consequently a reduction in metabolic stability.



Scheme 1.2: Influence of oxetane substitution on the basicity of proximal amine

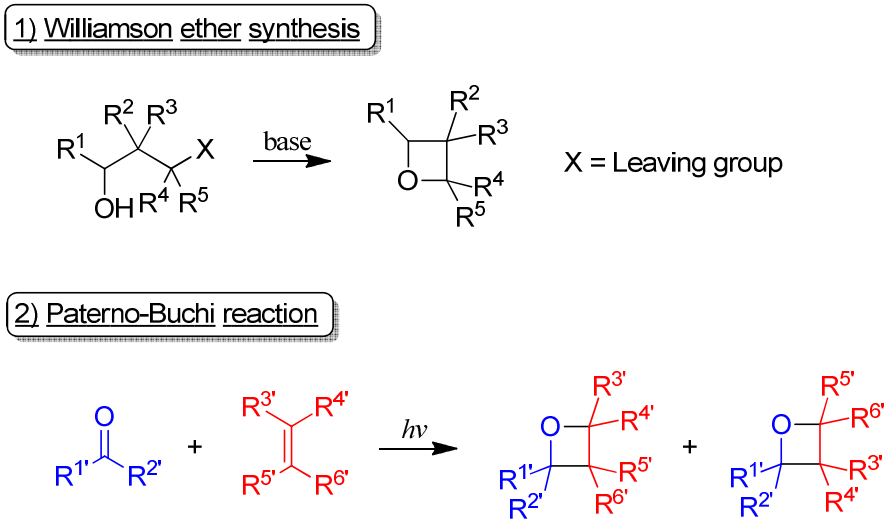
Compound	Sol.[a]	hCLint[b]	mCLint[c]	logD (logP)[d]	pKa[e]
11	< 1	16	417	1.8 (4.3)	9.9
ω-substituted	4400	0	43	0.8 (3.3)	9.9
12	270	0	147	1.7 (3.9)	9.6
13	4100	6	13	1.7 (3.5)	9.2
14	25	42	383	3.3 (4.0)	8.0
15	57	13	580	3.3 (3.6)	7.2

[a] Sol. = intrinsic thermodynamic solubility (mg.mL-1) in 50 mM phosphate buffer (at pH = 9.9); [b] hCLint = human intrinsic clearance [min-1/mgproteinmL-1]; [c] mCLint = mouse intrinsic clearance [min^{-1}/mgproteinmL^{-1}]; [d] log D = logarithm of the *n*-octanol/water coefficient at pH 7.4, log P = intrinsic lipophilicity of the neutral base; [e] amine basicity in water measured at 24°C.

Table 1.1:

4. Synthesis of the oxetane ring

The strategies to synthesize the oxetane moiety are numerous and varied. Among them, two approaches can be considered as general enough to encompass most routes (Scheme 1.3). The first one, the Williamson ether synthesis, involves an intramolecular cyclisation by nucleophilic displacement. The second one, the Paternò-Buchi synthesis, involves a [2+2] cycloaddition between a carbonyl and an alkene.



Scheme 1.3: General approaches for the oxetanes synthesis

4.1. *Cyclisation: Williamson ether synthesis*

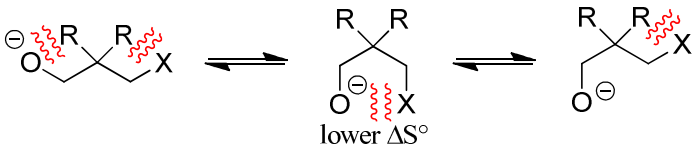
4.1.1. Generalities

The Williamson ether synthesis of oxetanes is a ring closure reaction. In this process, the oxygen plays the role of the nucleophile. The four-membered ring cyclisation is usually slow due to unfavorable enthalpy and entropy costs associated with the increase in the ring strain of the product.[22]

However, some modifications of the substrate's structure can reduce the unfavorable enthalpy effect. The most well-known effect is the *gem*-dimethyl effect, also known as Thorpe-Ingold effect which increases the rate of ring formation. Specifically, in 1915, Thorpe and Ingold showed that the replacement of the hydrogens in the alkyl chain by two alkyl groups on the same carbon reduces the angle α between the groups X and Y (Figure 1.7).[23] In fact, the repulsion of the two R alkyl groups will cause an augmentation of the angle β and so reduce the angle α. This reduction of the angle α will place the groups X and Y closer together and facilitate the cyclisation.

Figure 1.7:

In 1960, Bruice and Pandit suggested that the *gem*-dimethyl substitution increases the concentration of reactive rotamers bringing the reactive ends closer (Scheme 1.4).[24] In fact, the presence of the *gem*-dimethyl substituents hinders the rotation of the other groups into that region of space. The transition state can adopt a conformation with the lower ΔS°, and so reduces entropy loss during cyclisation resulting in faster ring formation.

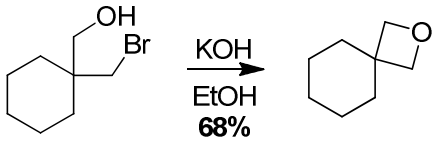


Scheme 1.4: Reactive rotamers

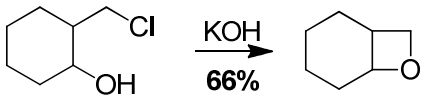
4.1.2. Examples

In 1960, Tamres *et al.* reported a synthesis of 2-oxaspirane (Scheme 1.5),[25] and a year later Rosowsky and Tarbell reported the synthesis of 3-oxaspirane (Scheme 1.7) and 7-oxabicyclo-octane (Scheme 1.6).[26] In each case, the cyclisation was undertaken under basic conditions. Indeed, under acidic conditions, the cyclisation

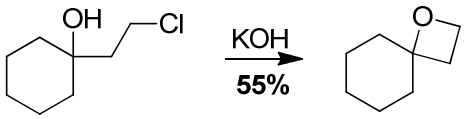
was found to produce more side-reactions, such as ring cleavage, leading to low product yields.



Scheme 1.5: Synthesis of 2-oxaspirane

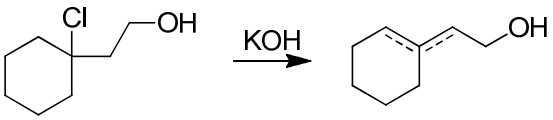


Scheme 1.6: Synthesis of 7-oxabicyclo-octane



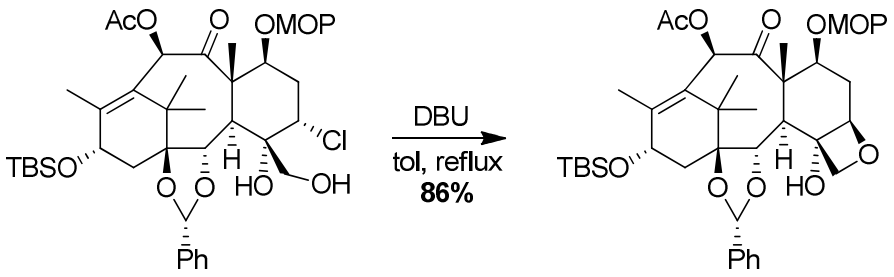
Scheme 1.7: Synthesis of 3-oxaspirane

Tarbell *et al.* observed a mixture of unsaturated alcohols after treatment of the corresponding chlorohydrin with potassium hydroxide. Slow cyclisation appears to occur when the leaving group is located on a tertiary alkyl group (Scheme 1.8).[26]



Scheme 1.8: Formation of unsaturated alcohols

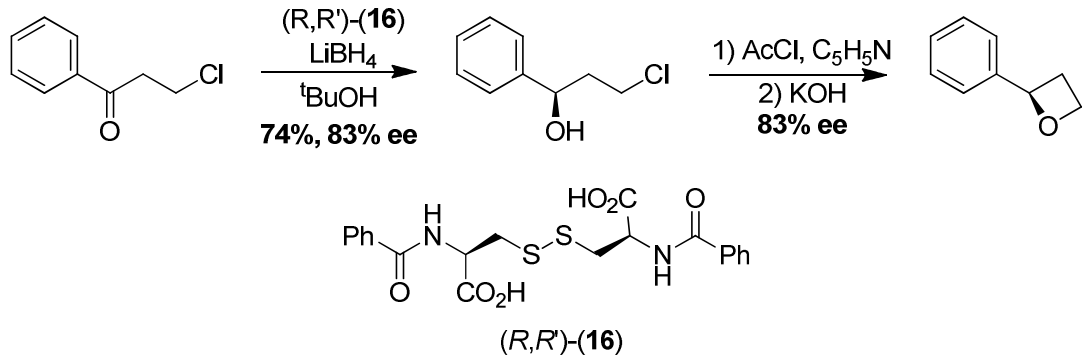
In 2000, Kuwajima and co-workers reported the formation of the ABCD tetracyclic moiety of taxol by treatment of the ABC tricyclic ring system with DBU in toluene at reflux with 86% yield (Scheme 1.9).[27]



Scheme 1.9: Synthesis of the ABCD tetracyclic moiety of taxol

4.1.3. Stereoselective Williamson ether synthesis

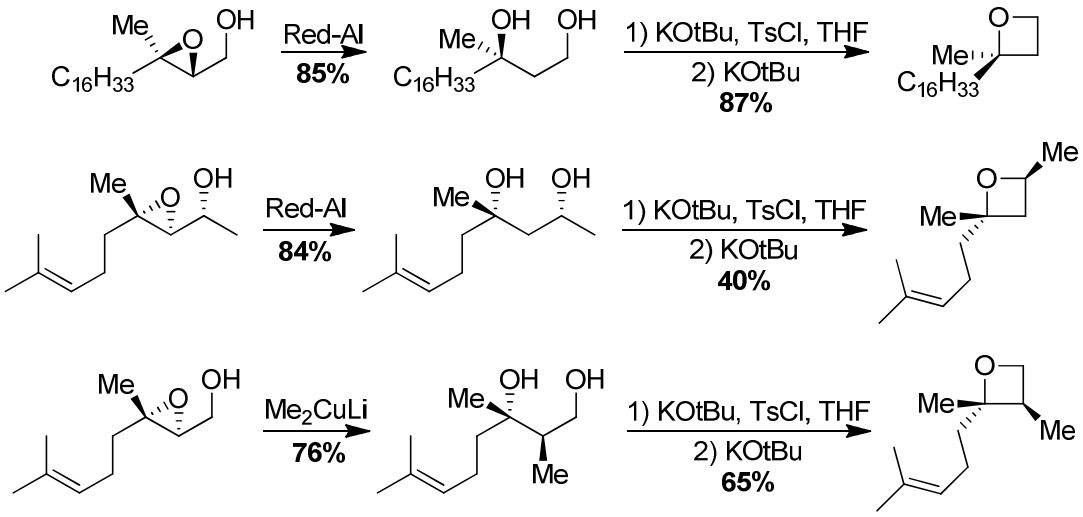
Chiral oxetanes can be prepared *via* a Williamson ether synthesis from enantiopure alcohols. In 1986, Soai *et al.* reported an asymmetric synthesis of 2-arylsubstituted oxetanes by enantioselective reduction of β-halogenoketones.[28] The reduction of β-halogenoketones with lithium borohydride in presence of (*R,R'*)-*N,N'*-dibenzoylcystine (**16**) provided the (*R*)-chloro-alcohol with 83% ee in 74% yield (Scheme 1.10). The one-pot acetylation, followed by cyclisation using KOH afforded the (*R*)-oxetane with 83% ee.



Scheme 1.10: Preparation of chiral oxetanes by Williamson ether synthesis

In 2002, Dussault and co-workers reported a stereoselective synthesis of mono-, di- or tri-substituted oxetanes.[29] The ring opening of chiral 2,3-epoxyalcohols with Red-Al, $LiAlH_4$, or lithium dimethyl cuprate afforded enantiomerically enriched 1,3-diols. The diol was then treated with tosyl chloride and potassium *tert*-butoxide to produce

a mono-tosylated alcohol which delivered the oxetane after treatment by potassium *tert*-butoxide. These two last steps could be performed in a one-pot reaction. This method allowed the synthesis of enantioenriched 2,2-disubstituted, 2,2,4-trisubstituted and 2,2,3-trisubstituted oxetanes in moderate to good yield (Scheme 1.11).

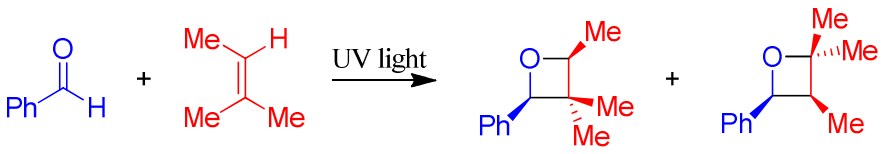


Scheme 1.11: Stereoselective synthesis of substituted oxetanes

4.2. Photochemical pathway: The Paternò-Buchi reaction

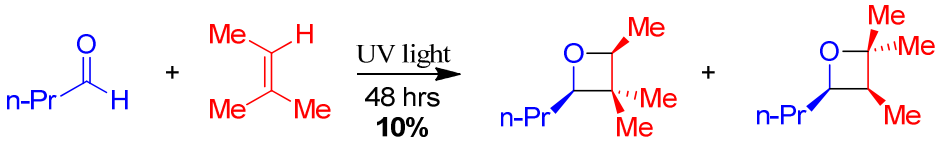
4.2.1. Generalities

The Paternò-Buchi reaction is the synthesis of an oxetane ring by a [2+2] cycloaddition between an olefin and a carbonyl group under UV-radiation. After the observation of the photochemical transformation of carvone to camphor in 1909, Paternò and Chieffi reported the first example of [2+2] cycloaddition between the olefin and the carbonyl to form the oxetane rings.[30]



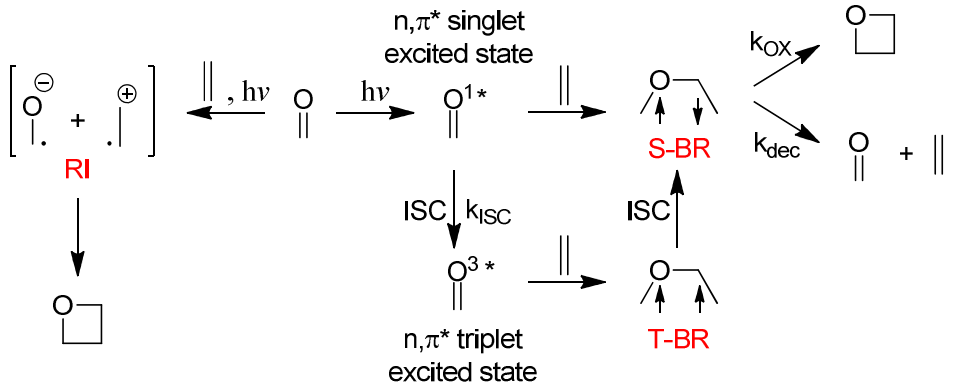
Scheme 1.12:

In 1954, Buchi *et al.* studied the mechanisms and the structures of the products of the reaction.[31]



Scheme 1.13:

The general mechanism of the reaction is described in Scheme 1.14.[32] In general, two types of reactive radical intermediates are involved; a radical-ion pair (RI) and a 1,4-biradical (BR). The radical-ion pair (RI) is generally formed when an electron-rich alkene reacts with an excited carbonyl compound. Otherwise, the 1,4-biradical (BR) is involved in the reaction between an electron-poor alkene and a ketone. In this case, the excitation of the carbonyl compound by light provides a singlet excited state. When its lifetime is long enough to interact with the alkene, the singlet biradical (S-BR) intermediate can be formed directly by the interaction between the singlet excited state of carbonyl and the alkene. The singlet biradical can then form the oxetane or give back the starting materials. However, when the intersystem crossing (ISC) rate constant, k_{ISC}, is faster than the diffusion rate constant, the singlet excited state gives a triplet excited state which will then react with the alkene to give a triplet 1,4-biradical (T-BR). This intermediate can then produce the oxetane ring after its conversion to the singlet 1,4-biradical via ISC.



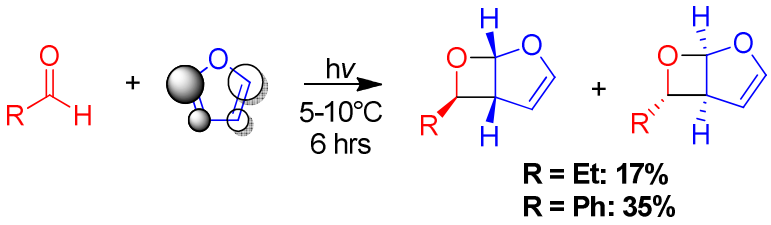
Scheme 1.14: General mechanism of Paternò-Buchi

When unsymmetrically substituted alkenes or carbonyl compounds are used, the reaction can produce regioisomers, and up to three chiral stereogenic centers.

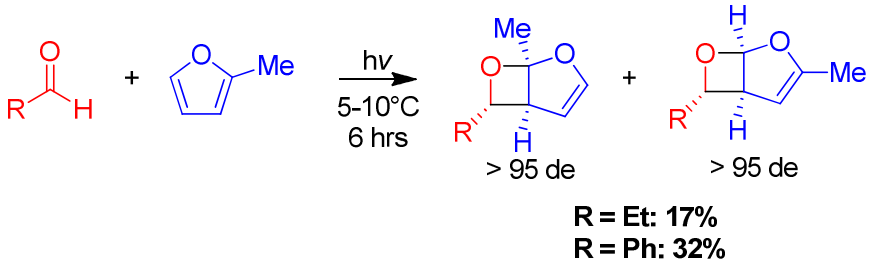
4.2.2. Paternò-Buchi regioselectivity

The reaction regioselectivity is highly dependent on substrate type and on the radical intermediate stability. In fact, when the nucleophilicity of the alkene carbon atoms are similar, the electrophilic oxygen can attack both carbon atoms to give regioisomers. But, when nucleophilicities are significantly different, the oxygen will attack preferentially one carbon to produce a major 1,4-biradical intermediate.

Regioselective cycloaddition of aldehydes or ketones on furan and vinyl ethers were reported by various groups. For example, in 1965, Sakurai *et al.* reported a regioselective formation of oxetane from aldehydes and furans (Scheme 1.15).[33] They have shown that 2-alkoxyoxetanes were preferentially formed. This formation is explained by the fact that the bi-radical intermediate formed by this pathway is more stable than its regioisomer, formed by the attack of the oxygen on the 3-position of furan. In fact, the biradical formed has more resonance stabilization with the delocalization of the unpaired electrons of the furan. Moreover, the excited oxygen will attack the site which has the largest HOMO coefficient. They have also shown that, when the 2-methylfuran ring was used, mixtures of regioisomers were observed (Scheme 1.16).

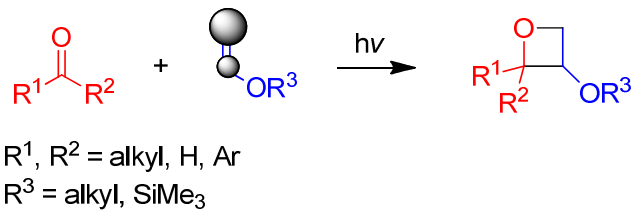


Scheme 1.15: Paternò-Buchi reaction between aldehyde and furan



Scheme 1.16: Paternò-Buchi reaction between aldehyde and 2-methylfuran

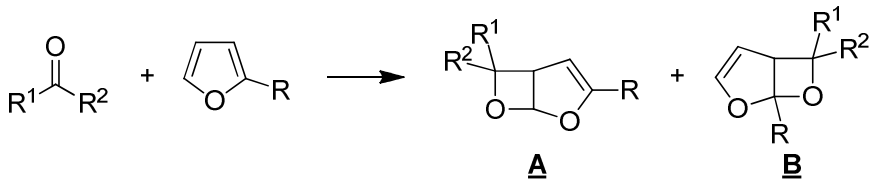
In 1969, the same resonance stabilization argument was put forward by Orlando *et al.* in the reaction of vinyl ethers and ketene diethyl acetal derivatives with various ketones or aldehydes (Scheme 1.17).[34] In 1983, Tsuno *et al.* reported the synthesis of oxetane derivatives from ketone and enol trimethylsilyl ethers.[35] In each case, 3-alkoxyoxetanes were obtained as the major product. This result could be predicted by the consideration of the HOMO energies and the stabilization of the intermediate states.



Scheme 1.17: Paternò-Buchi reaction between aldehyde and vinyl ethers

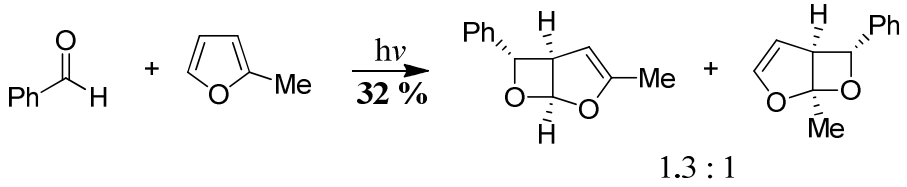
4.2.3. Paternò-Buchi site-selectivity on unsymmetrical furans

As highlighted earlier in scheme 1.14, the photochemical reaction of a carbonyl compound on an unsymmetrical furan can provide two regioisomers **A** and **B**. In fact, the carbonyl excited state can interact with both double bonds (Scheme 1.18).

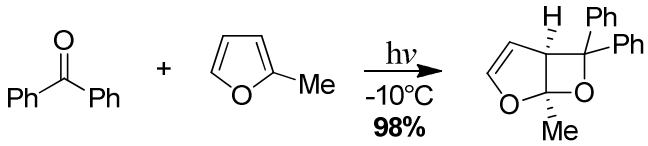


Scheme 1.18: General Paternò-Buchi reaction between carbonyl compound and asymmetric furan

In 1965, Toki and co-workers reported the regio-random photochemical addition of benzaldehyde on 2-methylfuran leading to 1:1 mixture of **A** and **B** type bicycles (Scheme 1.19).[33] However, in 1967, Rivas *et al.* reported the selective synthesis of higher substituted oxetanes of type **B** by the photoaddition of benzophenone on 2-methyl and 3-methylfuran (Scheme 1.20).[36]

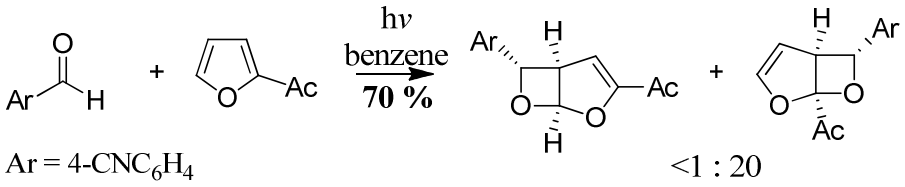


Scheme 1.19: regio-random photochemical addition



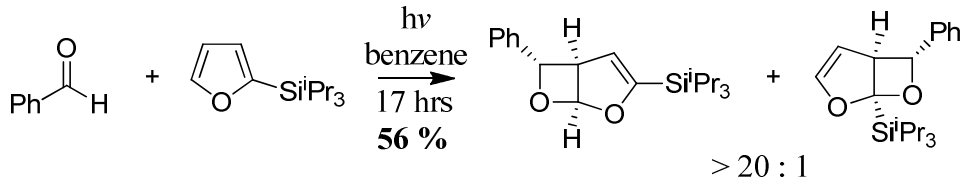
Scheme 1.20: selective synthesis of higher substituted oxetanes

Later work by Carless also showed the selective synthesis of higher substituted oxetanes of type **B** from aromatic aldehydes and acetylfurans (Scheme 1.21).[37] Bicyclic products were generated with a site selectivity of up to 1:20 **A** and **B**.

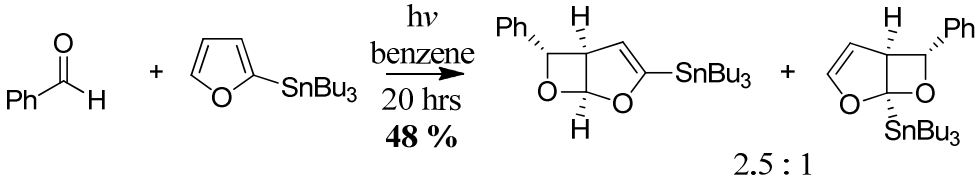


Scheme 1.21: selective synthesis of higher substituted oxetanes

In contrast, Schreiber has reported the selective synthesis of the less substituted oxetanes of type **A** from benzaldehydes and bulky 2-silylfuran (Scheme 1.22) and 2-stannylfuran (Scheme 1.23).[38] A site-selectivity of up to 20:1 was reported for the addition of the aldehyde on the unsubstituted double bond.



Scheme 1.22: selective synthesis of the less substituted oxetanes

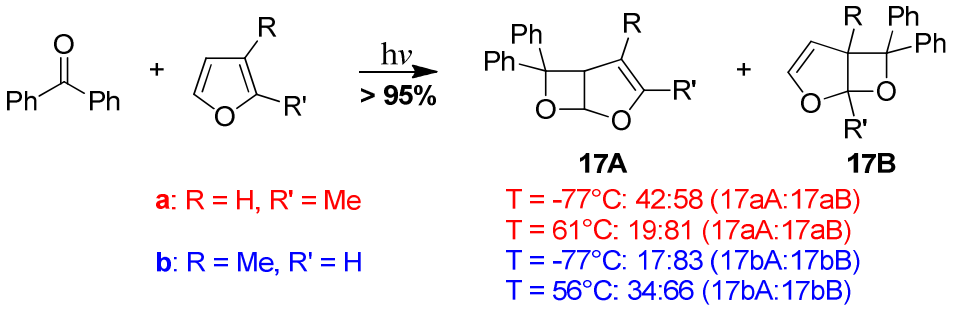


Scheme 1.23: selective synthesis of the less substituted oxetanes

- Temperature effect on site-selectivity[39,40]

The site-selectivity of the photo-cycloaddition of aldehydes and 2-methyl or 3-methylfuran is generally independent of reaction temperature. In contrast, the reaction of aromatic ketones and 2-methyl or 3-methyl furan is highly temperature dependent. In fact, when the reaction between benzophenone and 2-methylfuran was carried out at -77 °C, both site-isomers (42:58) (**17aA**:**17aB**) were obtained in high yield. But, when the reaction was carried out at 61 °C, the higher substituted bicyclic

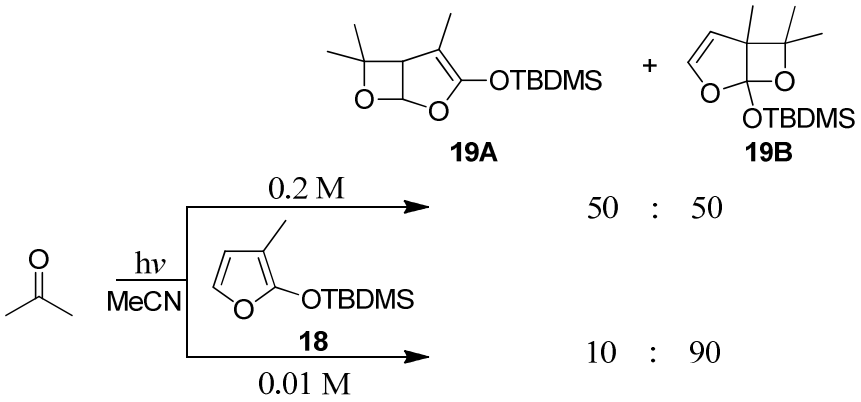
oxetane was obtained as the major product (19:81) (**17aA**:**17aB**). In contrast, at high temperature little selectivity (34:66) (**17bA**:**17bB**) was observed in the reaction of benzophenone and 3-methylfuran, and at low temperature, a good selectivity (17:83) (**17bA**:**17bB**) was observed.



Scheme 1.24:

- Concentration effect on site-selectivity[41]

Abe and co-workers have reported a concentration effect on site-selectivity in the reaction of acetone and 2-siloxy-3-methylfuran (**18**) (Scheme 1.25). They have observed the selective synthesis of the higher substituted oxetane (**19B**) at low concentration of 2-siloxyfuran (**18**), and a site-random synthesis of both bicyclic oxetanes at higher concentration.

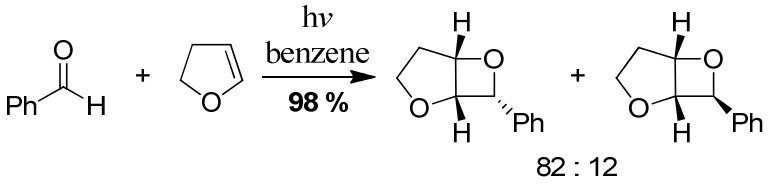


Scheme 1.25: Concentration effect on site-selectivity

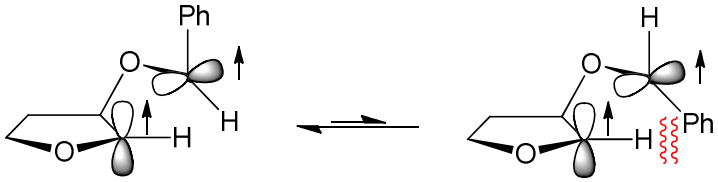
4.2.4. Paternò-Buchi Stereoselectivity

The Paternò-Buchi reaction can produce up to three stereocenters, and so the control of stereochemistry in this reaction is particularly challenging. The selectivity of the product is usually determined by the conformation of the biradical-intermediate. The biradical-intermediate can adopt different conformations: endo, exo.

Griesbeck *et al.* reported, in 1994, an endo-selective formation of oxetanes during the Paternò-Buchi reaction between benzaldehyde and dihydrofuran (Scheme 1.26).[42]

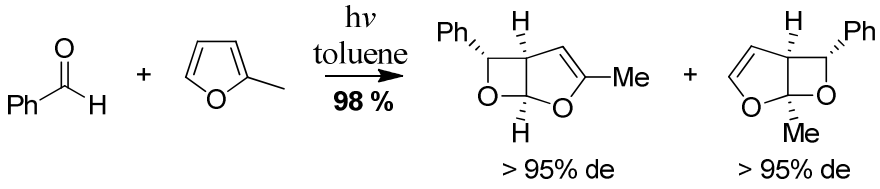


Scheme 1.26: endo-selective formation of oxetanes

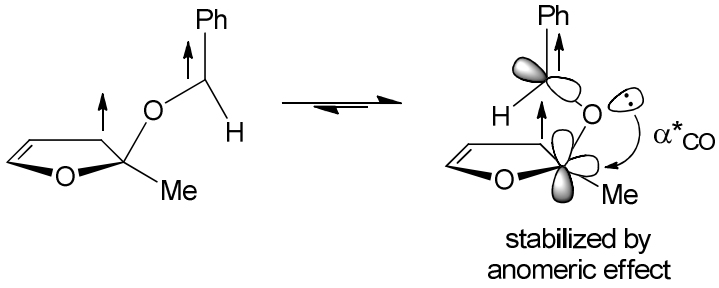


Scheme 1.27: conformation of the intermediate

Abe and co-workers have reported the site-random but exo-selective synthesis of bicyclic oxetanes from benzaldehyde and 2-methylfurans (Scheme 1.28).[39] The observed high stereoselectivity was explained by the fact that the conformation of the biradical triplet intermediate is stabilized by the anomeric effect (Scheme 1.29).



Scheme 1.28: exo-selective synthesis of oxetanes



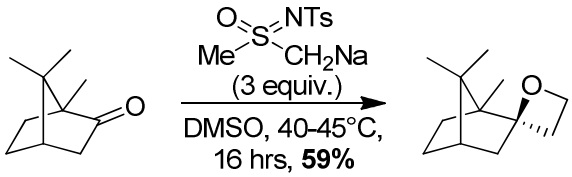
Scheme 1.29: intermediate conformation

4.3. Other syntheses

4.3.1. Reaction of sulfoximine on ketones or epoxides

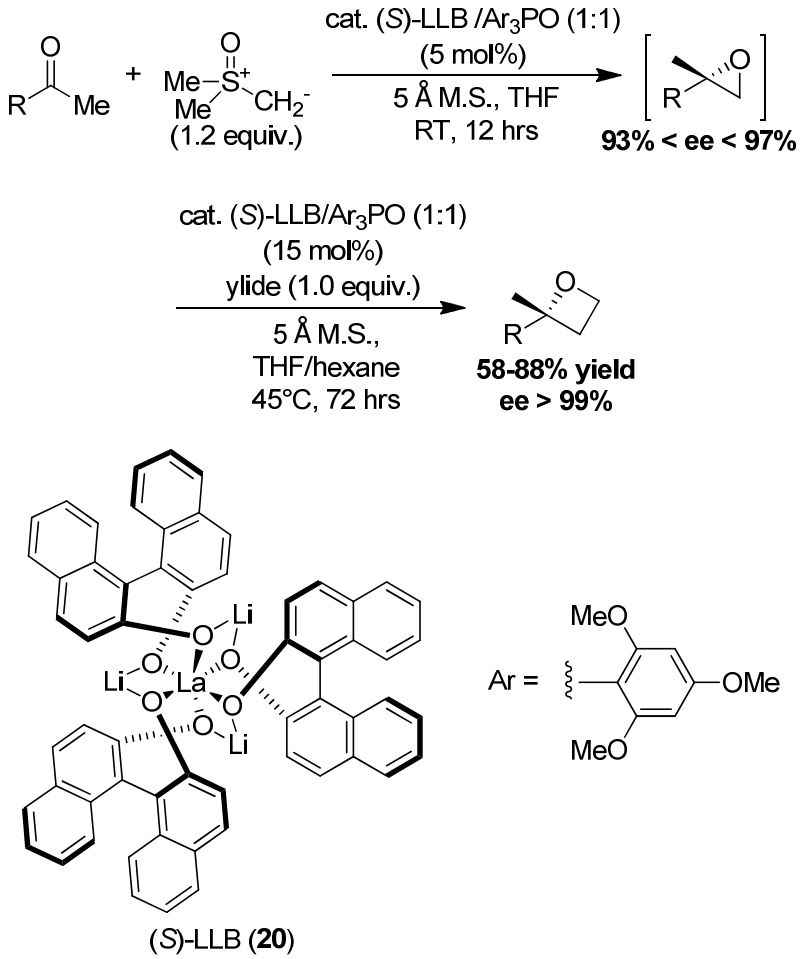
2,2-Disubstituted oxetane rings can be directly prepared from ketones via an epoxide intermediate, or directly by the expansion of an epoxide starting material using a methylene transfer reagent. Different groups have reported variants of the Corey-Chaykovsky reaction for the preparation of oxetanes using sulfur ylides as strong methylene transfer reagents. First, the ylide attacks the carbonyl group to form an oxydialkylsulfoximine intermediate which will undergo a ring closure to form the oxirane ring. The excess of ylide will react again on the oxirane to form the oxetane.

Using this method, Welch and co-workers have reported the transformation of camphor to its oxetane equivalent in 1983 (Scheme 1.30).[43] They have shown that the treatment of camphor by an excess (three equivalents) of *S*-methyl-*S*-(sodiomethyl-*N*-(4-tolylsulfonyl)sulfoximine led in one step to one stereoisomer of the oxetane equivalent with 59% yield.



Scheme 1.30: formation of oxetane equivalent of camphor

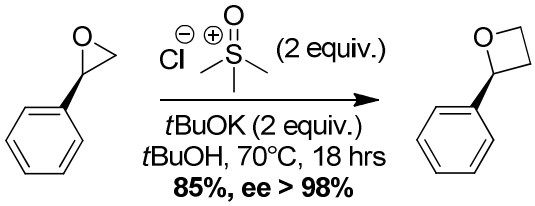
Following their studies, Shibasaki *et al.* have reported a direct asymmetric synthesis of 2,2-disubtituted oxetanes from a ketone.[44] The treatment of an alkyl methyl ketone with dimethyloxosulfonium methylide with phosphine additive and a catalytic amount of a lanthanum complex (**20**) produces epoxides in good yield and in good ee (Scheme 1.31). An additional 15 mol% of the complex and another equivalent of ylide were added to compensate for the low reaction rate of the ring opening of epoxide to afford a 2,2-disubsituted oxetane in good yield and up to 99% ee. They have observed a chiral amplification in the second step.



Scheme 1.31: direct asymmetric synthesis of 2,2-disubtituted oxetanes from a ketone

In 2010, Schreiner and Fokin reported the synthesis of chiral oxetanes from chiral epoxides with complete retention of configuration during the ring expansion reaction (Scheme 1.32).[45] In fact, the mechanism of the reaction of the asymmetric epoxide

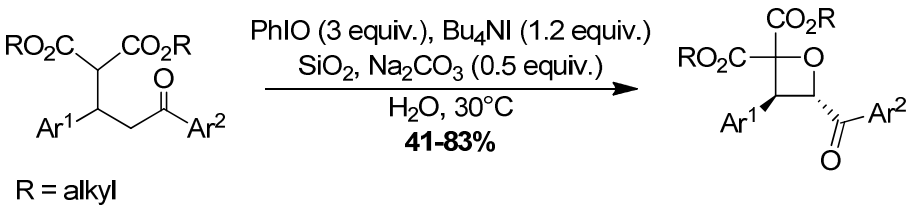
with dimethylsulfoxonium methylide proceeds *via* a betaine intermediate, and so leaves the stereogenic center untouched.



Scheme 1.32: synthesis of chiral oxetanes

4.3.2. Oxidative cyclisation of Michael adduct of malonate with chalcones

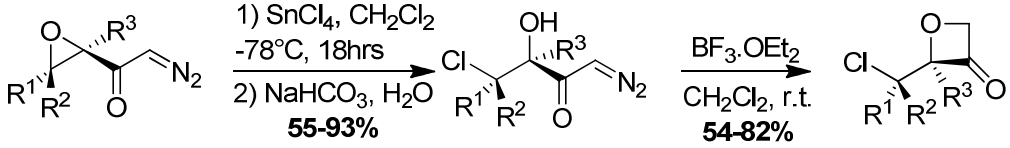
Fan and co-workers have reported a solvent-controlled oxidative cyclization for the preparation of functionalized oxetanes and cyclopropanes (Scheme 1.33).[46] The treatment of a Michael adducts of malonates with chalcones in combination with iodosobenzene and tetrabutylammonium iodide in different solvents provides a selective synthesis of oxetanes or cyclopropanes. The selective synthesis of cyclopropane is achieved in methanol, whilst the selective synthesis of oxetanes is achieved in water and in an open air flask. Moreover, a high diastereoselectivity (anti:syn >95:5) was achieved by this method.



Scheme 1.33: Synthesis of oxetanes from a Michael adduct

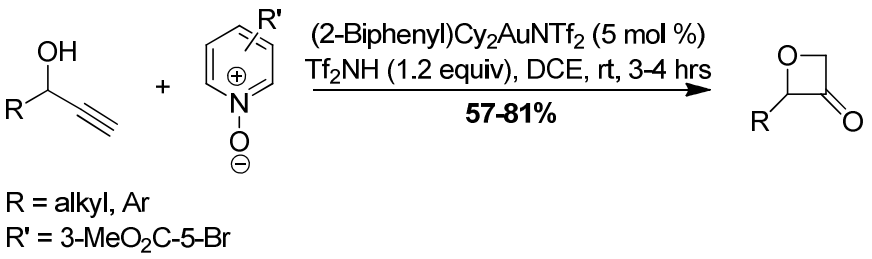
4.3.3. Intramolecular cyclisation via carbene intermediates

A synthesis of oxetan-3-one compounds from α,β-epoxy diazomethyl ketones was reported by Zwanenburg *et al.* in 1992 (Scheme 1.34).[47] The epoxide ring was first opened by treatment with $SnCl_4$ to produce a β-chloro-α-hydroxy diazoketone with retention of configuration. This compound undergoes a diazo decomposition by treatment with a Lewis acid, $BF_3.OEt_2$, to undergo an intramolecular ring closure to produce the oxetanone compound with retention of configuration.

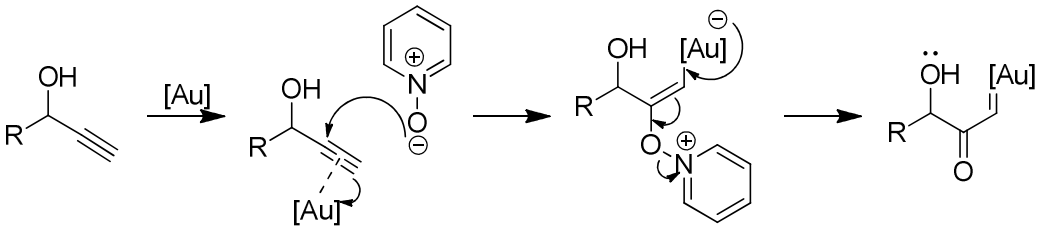


Scheme 1.34: Intramolecular cyclisation from diazomethyl ketone

A gold catalysed synthesis of oxetan-3-one from propargylic alcohols was recently described by Zhang *et al.* in 2010 (Scheme 1.35).[48] The terminal alkyne undergoes an intermolecular oxidation with a gold catalyst in the presence of a pyridine *N*-oxide derivative to provide an α-oxo gold carbene intermediate (Scheme 1.36).[49] An acid species must be added in the reaction to quench the basic pyridine that can deactivate the gold catalyst. This method is compatible with a range of functionalities such as an aromatic, a vinyl, a MOM-protected alcohol or azide group. By this method oxetan-3-one was synthesized in one-step with 71% yield, unlike in four or five steps with 23% or 13% yield, respectively, by traditional methods. Moreover, under these conditions chiral non-racemic oxetan-3-ones can be easily synthesized from the corresponding chiral propargylic alcohols.



Scheme 1.35: Gold catalysed synthesis of oxetan-3-one



Scheme 1.36: Possible mechanism of formation of α-oxo gold carbene intermediate

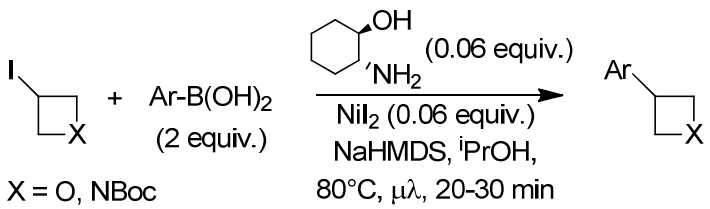
5. Applications of the oxetane ring in synthetic organic chemistry

Oxetane rings can be important intermediates in the synthesis of more complex oxetane analogues.

5.1. Elaboration of 3-iodooxetanes

Elaboration of 3-substituted oxetanes has been well documented because these transformations have the convenience of not introducing a stereogenic center.

Recently, Duncton and co-workers reported a preparation of aryloxetanes by nickel catalyzed Suzuki coupling (Scheme 1.37).[50] They showed that the treatment of 3-iodooxetane with a range of aromatic and heteroaromatic boronic acids in presence of nickel iodide and *trans*-2-aminocyclohexanol produces the corresponding aryloxetane. This method is also effective for the introduction of a *N*-Boc-3-iodoazetidine moiety to an aryl compound.



Scheme 1.37: preparation of aryloxetanes by nickel catalyzed Suzuki coupling

One year later, Duncton reported the preparation of heteroaryloxetanes by a Minisci reaction (Scheme 1.38).[51] They showed that the dropwise addition of H_2O_2 to a mixture of heteroaromatic bases, such as quinoline, pyridine and quinazoline provides, in the presence of sulfuric acid and a catalytic amount of $FeSO_4$, the heteroaryloxetane compound in low-to-moderate yield. This method is also compatible for the introduction of an azetidine group into heteroaromatic compounds.

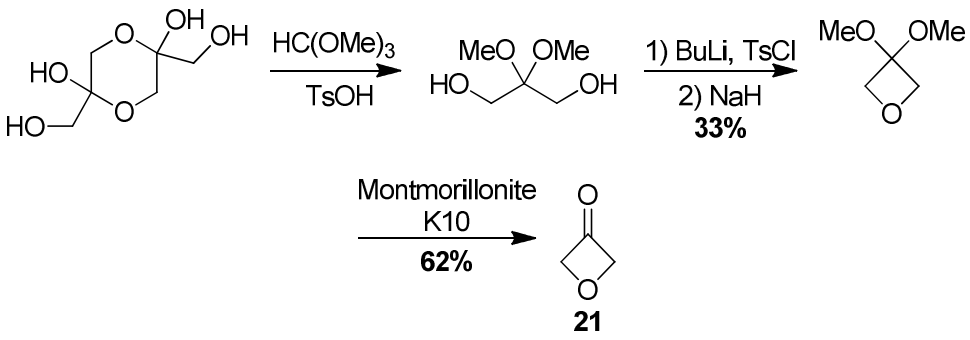
Scheme 1.38: preparation of heteroaryloxetanes by a Minisci reaction

5.2. Elaboration of oxetan-3-one

Oxetan-3-one also represents a good starting point for the introduction of a 3-substituted oxetane ring into various scaffolds.

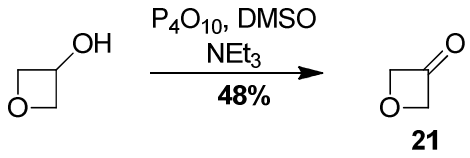
5.2.1. Synthesis of oxetan-3-one

In 2006, Carreira and Rogers-Evans reported the synthesis of oxetane-3-one from dihydroxyacetone dimer (Scheme 1.39).[20] The reaction of dihydroxyacetone dimer with trimethyl orthoformate provides the corresponding dimethyl ketal which was then treated with tosyl chloride in presence of BuLi, and later with sodium hydride to allow the ring closure and afford the intermediate. The deprotection of the ketone was undertaken under acidic conditions using Montmorillonite K10 to furnish oxetane-3-one.



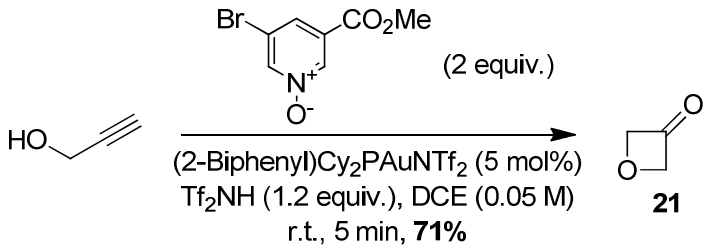
Scheme 1.39: synthesis of oxetane-3-one from dihydroxycetone dimer

The synthesis of oxetane-3-one usually presents some practical difficulties, such as the use of GC chromatography for purification. Moreover, the isolation and purification of oxetane-3-one delivers the product in low yield due to its volatility and hydrophilicity. In 2010, Carreira and Rogers-Evans reinvestigated the oxidation of oxetane-3-ol into oxetane-3-one in order to avoid these complications (Scheme 1.40).[19] They found that the oxidation of oxetan-3-ol with phosphorous pentoxide in DMSO in the presence of triethylamine provides the product in 48% yield after distillation.



Scheme 1.40: oxidation of oxetane-3-ol into oxetane-3-one

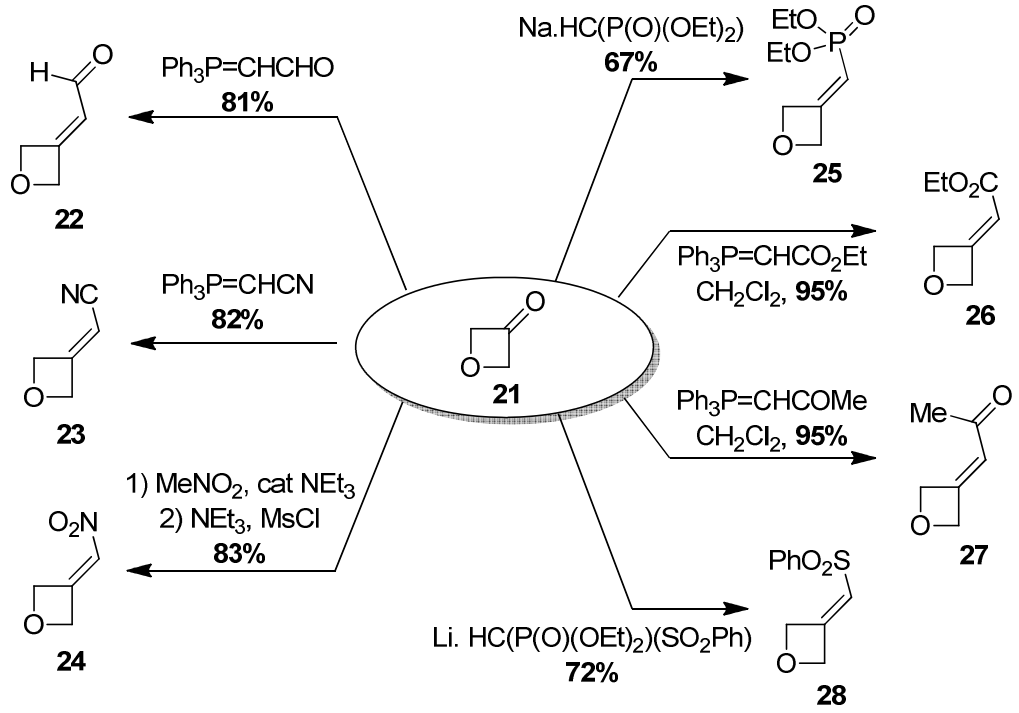
The same year, Zhang and co-workers reported a one-step gold-catalysed (Scheme 1.33) synthesis of oxetane-3-one (**21**) from propargyl alcohol with 71% yield without purification (Scheme 1.41).[47]



Scheme 1.41: gold-catalysed synthesis of oxetane-3-one

5.2.2. Synthesis of Michael acceptors from oxetan-3-one

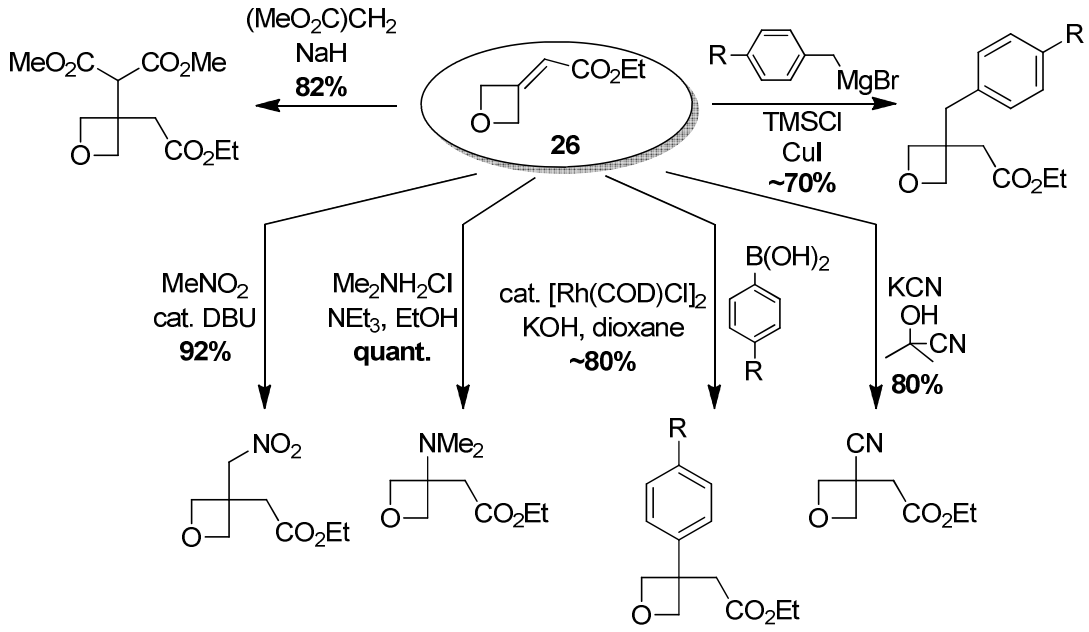
Oxetan-3-one (**21**) is an important intermediate for the synthesis of oxetane-based Michael acceptors (Scheme 1.42).[19] The Wittig reaction between oxetan-3-one (**21**) and an ylide furnishes aldehydes (**22**), ketones (**27**), α,β-unsaturated esters (**26**) and nitriles (**23**). The Horner-Wadsworth-Emmons reaction can provide sulfone (**28**), ketone and phosphonate (**25**) functionalized oxetane compounds. The condensation of oxetan-3-one (**21**) with nitromethane affords the nitroalkene oxetane derivatives (**24**) in good yield.



Scheme 1.42: Synthesis of Michael acceptors from oxetan-3-one

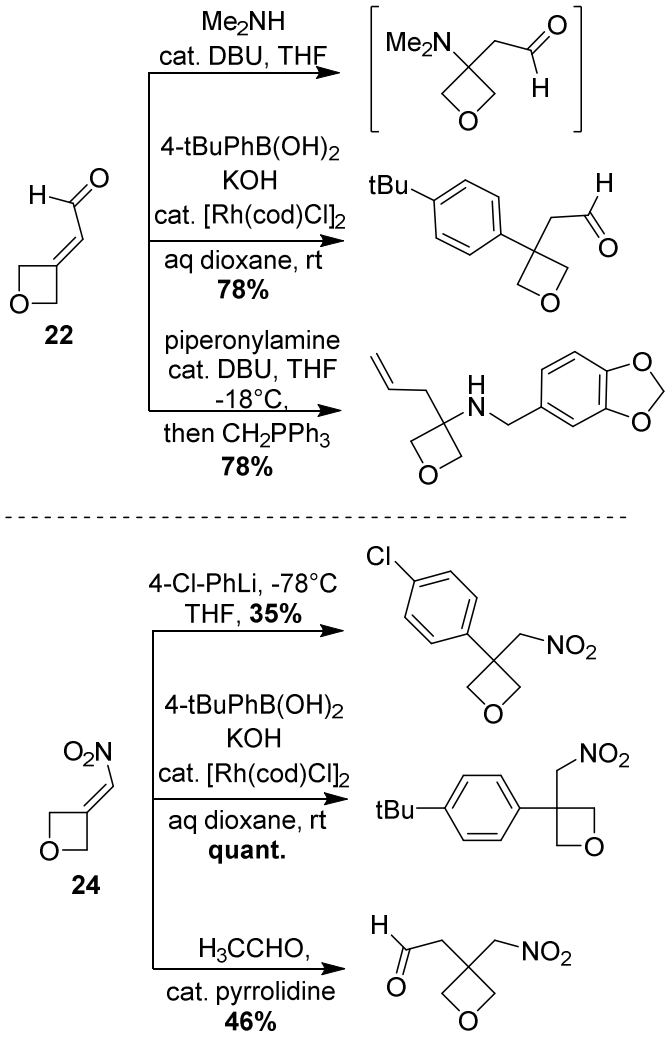
5.2.3. Further elaboration of oxetan-3-one's Michael acceptors

A wide range of 3,3-disubstituted oxetane compounds can be obtained by the elaboration of these Michael acceptors. In fact, the acrylate intermediate (**26**) can undergo conjugate addition with a large range of nucleophiles, such as amines, nitromethane, cyanides, malonates, cuprates, and boronic acids, to form elaborated oxetane scaffolds in good yield (Scheme 1.43).[19]



Scheme 1.43: Further elaboration of acrylate intermediate

The acrolein intermediate compound (**22**) provides unstable β-aminoaldehydes after reaction with an amine. But, in reaction with an arylboronic acid, the acrolein (**22**) provides only the 1,4 addition compound (Scheme 1.44).[19] The nitroolefin intermediate (**24**) can also react with different nucleophiles, such as acetaldehyde, aryllithium reagents, and boronic acids (Scheme 1.44).[19]



Scheme 1.44: Further elaboration of acrolein and nitroolefin intermediates

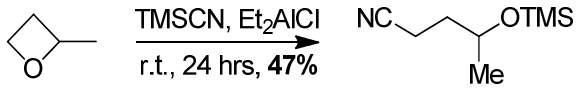
The functional groups on these scaffolds can be useful for further elaborating these structures.

5.3. Ring opening reaction of oxetanes

The oxetane ring can be opened with a strong Lewis or Brönsted acid or at high temperature, but under basic conditions the ring opening reaction of oxetane is slow.

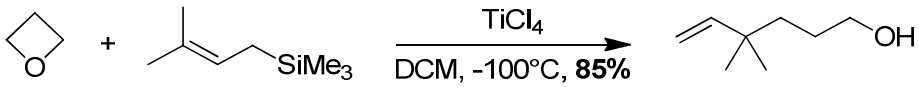
5.3.1. Intermolecular opening reaction

In 1982, Weber *et al.* reported the ring opening of oxetanes with trimethylsilyl cyanide in presence of diethylaluminum chloride (Scheme 1.45).[52] They noticed that the opening of 2-methyloxetane was regioselective providing 4-methyl-4-[(trimethylsilyl)oxy]butyronitrile in 47% yield.



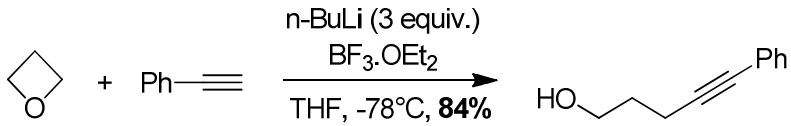
Scheme 1.45: ring opening of oxetanes with trimethylsilyl cyanide

Three years later, Weber and co-workers reported the synthesis of 5-hexen-1-ols from oxetane and allylic trimethylsilanes in presence of titanium tetrachloride (Scheme 1.46).[53]



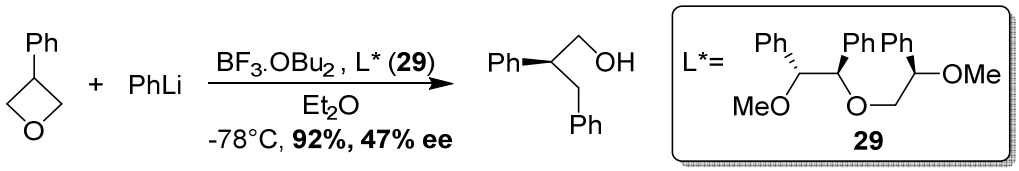
Scheme 1.46: synthesis of 5-hexen-1-ols

In 1983, Yamaguchi reported the preparation of γ-hydroxy-acetylenes from oxetane and metal-acetylide in presence of boron trifluoride in good yield (Scheme 1.47).[54,55]



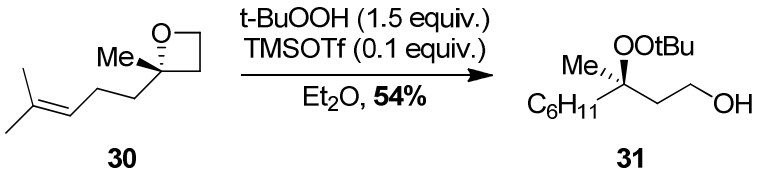
Scheme 1.47: preparation of γ-hydroxy-acetylenes

In 1997, Tomioka reported the enantioselective ring opening of oxetanes (Scheme 1.48).[56] They showed that the treatment of 3-phenyloxetane with phenyllithium in presence of a Lewis acid and a chiral ligand (**29**) provides α,β-diphenyl alcohol with a good yield and a promising ee.



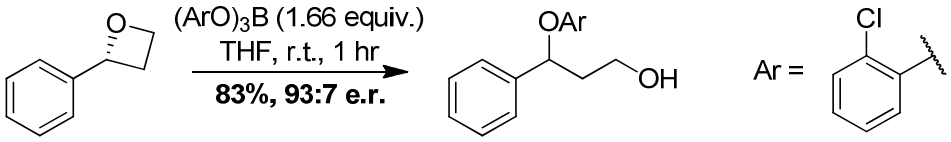
Scheme 1.48: enantioselective ring opening

In 2002, Dussault and co-workers reported the stereoselective ring opening of substituted oxetanes (**30**) with peroxides in presence of Lewis acid to provide corresponding 3-peroxyalkanols (**31**) in moderate yield (Scheme 1.49).[28]



Scheme 1.49: preparation of 3-peroxyalkanols

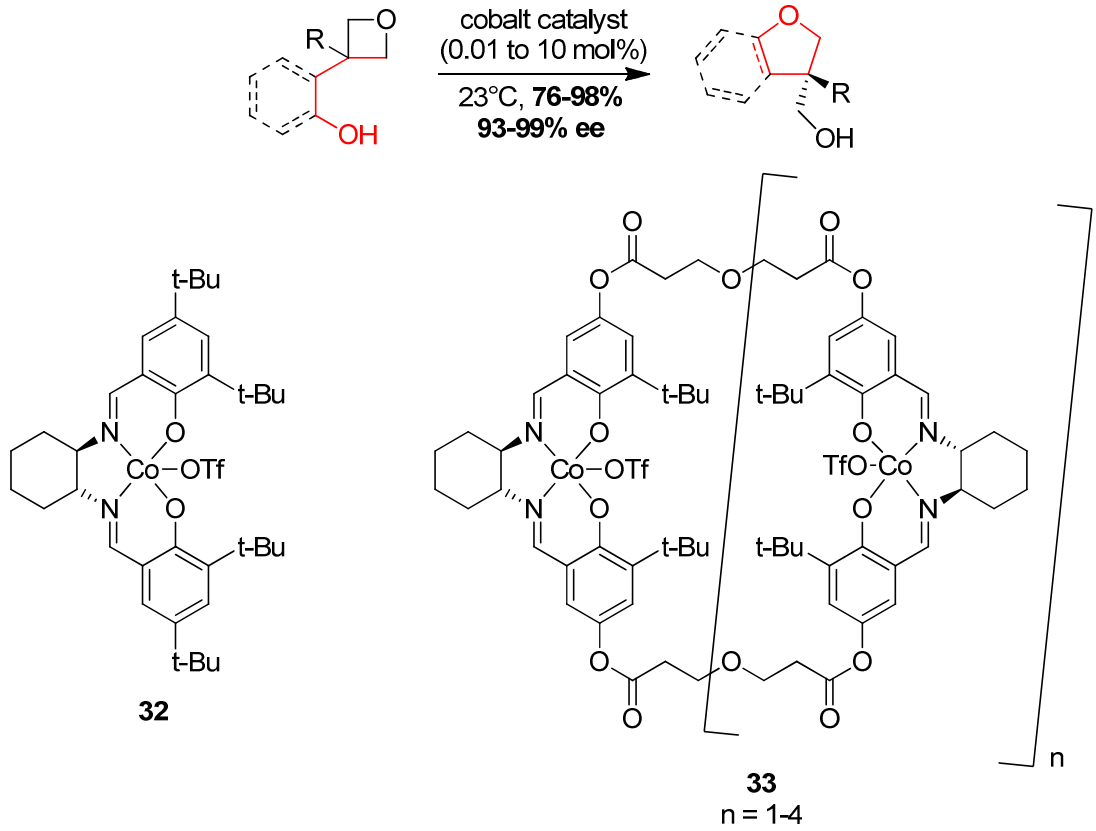
In 2008, Pineschi *et al.* reported the synthesis of 3-aryloxy alcohols by regioselective and stereoselective ring opening reaction of enantioenriched 2-aryloxetanes with arylborates (Scheme 1.50).[57]



Scheme 1.50: synthesis of 3-aryloxy alcohols

5.3.2. Intramolecular ring opening reaction

In 2009, Loy and Jacobsen described the enantioselective intramolecular ring opening of oxetanes (Scheme 1.51).[58] They showed that the treatment of oxetanes which have a pendant hydroxyl group with a catalytic amount of cobalt(III) salen Lewis acids (**32** and **33**), leads to tetrahydrofurans and benzodihydrofurans in high yield and good enantioselectivity.

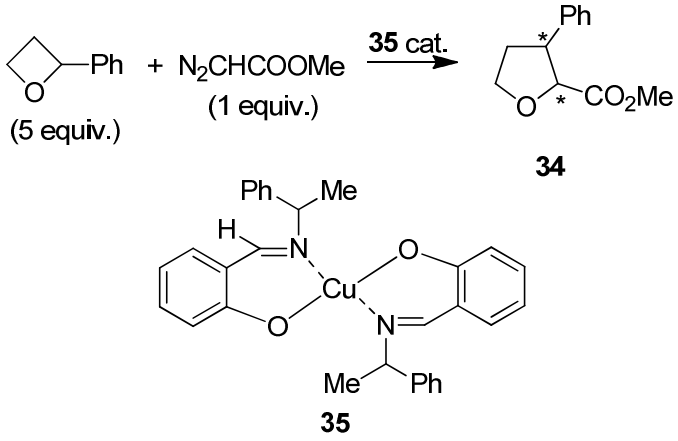


Scheme 1.51: enantioselective intramolecular ring opening

Both catalysts show efficiency for the ring opening reaction. However, the dimer catalyst (**33**) can be used with less than 0.01% loading and exhibits better enantioselectivity than the corresponding monomer (**32**).

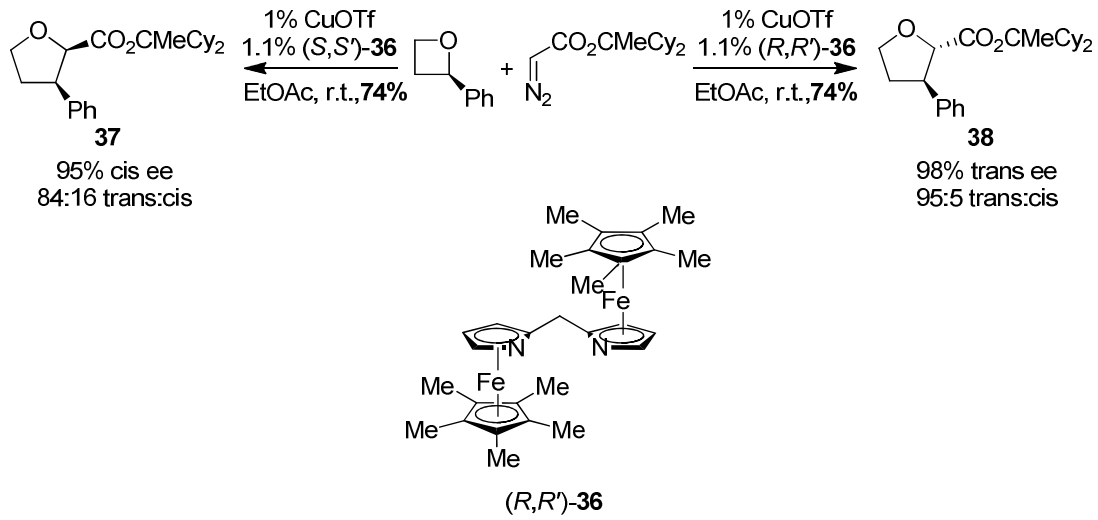
5.4. Ring expansion reaction of oxetanes

In 1966, Noyori and co-workers reported an asymmetric ring expension of 2-phenyloxetane with diazoacetate catalyzed by copper to afford a cis-trans mixture of tetrahydrofurans (Scheme 1.52).[59] The use of the (*R*,*R*)-chelate or (*S*,*S*)-chelate (**35**) provides access to both product enantiomers (**34**).



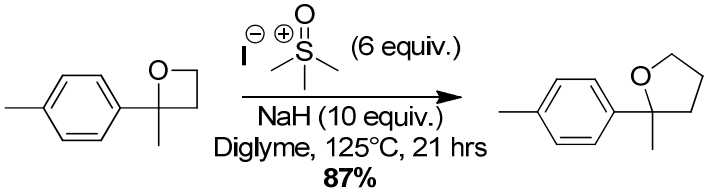
Scheme 1.52: asymmetric ring expension of 2-phenyloxetane

In 2001, Fu *et al.* reported a stereoselective synthesis of tetrahydrofurans from oxetanes catalyzed by a bis(azaferrocene) copper complex (**36**) (Scheme 1.53).[60] They showed that the expansion of enantiomerically enriched 2-substituted oxetanes provides trans-product (**38**) or the cis-diastereomer compound (**37**), depending on the catalyst used.

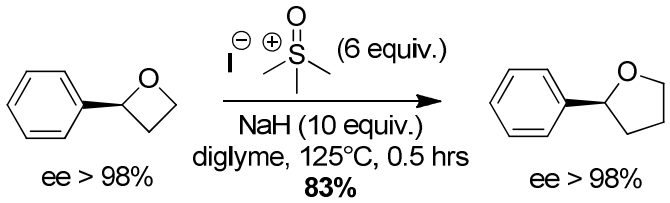


Scheme 1.53: stereoselective synthesis of tetrahydrofurans

The same method of epoxide ring expansion by methyl ylide can be carried out to expand oxetane rings into oxolanes. Fokin and co-workers described the conversion of oxetanes to oxolanes in the presence of dimethylsulfoxonium methylide under heating up to 125°C in moderate to good yield (Scheme 1.54).[45] They also showed the retention of configuration after reaction (Scheme 1.55).



Scheme 1.54: conversion of oxetanes to oxolanes



Scheme 1.55: conversion of oxetanes to oxolanes with retention of configuration

6. Conclusion

The different points highlighted above show that oxetanes are valuable compounds for pharmaceutical research. This has encouraged the development of new methods for the synthesis of oxetane-containing compounds. Among them, the elaboration of oxetane-3-one allows the preparation of various valuable building blocks. These intermediates can be derivatized later to obtain a range of substituted oxetanes. Moreover, new methods have been developed for the enantioselective synthesis of oxetanes. As highlighted in this review, the oxetane ring can also be opened to furnish valuable β-functionalized alcohols or tetrahydrofurans.

Chapter 2: Introduction of oxetane ring into heterocyclic and aromatic scaffolds

1. Introduction

Since their discovery by Earl and Mackney in 1935,[61] sydnones have received an extensive and continued interest over the last century. In fact, their structure, physical properties, reactivities and functionalization have been discussed in numerous reviews.[62] Also, the discovery of useful biological properties of sydnones, such as antibacterial, [63] antineoplastic [64] and anti-inflamatory activities, [65] make them interesting targets and have led to the development of new functionalisation methods.

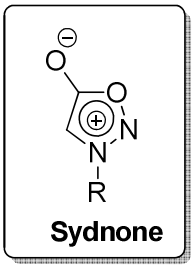
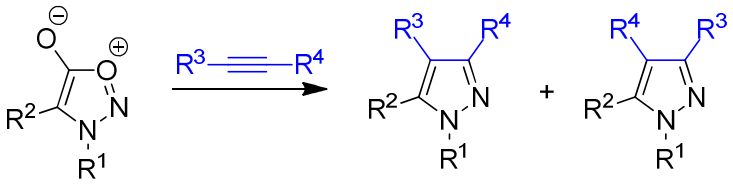


Figure 2.1:

Moreover, sydnones have also attracted significant interest with the discovery of their ability to act as precursors to pyrazoles and related species, through a cycloaddition reaction with alkynes (Scheme 2.1).[66] In fact, these heterocycles are commonly found as biologically active agents,[67] as ligands for transition metal catalysed reactions or in materials chemistry.[68]

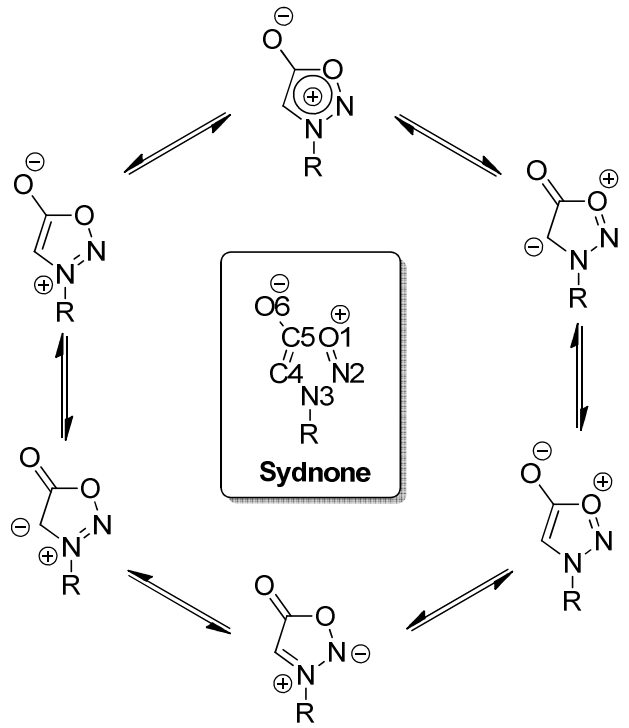


Scheme 2.1: cycloaddition of sydnones with alkynes

2. Properties and synthesis of sydnones

2.1. Properties of sydnones

Sydnones are five membered ring heterocycles belonging to the class of mesoionic compounds. Therefore, a non-charged canonical representation of sydnones cannot be drawn (Scheme 2.2). The electronic distribution and structure of sydnones has been studied but, the recorded data do not offer a single general structure.[69] Nonetheless, sydnones are usually represented by an enolate type exocyclic oxygen and with a positive charge on the endocyclic oxygen.



Scheme 2.2: representation of sydnones

The electronic distribution of sydnones was widely studied by molecular-orbital calculations in several reports (Figure 2.2).[69a] According to the calculation of the bond order (**39**), sydnones can be shown to have enolate type bonding for the exocyclic oxygen. This conclusion is supported by the value of the net charges.

Whereas, the calculated net charges of (**40**)[69b] and (**41**)[69] show some numerical divergence, the bond orders and the relative values of net charges suggest that the positive charge is mainly located on the nitrogen in position 3. The negative charge located on the exocyclic oxygen is also ascribed by the scaled dipole-moment calculated by Coulson.[69d] However, the proton attached to the carbon in position 4 has a pKa of 18-20,[70] which suggests that the conjugate base is stabilized by an adjacent ketone moiety. Moreover, the absorbance peak around 1730 cm^{-1} on the infrared spectra of a range of sydnones suggests the presence of a ketone moiety.

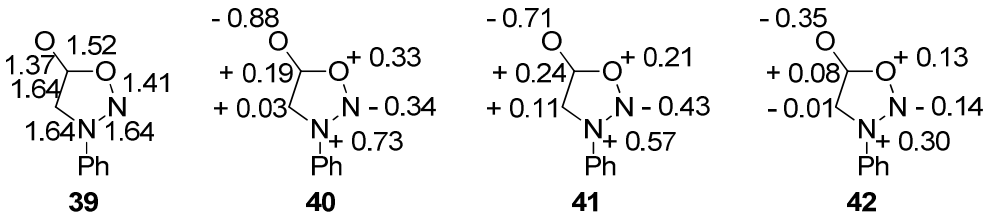


Figure 2.2

Nevertheless, the representation of (**39**), (**40**), (**41**) and (**42**) suggest that the nitrogen in position 3 has iminium-type character, and so, is acting as an electron-withdrawing group on the attached phenyl ring. However, several contrasting reports suggest that the nitrogen is neutral and shares some π-resonance with the attached phenyl ring.[71] With all of these observations, the sydnone ring can be drawn as enolate type bonding for the exocyclic oxygen and with a positive charge located on the endocyclic oxygen. The reactivity profile of sydnones can be summarized in Figure 2.3.

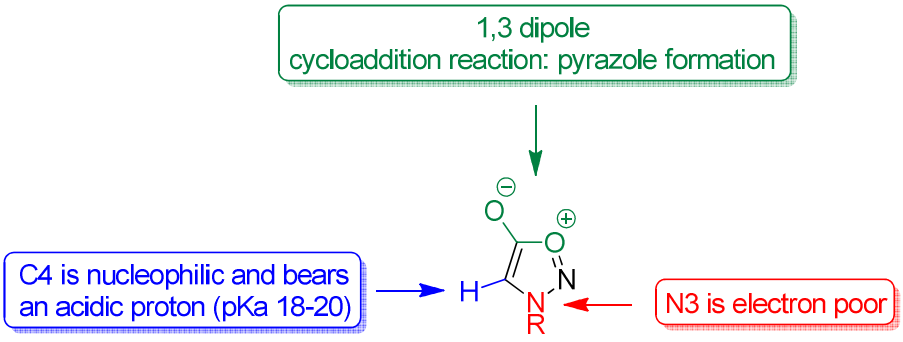
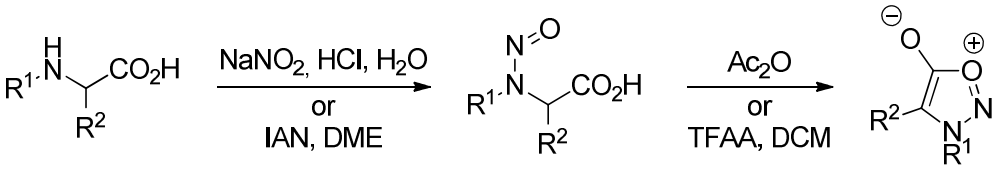


Figure 2.3

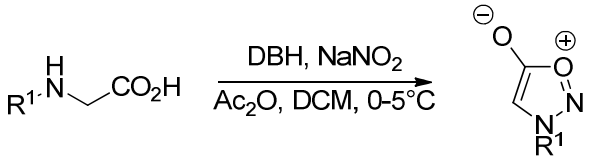
2.2. Synthesis of sydnones

Sydnones are classically synthesized in 2 steps from the corresponding substituted amino-acids (Scheme 2.3). The amino-acid is first nitrosated to form an *N*-alkyl or *N*-aryl *N*-nitroso-α-amino acid, which is then cyclodehydrated to form the mesoionic compound. The substituent R^1 cannot be hydrogen as these compounds form a diazonium salt during the nitrosation. The *N*-nitrosation step is often accomplished using sodium nitrite and concentrated hydrochloric acid in water. The nitrosamine intermediate is then usually heated in an excess of acetic anhydride to produce the cyclodehydrated compound. Alternatively, for acid-sensitive starting materials, Turnbull *et al.* have described the use of IAN (isoamyl nitrite) for the nitrosation step.[72] Moreover, to increase the rate of cyclisation, trifluoroacetic anhydride can be used instead of acetic anhydride.[73] Most sydnones are solids, air-stable and have been synthesized in quantities of up to 100 g.[74]



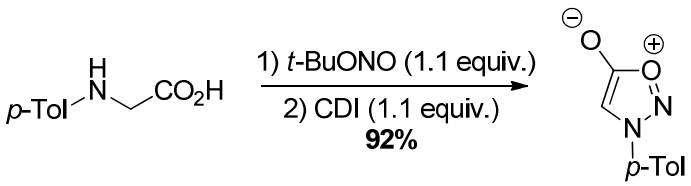
Scheme 2.3: Synthesis of sydnones

Azarifar *et al.* have reported an alternative nitrosation step avoiding the use of strong acid by employing dibromo-dimethylhydantoin (DBH) (Scheme 2.4).[75] This one-pot approach permits the use of a catalytic amount of DBH and avoids the isolation of the nitrosamine intermediate. Moreover, they have reported the one-pot synthesis of several sydnones in good yield.



Scheme 2.4:

Recently, Taran and co-workers have also reported the one-pot synthesis of sydnones from arylglycines without the isolation of the nitrosamine intermediate using CDI (Scheme 2.5).[76]



Scheme 2.5: one-pot synthesis of sydnones

3. Functionalization of sydnones at the C4 position

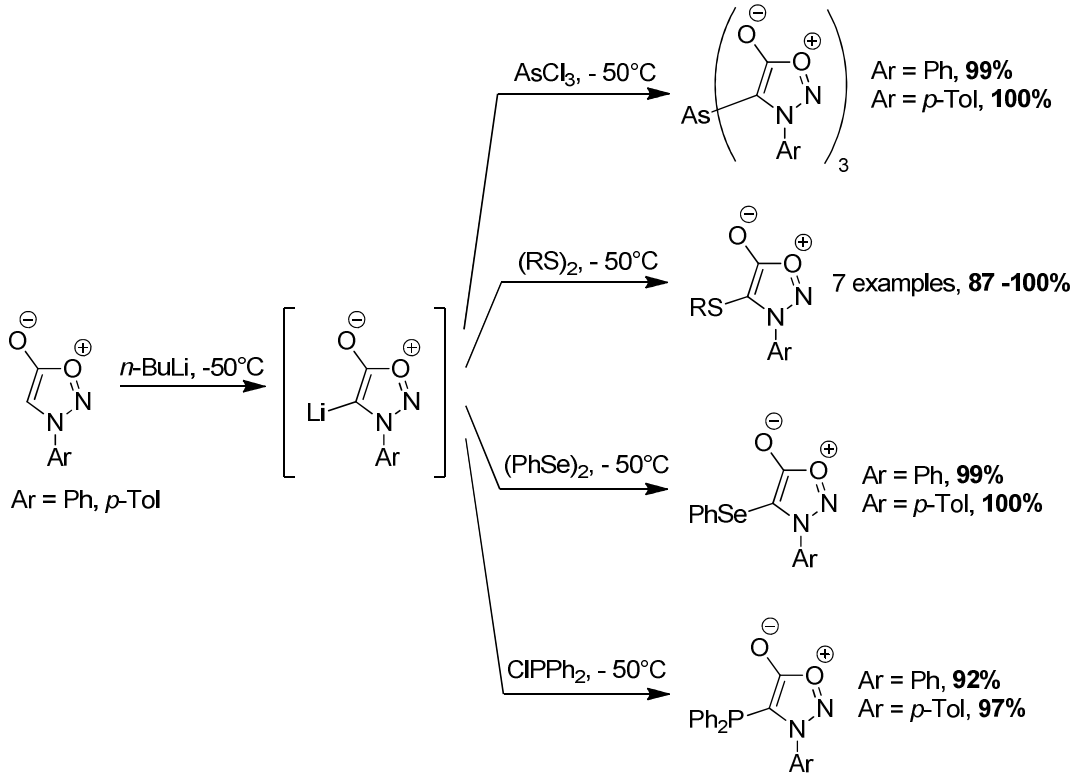
C4 substituted sydnones have been extensively studied, and are easily accessed from a range of α-substituted amino-acids that are either commercially available or easily synthesized. However, for the preparation of a library of sydnones, a divergent strategy would be more efficient than the linear nitrosation-cyclodehydration route. For this purpose, different methods have been reported for the homologation of sydnones at C-4 using either the inherent nucleophilicity of the carbon in position 4, or the acidicity of the proton. Specifically, two type of functionalisation can be considered:

- Deprotonation followed by electrophilic addition
- Electrophilic aromatic substitution

3.1. Deprotonation followed by electrophilic addition

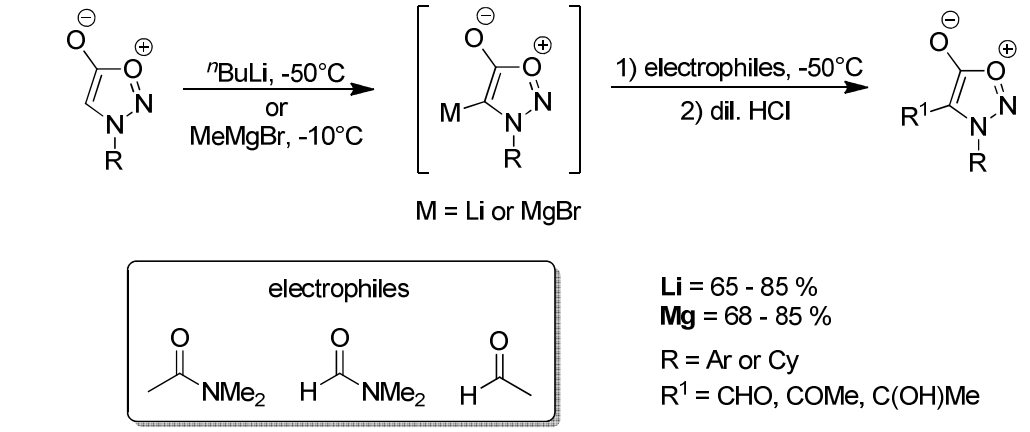
The acidity of the proton at C4 offers the opportunity to carry out direct functionalization at this position. The deprotonation step can be followed by the addition of an electrophile, potentially after a transmetalation step, to allow further chemistry to take place. In this way, lots of reports have described the functionalisation of sydnone by the method of deprotonation.

Fuchigami *et al.* have reported the synthesis of arylthio, alkylthio, selenide, arsenide and phosphide derived sydnones by this method (Scheme 2.6). The corresponding sydnones was deprotonated by treatment with *n*-butyllithium followed by the addition of the electrophile.



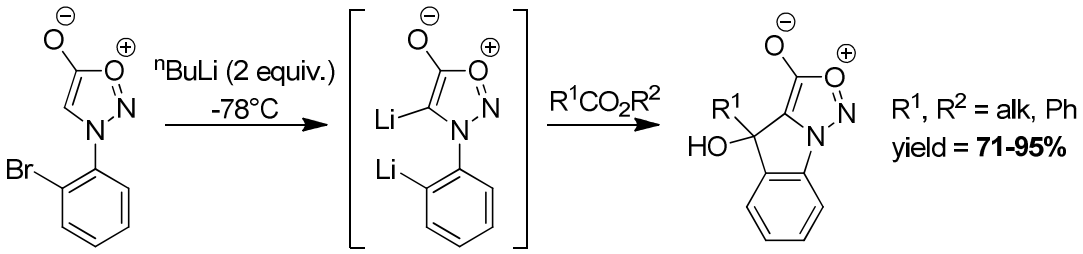
Scheme 2.6:

The introduction of carbonyl group at position 4 was described by Tien and co-workers (Scheme 2.7).[77] They have also reported the use of methyl magnesium bromide to generate the sydnone anion followed by quenching with an electrophile.

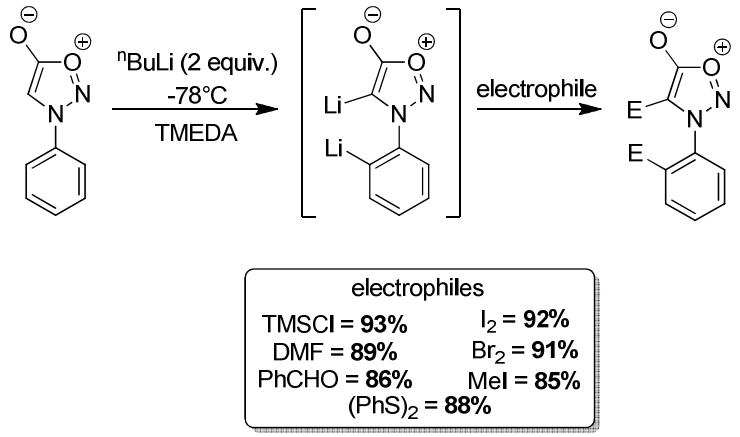


Scheme 2.7:

Turnbull *et al.* have reported the formation of fused tricyclic sydnone by dilithiation of 3-(2-bromophenyl)sydnone followed by treatment with an electrophile (Scheme 2.8).[78] They also demonstrated that the treatment of a non-halogenated sydnone with butyllithium in presence of TMEDA followed by the treatment with an electrophile provides di-halogenated-, di-alkylated- or dithioether-substituted products in good yield (Scheme 2.9).[79]

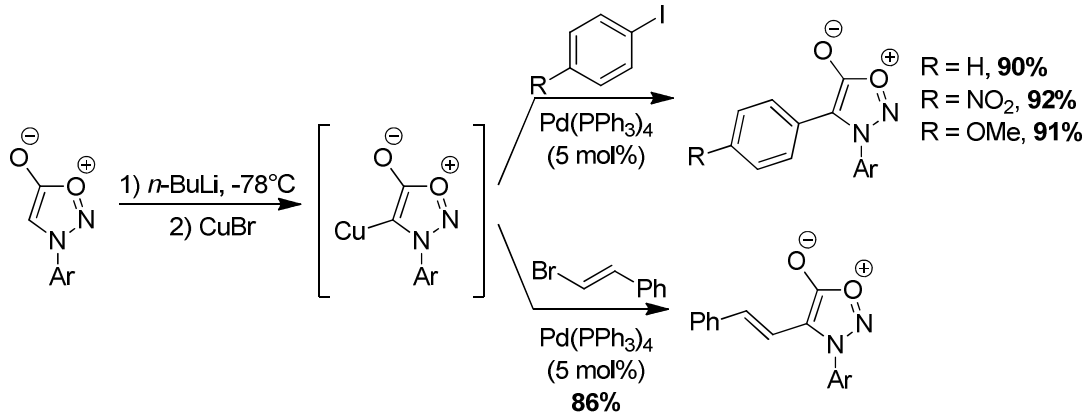


Scheme 2.8



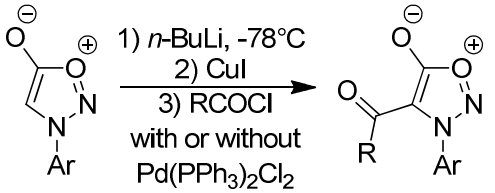
Scheme 2.9

Kalinin *et al.* have shown that the lithiated sydnone intermediate can be transmetalated by copper salts to generate the corresponding organocopper reagent. The sydnonylcopper intermediate can undergo palladium-catalysed coupling with alkenyl and aryl halides (Scheme 2.10).[80]



Scheme 2.10

Turnbull then extended this methodology to introduce an acyl and an aryl group in position 4 on the sydnone ring (Scheme 2.11).

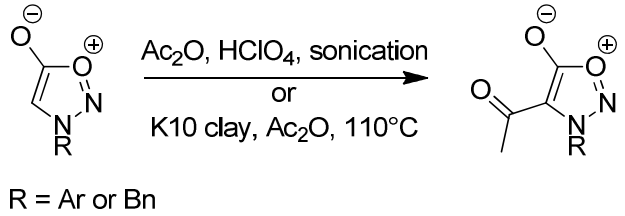


R	Yield (with [Pd])	Yield (without [Pd])
Me	97	86
Ph	96	93
4-ClC_6H_4	78	82
4-$MeOC_6H_4$	80	51
4-$NO_2C_6H_4$	38	56
Bn	63	95

Scheme 2.11

3.2. Electrophilic aromatic substitution

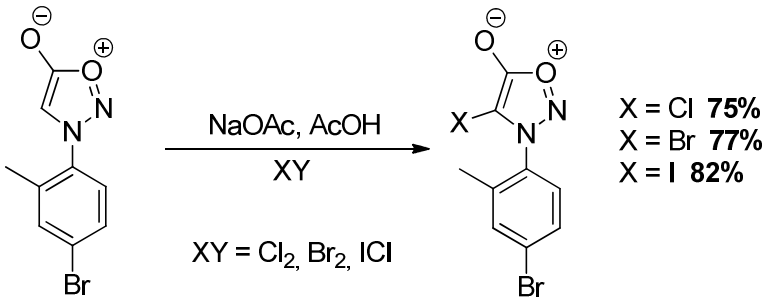
Tien and co-workers have reported the direct acylation of sydnones using perchloric acid and acetic anhydride under sonication conditions (scheme 2.11).[81] Furthermore, Turnbull *et al.* have developed an acylation process using heterogeneous clay-catalyst system (Scheme 2.12).[82] They have also reported the synthesis of related carbonyl compounds. Of particular interest, they described the synthesis of primary amide-sydnone using chlorosulfonyl isocyanate (Scheme 2.13).[83]



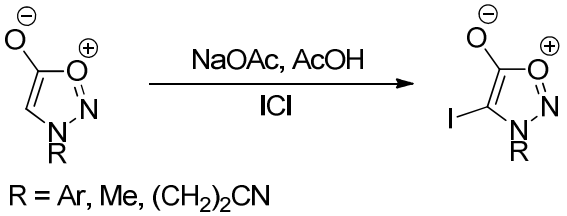
Scheme 2.12

Scheme 2.13

Halogenated sydnones provide a good alternative substrate for the synthesis of functionalized products. Dumitrașcu and co-workers have reported the synthesis of C4 halo-sydnones using a source of electrophilic halogen, acetic acid and sodium acetate (Scheme 2.14).[84] Under these conditions, a range of *N*-aryl and *N*-alkyl sydnones can be tolerated and furnished the 4-iodo sydnone in good to excellent yields with halogens, carboxylic acid, ethers, nitriles and esters on the *N*-aryl substituent (Scheme 2.15).

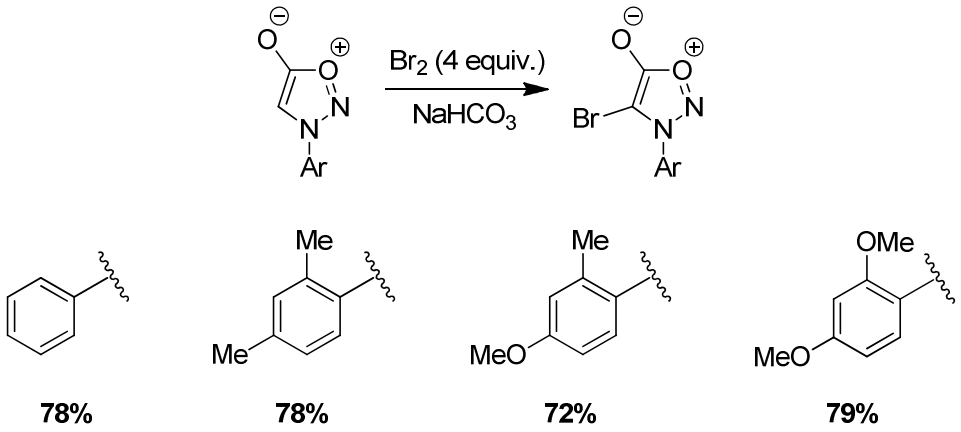


Scheme 2.14



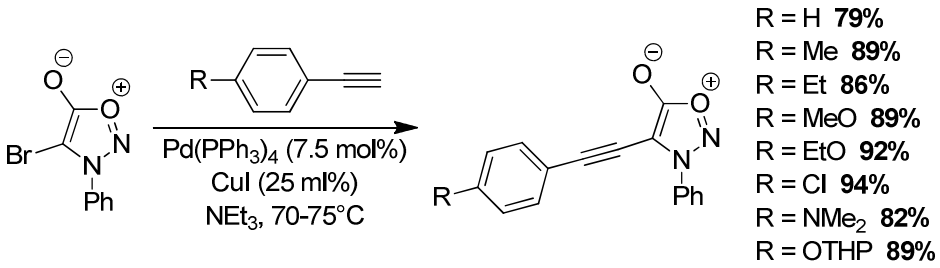
Scheme 2.15

The bromination reaction of sydnones has been widely studied. Kato and Turnbull have found that the use of bromine and sodium bicarbonate furnishes the brominated *N*-arylsydnone in good yield (Scheme 2.16).[85] Interestingly, it was demonstrated that for 3-aryl sydnones, the majority of electrophiles undergo substitution on the sydnone ring and not on the 3-aryl ring. This is due to the electron-withdrawing effect of the N3 which bears a significant positive charge and so deactivates the aryl substituent.



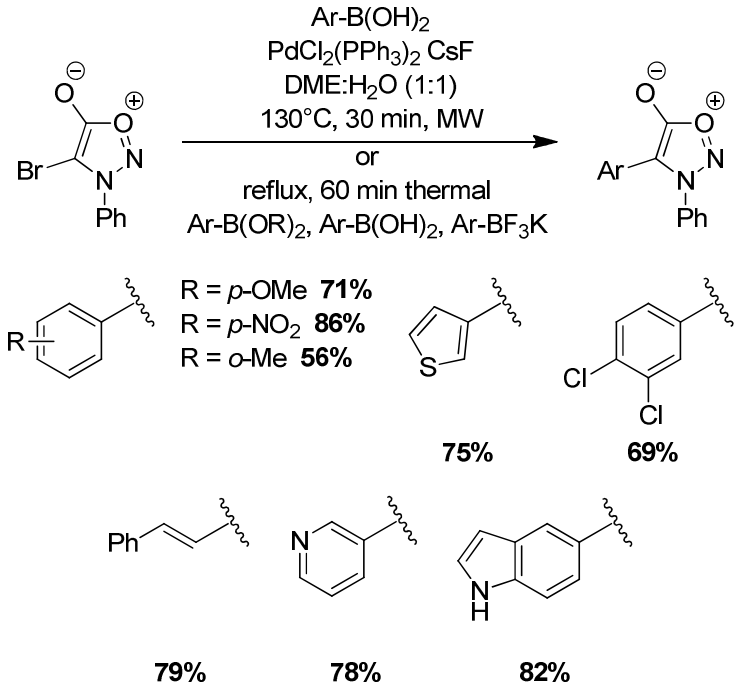
Scheme 2.16

4-Bromosydnones can be employed in transition metal catalysed cross-coupling reactions. For example, Turnbull and co-workers have reported Sonogashira coupling of 4-bromo-phenylsydnones catalysed by palladium affording 4-alkynylsydnones in good yield (Scheme 2.17).[86]



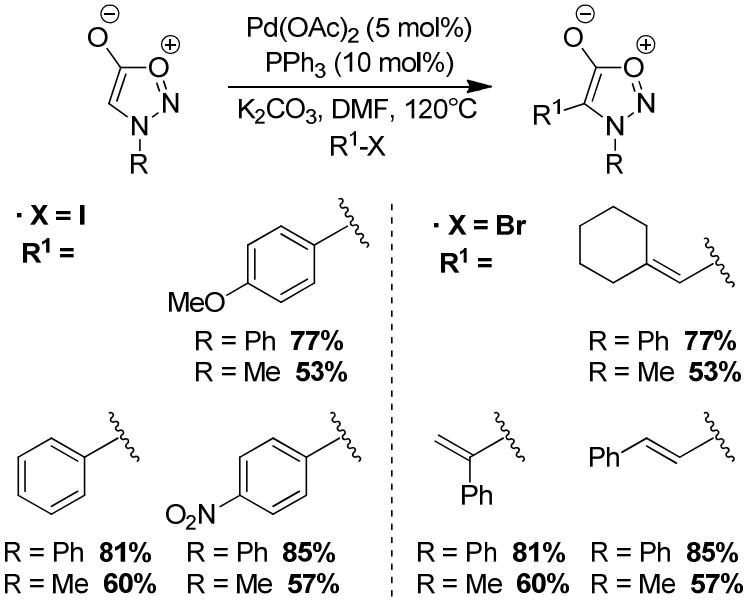
Scheme 2.17

Recently, the Harrity group has investigated the synthesis of 4-arylsydnones from 4-bromosydnones via Suzuki-Miyaura cross-coupling (Scheme 2.18).[87] A range of boron-derivatives can efficiently undergo the coupling step in good yield under various conditions. It was shown that arylboronic acids, esters and trifluoroborates can be coupled under microwave and thermal conditions to furnish the desired coupled products in good yield.



Scheme 2.18

In the last few years, Moran and co-workers have described the direct alkenylation, alkynylation and arylation at the C-4 position of sydnones (Scheme 2.19).[88] With this method, a range of aromatic iodide and bromo-alkene compounds can be coupled in moderate to good yield.

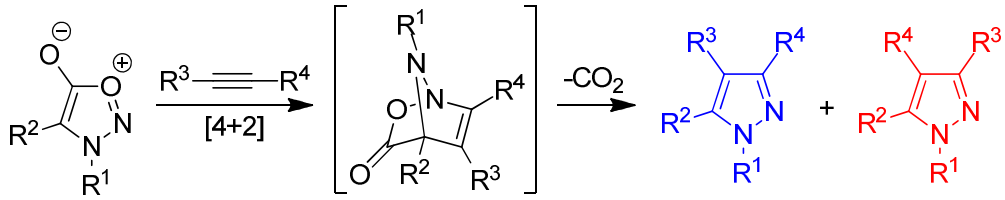


Scheme 2.19

4. Cycloaddition reactions

Sydnones can undergo cycloaddition reactions with alkynes and alkenes to furnish pyrazoles and pyrazolines with loss of carbon dioxide.

The cycloaddition-retrocycloaddition of sydnones with alkynes was first reported by Huisgen in 1962 (Scheme 2.20).[66] They demonstrated that the reaction is compatible with various hydrocarbon-substituted alkynes. It was also shown that a range of functional groups such as acetal, alcohol, ester and acyl can be tolerated under these conditions.



· R^1 = Ph, R^2 = H

R^3	R^4	Yield
H	H	75%
H	Ph	79%
Me	Ph	74% (1:1)
H	CO_2Me	92% (3:1)
CO_2Me	CO_2Me	92%

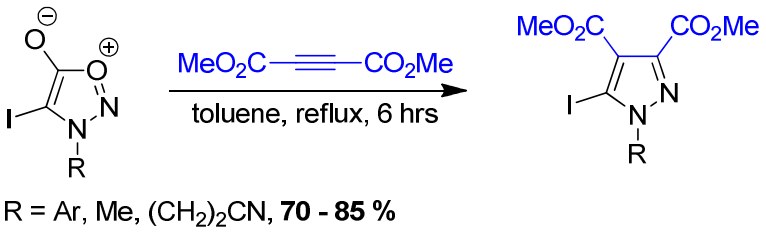
· R^1 = Ph, R^2 = Me

R^3	R^4	Yield
H	Ph	79% (4:1)
Ph	Ph	97%
CO_2Me	CO_2Me	99%

Scheme 2.20

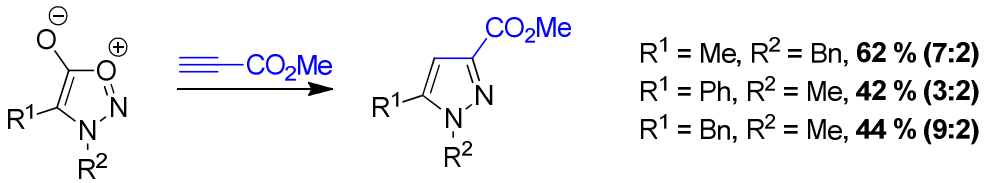
Pyrazoles have attracted significant interest in the last few years due to their potential biological activity. For this reason, the cycloaddition reaction between sydnones and alkynes has attracted particular interest and new methodologies to impact on the reaction regiocontrol have been developed.

Usually, electron-poor alkynes are used in the cycloaddition reaction of sydnones.[89] As shown in Scheme 2.21, dimethyl acetylenedicarboxylate undergoes the cycloaddition reaction with 4-iodo-*N*-arylsydnones in good yield.

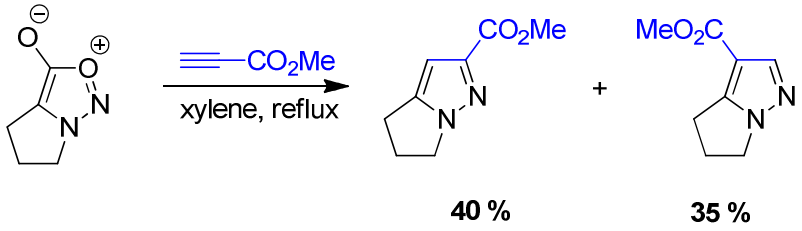


Scheme 2.21

Moreover, unsymmetrical alkynes can also be used to furnish orthogonally functionalized pyrazoles, although this brings the added complication of reaction regioselectivity. For example, Padwa and co-workers have investigated the regioselectivity of the reaction between a range of C4-substituted sydnones and methyl propiolate (Scheme 2.22).[90] It was shown that the reaction proceeds in moderate yield and with modest regioselectivity. However, the favoured isomer was in all cases, the 3,5-disubstituted pyrazole. Later, Ranganathan *et al.* demonstrated that the cycloaddition of proline-derived sydnones with methyl propiolate proceeded in high yield but with little regiocontrol (Scheme 2.23).[91]



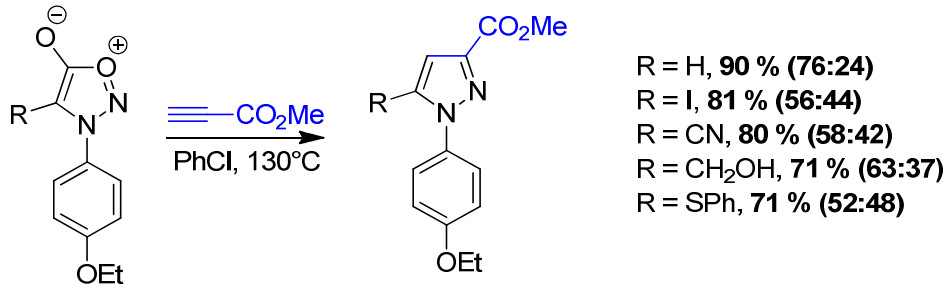
Scheme 2.22



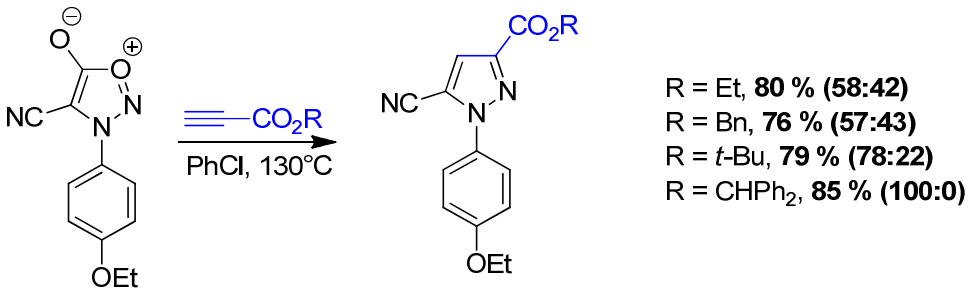
Scheme 2.23

In order to understand the low regiocontrol in the cycloaddition of propiolate compounds with sydnones, Wong and co-workers have studied the influence of the

substituent in the position 4 on the sydnone ring and size of the ester group (Scheme 2.24).[92] It was demonstrated that the cycloaddition of a range of 4-substituted sydnones with methyl propiolate furnishes the corresponding 3,5-disubstituted isomer with low or moderate regioselectivity. However, an improvement of regiocontrol was observed when the size of the ester substituent was increased (Scheme 2.25). Indeed, complete regiocontrol was observed when diphenylmethyl propiolate was used.

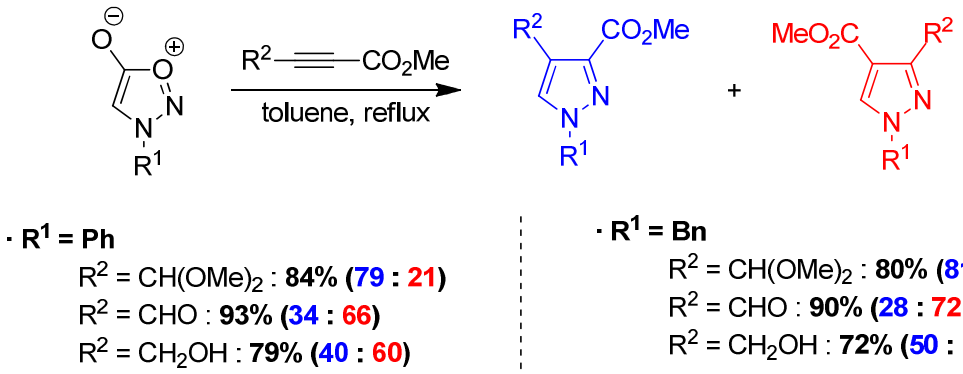


Scheme 2.24



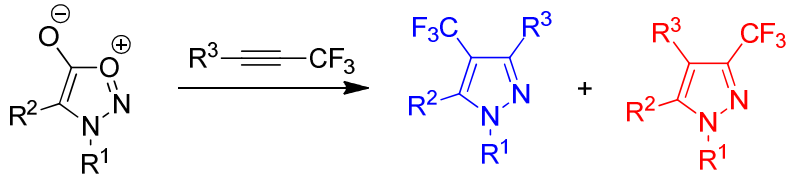
Scheme 2.25

Fariña *et al.* have investigated the regioselectivity of the cycloaddition reaction of substituted alkynyl esters and sydnones (Scheme 2.26).[93] They have observed an inversion of the regioselectivity when propiolates bearing aldehydes, acetal or carbinol groups were employed. Cycloaddition of propiolates bearing an acetal group furnished preferentially the 3-ester pyrazole. However, the cycloaddition of propiolates bearing an acetal group furnishes the 4-ester pyrazole as the major product. Nevertheless, no or low regiocontrol is obtained by using a propiolate bearing a carbinol substituent.



Scheme 2.26

Good regiocontrol has been obtained in cycloaddition reactions of acetal-substituted propionitriles,[93] α-β-acetylenic ketones[94] and trifluoromethyl-substituted alkynes.[95] Interestingly in the latter case, the formation of 4-CF_3 substituted pyrazoles was favoured even in the case of C4-substituted sydnones (Scheme 2.27).

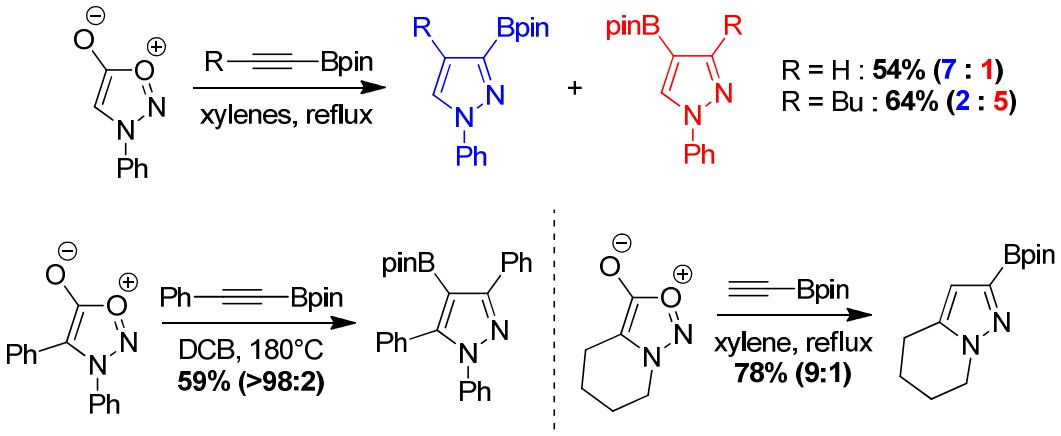


R^1	R^2	R^3	Yield (%)
Ph	H	4-$MeOC_6H_4$	56 (93 : 7)
Ph	H	4-$O_2NC_6H_4$	93 (93 : 7)
4-$MeOC_6H_4$	H	4-ClC_6H_4	84 (93 : 7)
Bn	H	4-ClC_6H_4	65 (91 : 9)
t-Bu	H	4-ClC_6H_4	58 (93 : 7)
Ph	Me	4-ClC_6H_4	75 (84 : 16)
Ph	4-ClC_6H_4	4-ClC_6H_4	57 (60 : 40)
Ph	Br	4-ClC_6H_4	43 (71 : 29)
Ph	MeS	4-ClC_6H_4	62 (43 : 57)

Scheme 2.27

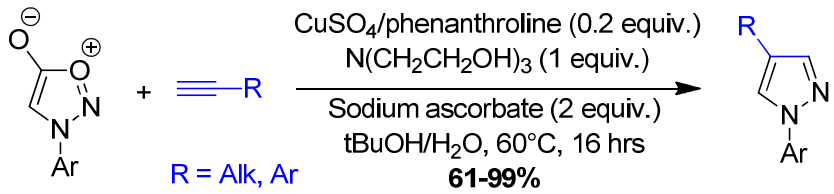
These last few years, the Harrity group has developed a methodology to access pyrazoleboronic ester compounds directly via the cycloaddition of sydnones and alkynylboronates (Scheme 2.28).[96] This method can allow a further functionalisation of the pyrazoles by established organoboron chemistry.

They have demonstrated that the cycloaddition between 4-unsubstituted *N*-phenyl-sydnones and terminal alkynylboronates provides the corresponding 3-borylated pyrazoles in good regioselectivity, while moderate selectivities were obtained using substituted alkynes (Scheme 2.28). Interestingly, an inversion of selectivity was observed when terminal alkynes were used. However, 4-substituted sydnones generally provide the corresponding pyrazoles with good regiocontrol (Scheme 2.28).



Scheme 2.28

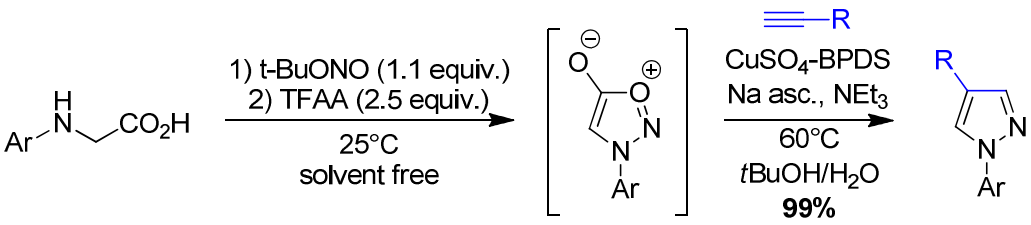
Recently, Taran *et al.* have reported the regioselctive synthesis of 1,4-pyrazoles using arylsydnones and terminal alkynes catalysed by copper-(I)-phenanthroline complexes under mild and environmentally friendly conditions (Scheme 2.29).[97] Their method has associated advantages of chemoselectivity and biocompatibility associated with click type processes.



Scheme 2.29: Cu(I)-catalysed synthesis of 1,4-pyrazoles from arylsydnones

They have also reported the one-pot synthesis of 1,4-pyrazoles from arylglycines without the isolation of the intermediate sydnones.[97] Optimization studies showed

that nitrosation and cyclisation using TFAA followed by Cu-catalyzed alkyne cycloaddition allowed the formation of pyrazole in 'one-pot' from the glycine starting material in good yield (Scheme 2.30).



Scheme 2.30: 'one-pot' synthesis of 1,4-pyrazoles

5. Aims

In the past few years, the Harrity group has studied the cycloaddition reactions of a range of alkynes and sydnones to form a library of pyrazoles. In an effort to expand the scope of this methodology, the introduction of an oxetane ring to a sydnone moiety offers a promising concept for the synthesis of a range of pyrazoles containing this useful *O*-heterocycle fragment (Figure 2.4).

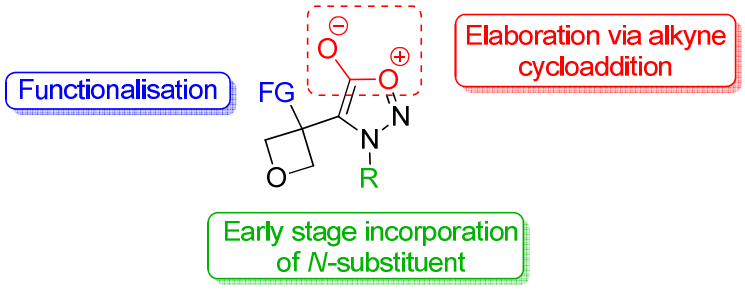
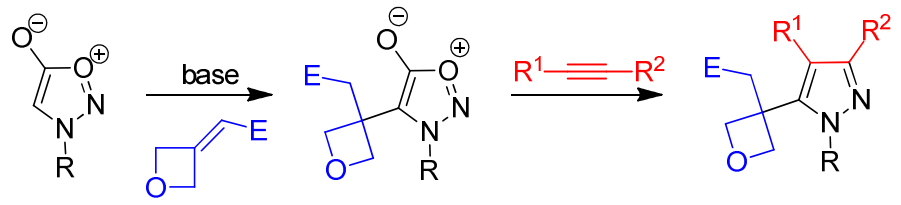


Figure 2.4

Indeed, using the acidity of the proton at C-4 of the sydnone ring, the sydnone can be easily deprotonated and an electrophilic oxetane related compound can be added to furnish a C-4 oxetane substituted sydnone moiety. This 4-substituted sydnone can then undergo a cycloaddition process with different alkynes to furnish pyrazoles

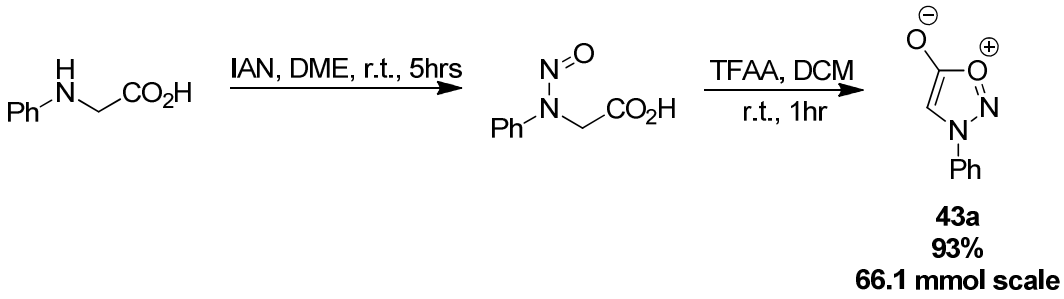
(Scheme 2.31). Also, this method has the potential to provide an interesting divergent strategy for the elaboration of a library of oxetane containing pyrazoles.



Scheme 2.31: Strategy

6. Investigations on the introduction of an oxetane ring into a sydnone

The first goal was to investigate an efficient method for coupling the oxetane ring to the sydnone C4 position. *N*-Phenyl sydnone **43a** was chosen for the optimization studies as it can be prepared in two steps on multi-gram scale from commercially available *N*-phenylglycine in high yield (Scheme 2.32).



Scheme 2.32: Synthesis of phenylsydnone

N-Phenylglycine was first nitrosated with IAN in DME at room temperature following Turnbull's methodology.[72] The nitrosamine intermediate was then treated with TFAA in DCM to promote the cyclodehydration and furnish the desired sydnone **43a** in good yield after concentration and recrystallisation in ethanol. Due to the carcinogenic properties of the nitrosamine intermediate, it was not isolated or characterised.

The next task was to investigate the introduction of the oxetane ring. We began with a model study using cyclohexanone in place of 3-oxetanone for the optimization studies because of the ready availability and lower cost of the larger ring compound.

6.1. Investigation of the introduction of cyclohexanone derivatives

6.1.1. Synthesis of cyclohexanone electrophiles

For the optimization studies, two cyclohexanone derived electrophiles were chosen: an α,β-unsaturated ester **44** and an α,β-unsaturated nitro compound **45** (Figure 2.5).

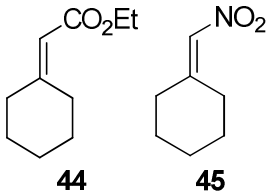
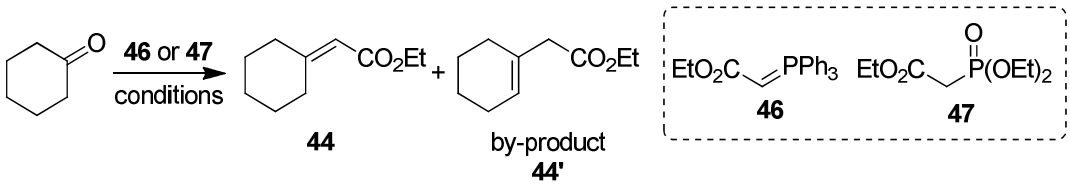


Figure 2.5: cyclohexanone derived electrophiles

The unsaturated ester intermediate (**44**) was synthesized from cyclohexanone using Wittig reagents. The conditions described by Rogers-Evans, Müller, and Carreira using 3-oxetanone with the Wittig reagent (**46**) in dichloromethane did not provide the desired cyclohexene ester intermediate (Entry 1).[19, 20] Pleasingly however, the conditions reported by Ando using the Wittig reagent **47** provided the desired compound **44** in 46% yield (Entry 2).[98] Unfortunately, the compound was contaminated by 25% of an inseparable by-product (**44'**). To optimize the reaction, the previous conditions were examined with the reagent (**46**) instead of (**47**) (Entry 3). Unfortunately, no product was isolated, and the reaction led to the recovery of the starting material. When K_2CO_3 was used instead of Cs_2CO_3 with the Wittig reagent (**47**), no improvement was observed (Entry 4). However, the product was obtained

with 62% and 36% respectively, and with no by-product (Entry 5 and 6) following the conditions described by Gilmore [99] or Hiatt [100].



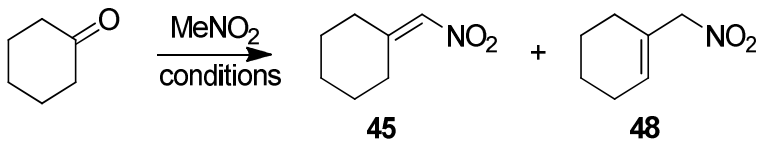
Entry	Wittig reagent	Conditions	Yield (44:44')
1	**46** [a]	DCM, r.t., 2 days	No reaction
2	**47** [b]	DBU (1.5 equiv.), Cs_2CO_3 (1.2 equiv.), r.t., 1 day	46% (4 :1)
3	**46** [b]	DBU (1.5 equiv.), Cs_2CO_3 (1.2 equiv.), r.t., 2 days	No reaction
4	**47** [b]	DBU (1.5 equiv.), K_2CO_3 (1.2 equiv.), r.t., 4 days	44% (3.3 : 1)
5	**46** [b]	Toluene, reflux, o/n	62% (1 : 0)
6	**46** [b]	NaH (1.05 equiv.), DME, r.t., o/n	36% (1 : 0)

[a] using 1.1 equiv. of Wittig reagent; [b] using 1.2 equiv. of Wittig reagent.

Table 2.1: Optimisation studies for the synthesis of **44**

We planned to prepare the unsaturated nitro intermediate (**45**) using nitromethane. The first attempt using the conditions described by Rogers-Evans, Müller, and Carreira employing nitromethane in presence of triethylamine, and then methanesulfonyl chloride and triethylamine did not provide the desired nitro compound (Entry 1). Using the same conditions at a higher temperature did not provide the desired compound either (Entry 2). In fact, 16% of a mesylated compound was recovered. Yao and co-workers have described a one-pot method to synthesize 2,2-disubstituted 1-nitroalkenes (Entry 3 and 4).[101] Unfortunately, this method did not provide the desired product. Wall *et al.* described a method to form nitroalkenes using nitromethane with a sodium base to form a β-hydroxy nitro intermediate, which was then treated with acetyl chloride and sodium carbonate to furnish the desired compound.[102] To obtain the hydroxyl intermediate, two bases were tested: sodium methoxide and sodium hydroxide. Unfortunately, using sodium methoxide, no hydroxyl intermediate was observed (Entry 5). In contrast, the use of sodium hydroxide provided the desired addition product, however, after treatment with acetyl chloride and sodium carbonate, the isomer **48** of the desired nitroalkene

45 was obtained in 19% overall yield (Entry 6). Attempts to prepare **45** were subsequently abandoned.



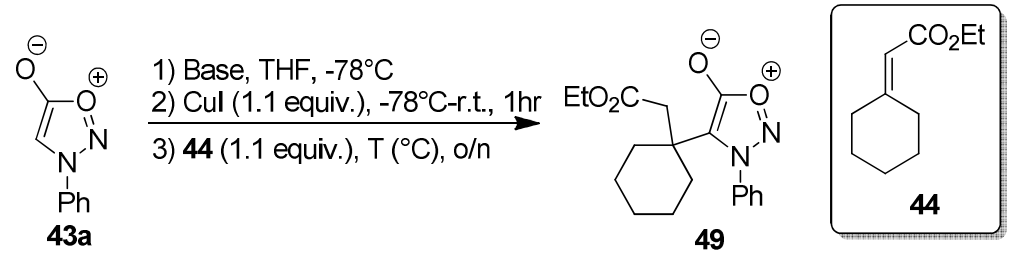
45 **48**

Entry	Conditions	Outcome
1	1) $MeNO_2$ (20 equiv.), NEt_3 (cat.), r.t., 2 hrs 2) MsCl (3 equiv.), NEt_3 (4.4 equiv.), DCM, -78°C-r.t.	No reaction
2	1) $MeNO_2$ (1.1 equiv.), NEt_3 (0.2 equiv.), r.t., 1.5 hrs 2) MsCl (1.1 equiv.), NEt_3 (2 equiv.), THF, r.t.-40°C, 2 days	SM and 16% of mesylated product obtained
3	$MeNO_2$, piperidine, $PhCH_2SH$, MeCN, reflux	Complex mixture
4	1) $MeNO_2$, piperidine, $PhCH_2SH$, MeCN, reflux 2) mCPBA (4 equiv.), $(CH_2Cl)_2$, reflux, 1 day	Complex mixture
5	$MeNO_2$, CH_3ONa (1.1 equiv.), r.t.	No reaction
6	1) $MeNO_2$ (10 equiv.), NaOH (1.1 equiv.), r.t. 2) AcCl (exc.), r.t., 2 hrs 3) Na_2CO_3 (1.1 equiv.), THF, reflux, o/n	No product 19% of **48**

Table 2.2: Optimisation studies for the synthesis of **45**

*6.1.2. Investigations of the conjugate addition of phenylsydnone **44** to cyclohexenone derivative **44***

Using the acidity of the proton at C-4 of the sydnone ring, the coupling of *N*-phenylsydnone **43a** and the cyclohexenone **44** was attempted. Disappointingly, using general conditions of deprotonation with a Grignard reagent (Entry 1 and 2) followed by the addition of the electrophile, no desired product was obtained. The use of a lithium base instead of a Grignard in presence of a Lewis acid (Entry 3) also failed to furnish the desired product.[103] In all cases the starting sydnone was recovered.

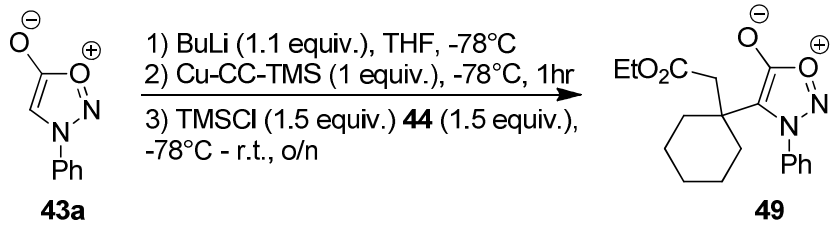


Entry	Base	T (°C)	Outcome
1	MeMgBr	r.t.	No reaction
2	MeMgBr	Reflux	No reaction
3	*n*-BuLi [a]	Reflux	No reaction

[a] $BF_3.OEt_2$ (1.1 equiv.) was added

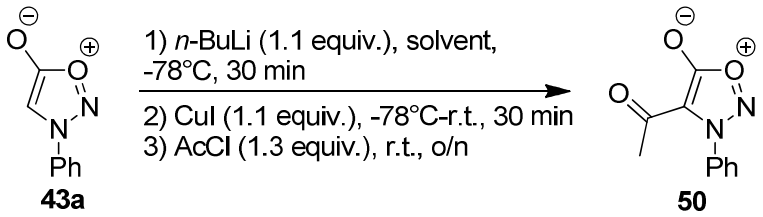
Table 2.3: Conjugate addition attempts

The conditions developed by Kuwajima using a combination of chlorotrimethylsilane and a copper (I) trimethylsilylacetylide reagent to accelerate the 1,4-addition reaction between an α,β-unsaturated ester and an alkyllithium were attempted without success (Scheme 2.33:).[104] In this case, no desired product **49** and no starting sydnone compounds **44** were recovered.



Scheme 2.33:

In order to explore the efficiency of the addition of electrophiles to sydnones, Turnbull's conditions were tested in two different solvents. The desired acetylated phenyl sydnone **50** was obtained in 49% yield when the reaction was carried out in THF. In contrast, this reaction failed when carried out in CH_2Cl_2 (Table 2.4). In the context of the cyclohexenone conjugate addition studies outlined earlier, these results suggest that the deprotonation step occurs but not the 1,4-addition on the α,β-unsaturated ester **44**.

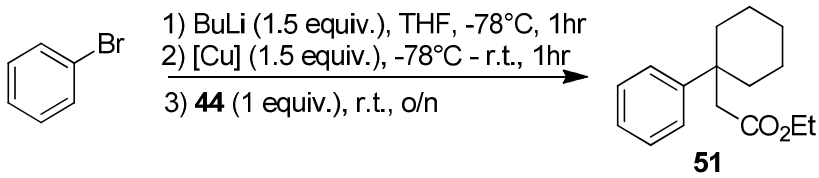


43a **50**

Entry	Solvent	Outcome
1	DCM	No reaction
2	THF	49%

Table 2.4

To examine the introduction of an aromatic group on the α,β-unsaturated ester intermediate, the reaction conditions of Davies were examined using an organolithium reagent.[105] The reaction was carried out using bromobenzene and butyllithium in presence of copper cyanide (entry 1) or copper iodide (entry 2). Unfortunately the desired compound was not obtained under either set of conditions and starting ester was recovered.



51

Entry	Copper	Outcome
1	CuCN	No reaction
2	CuI	No reaction

Table 2.5

The lack of reactivity observed with the α,β-unsaturated ester cyclohexanone derivatives can be explained by a combination of the steric hindrance of the cyclohexane cycle during nucleophilic attack, and the low nucleophilicity of the sydnone anion (Figure 2.6).

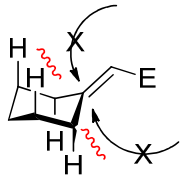


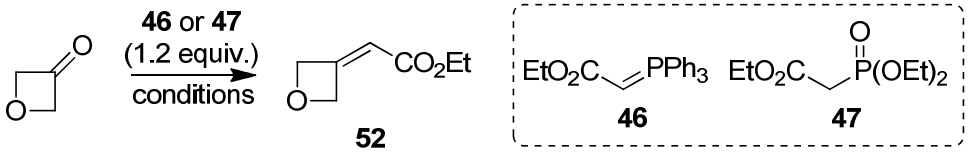
Figure 2.6: steric hindrance of the attack of the anion

6.2. Investigation of the introduction of oxetanone derivatives

Although the model studies proved to be disappointing, the incorporation of the oxetane ring by conjugate addition of a sydnone to a suitably activated oxetane system was investigated on the basis that the small heterocyclic ring may be subject to less steric hinderance as compared to the cyclohexanone derived system.

6.2.1. Synthesis of oxetan-3-one electrophiles

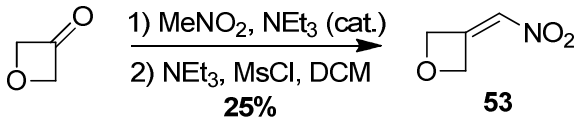
To form the oxetan-3-one based α,β-unsaturated ester, the optimal conditions developed for their cyclohexanone analogues was used (see Table 2.1: Entry 5 and 6; and Table 2.2: Entry 6). The results for the synthesis of the ester intermediate **52** are summarized in Table 2.6. The desired α,β-unsaturated ester of oxetane **52** was obtained in good yield using the conditions described by Gilmore for the cyclohexyl derivatives. Due to the potential volatility of the target compound, dichloromethane was used instead of toluene. Moreover, as expected, no isomerisation by-product was observed due to the ring strain present in this compound.



Entry	Wittig reagent	Conditions	Outcome
1	**46**	DCM, reflux, o/n	96%
2	**47**	NaH (1.05 equiv.), DME, r.t., o/n	22%

Table 2.6: Synthesis of **52**

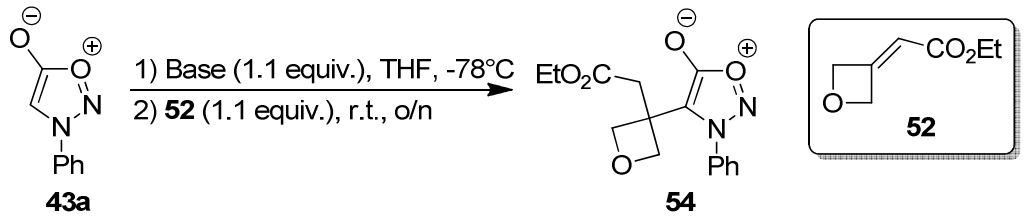
Using the conditions found for cyclohexanone derived α,β-unsaturated nitro intermediate, the corresponding oxetane **53** was obtained in 25% yield (Scheme 2.34).



Scheme 2.34: Synthesis of **53**

6.2.2. Investigations on the conjugate addition of phenylsydnone to oxetanone electrophiles

The α,β-unsaturated ester intermediate of oxetane **52** was chosen initially to investigate the introduction of the sydnone ring due to its easy and efficient synthesis. For this purpose, different bases were tested. No reaction was observed using butyllithium or methylmagnesium bromide (entry 1 and 2). Unfortunately, the addition of a copper additive (entry 3 and 4) and the use of trimethylsilyl chloride as a co-catalyst (entry 5 and 6) or a Lewis acid (Entry 7 and 8) did not furnish the desired compound **54**.

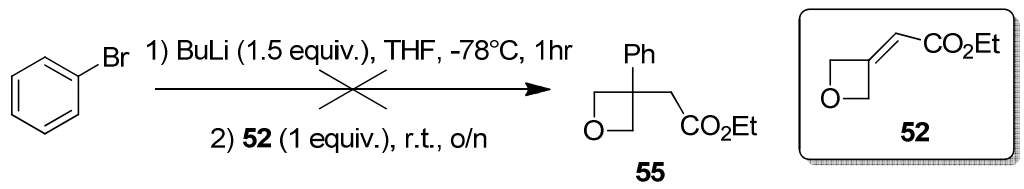


Entry	Base	Outcome
1	*n*-BuLi	No reaction
2	MeMgBr	No reaction
3	*n*-BuLi [a]	No reaction
4	MeMgBr [a]	No reaction
5	*n*-BuLi [a], [b]	No reaction
6	MeMgBr [a], [b]	No reaction
7	*n*-BuLi [a], [b], [c]	No reaction
8	MeMgBr [a], [b], [c]	No reaction

[a] CuI (1.1 equiv.) added; [b] TMSCl (1.1 equiv.) added;
[c] $BF_3.OEt_2$ (1.1 equiv.) added.

Table 2.7: Conjugate addition attempts

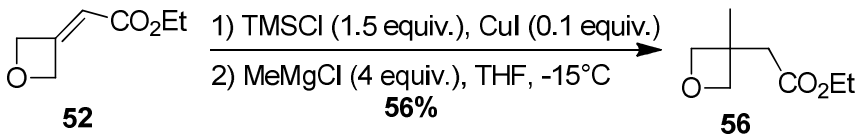
To investigate the nucleophilic addition to the oxetane-ester intermediate **52**, the addition of bromobenzene was attempted (Scheme 2.35). Unfortunately, no product was observed when bromobenzene was treated with *n*-butyllithium and added to the electrophile. Moreover, no reaction was observed when a copper additive (copper iodide) and a co-catalyst (trimethylsilyl chloride) were also added.



Scheme 2.35: attempted 1,4-addition on **55** using aryllithium reagent

Gobbi *et al.* have described an alkylation method of the oxetane-ester **52** using methyl magnesium chloride in presence of chlorotrimethylsilane and copper iodide

(Scheme 2.36).[106] Using these conditions, the desired product **56** was obtained in 56% yield. This result suggests that the addition to the electrophilic ester **52** is not directed by steric interactions but more by the lack of electrophilicity of the unsaturated ester **52** or the lack of nucleophilicity of the aromatic or sydnone organometallic compound.

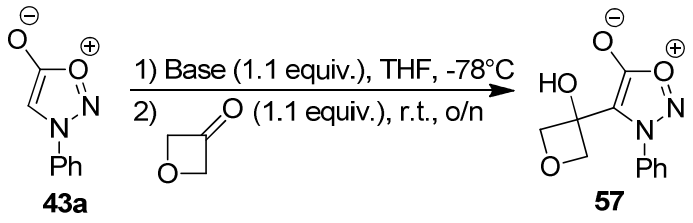


52 **56**

Scheme 2.36: conjugate addition of MeMgCl on **52**

6.2.3. Use of oxetan-3-one for sydnone ring coupling

As the conjugate addition of C4-metallated sydnones to α,β-unsaturated esters and nitro compounds were unsuccessful, the 1,2-addition to 3-oxetanone was attempted. Initially, using *n*-butyllithium to deprotonate the position 4 of the sydnone ring with or without a copper additive followed by the addition of oxetane-3-one failed to provide the desired product (Entry 1 and 2). However, to our delight, when methyl magnesium bromide was used instead of a lithium base, 20% of target material was obtained after purification by flash chromatography on silica gel (Entry 3).



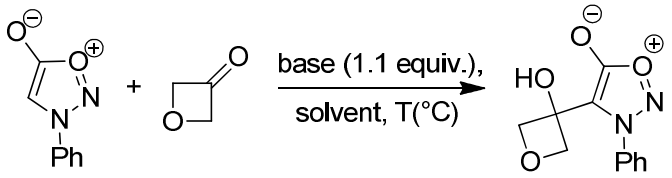
43a **57**

Entry	Base	Outcome
1	*n*-BuLi	No reaction
2	*n*-BuLi [a]	No reaction
3	MeMgBr	20%

[a] CuI (1.1 equiv.) added

Table 2.8: 1,2-addition to 3-oxetanone

In order to optimize the reaction, parameters such as the choice of the base, solvent and temperature were investigated. The use of lithium base (Entry 1 and 2, Table 2.9) provided no or little conversion of starting material. However when a Grignard base was used instead, the desired product was detected. The use of methylmagnesium bromide instead of methylmagnesium chloride delivered a higher conversion of starting material. The reaction temperature was also studied, as shown in Table 2.9, the conversion of starting material was greater at -15 °C or 0 °C than at -78 °C. But, at 0 °C the reaction provided more degradation. Using toluene as a solvent, low conversion of starting material was observed. Better conversion was observed when a more polar solvent was used, and, the best result was obtained using THF as solvent.



43a **57**

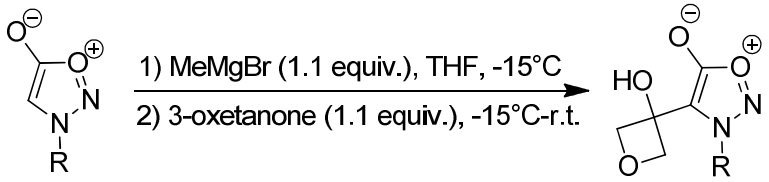
Base [a]	**Conversion**	**T(°C)** [b]	**Conversion**	**Solvent** [c]	**Conversion**
n-BuLi	0%	-78°C	50%	**THF**	**90%**
t-BuLi	5%	**-15°C**	**90%** [d]	DCM	60%
MeMgCl	33%	0°C	90% [e]	Toluene	30%
MeMgBr	**50%**			Dioxane [f]	70%

[a] Reactions carried out in THF at -78°C; [b] Reactions carried out with MeMgBr (1.1 equiv.); [c] Reactions carried out with MeMgBr (1.1equiv.) at -15°C; [d] Isolated yield: 90%; [e] Isolated yield: 65%; [f] Reaction carried out at 10 °C.

Table 2.9: Optimisation of the addition of phenylsydnone to 3-oxetanone

The oxetane-containing sydnones were purified by trituration with ethanol due their instability on silica gel and their poor separation on florisil and alumina.

This method of introducing an oxetan-3-one was expanded to different N3-substituted sydnones. Comparable yields were obtained using *para*-methoxyphenyl sydnone instead of phenylsydnone. The reaction between *N*-benzyl-sydnone and oxetane-3-one gave a slightly lower yield.



Entry	R	Isolated Yield
1	Ph	69% **57**
2	PMP [a]	63% **58**
3	Bn	54% **59**

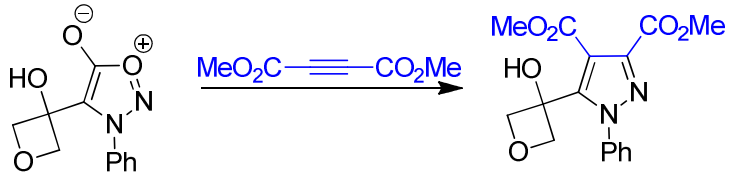
[a] 4-Methoxyphenyl

Table 2.10: Introduction of 3-oxetanone into *N*-substituted sydnones

7. Investigations of the cycloaddition reaction of 4-oxetanylsydnone intermediates

With oxetane substituted sydnones in hand, the cycloaddition of these reagents with alkynes was explored. In this study, the preliminary reactions were carried on the *N*-phenyl-substituted sydnone **57** because of its easy preparation on large scale.

As highlighted in Table 2.11, the first investigation using an electron-deficient alkyne, DMAD, was promising. In fact, by heating under microwave irradiation in DCB within a short time, the product was obtained in excellent yield (Entry 1). A slightly lower yield was obtained by heating at reflux over a longer time (entry 2).

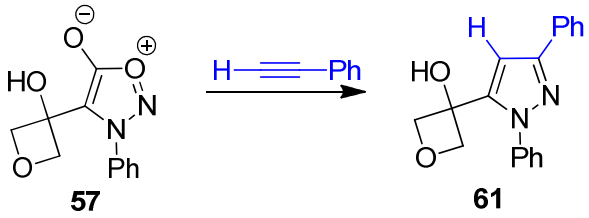


57 **60**

Entry	solvent	heating	Time	Outcome
1	DCB	180 °C, MW	5 min	92%
2	xylenes	Reflux	6 hrs	78%

Table 2.11

As preliminary investigations looked promising, the efficiency of the cycloaddition was then explored with phenylacetylene, our results are summarized in Table 2.12. Unfortunately, the product was obtained in poor or moderate yield. As shown in Table 2.11 and Table 2.12, the best conditions of the cycloaddition with an electron-deficient or neutral alkynes is obtained by heating under microwave irradiations in xylenes or DCB. The use of a Cu-Lewis acid was also investigated in order to promote cycloaddition. However, this condition failed to provide any pyrazole in the one-attempt examined (entry 8). The regioselectivity of the reaction was assigned compared to the precedent literature.[107]



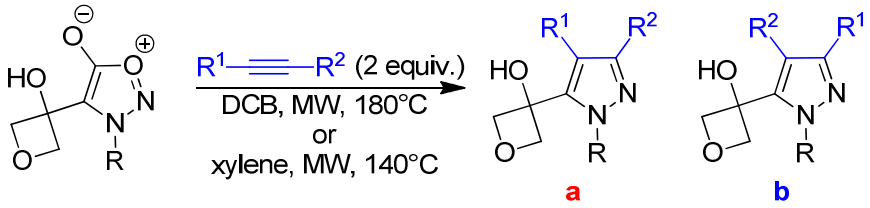
Entry	Solvent	Conditions	Time	Yield
1	Xylenes	Reflux	48 hrs	27%
2	Xylenes	MW, 140 °C	6 hrs	51%
3	DCB	MW, 180 °C	45 min	-
4	DCB	Sealed tube, 140 °C	2 hrs	5%
5	Xylenes	Sealed tube, 140 °C	6 hrs	10%
6	Neat	Sealed tube, 140 °C	2 hrs	11%
7	Neat	MW, 140 °C	30 min	13%
8 [a]	Xylenes	MW, 140 °C	30 min	-

[a] $Cu(OTf)_2$ added

Table 2.12

Using the optimized conditions, the scope of the cycloaddition reaction was investigated. The cycloaddition of sydnone **57** with an electron deficient alkyne promoted by microwave irradiation provided the corresponding pyrazoles **60** and **62** in high yield and good regiocontrol (entries 1 and 2). In contrast, neutral alkynes such as phenyl- and trimethylsilyl-acetylene afforded the products **61** and **63** in 51% and 17% yield respectively but with good regiocontrol (entries 3 and 4). However,

the cycloaddition of *N-para*-methoxyphenylsydnone **58** with electron-deficient alkynes was found to be less effective than the *N*-phenyl analogue **57** (entries 5 and 6). Moreover, the cycloaddition reaction of *N*-benzyl-substituted sydnone **59** furnished the corresponding pyrazoles in poor yield and regiocontrol (entry 7). In fact, it appeared that it was less effective because it underwent decomposition at high temperature during the cycloaddition process. The regioselectivity of the reaction was assigned compared to the precedent literature.[107]

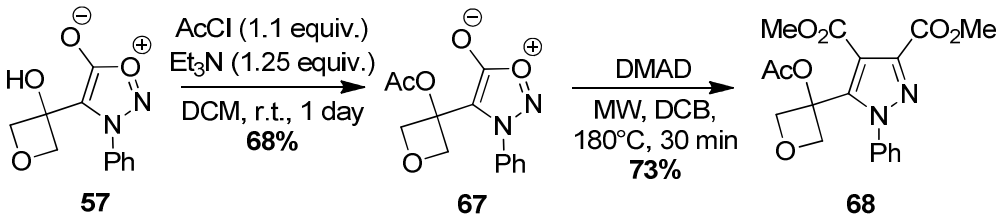


Entry	R	R^1	R^2	Yield (a:b)
1 [a]	Ph	CO_2Me	CO_2Me	92% **60**
2 [b]	Ph	H	CO_2Et	66% (7:1) **62**
3 [b]	Ph	H	Ph	51% (>98:2) **61**
4 [b]	Ph	H	TMS	17% (>98:2) **63**
5 [a]	PMP [c]	CO_2Me	CO_2Me	60% **64**
6 [b]	PMP [c]	H	CO_2Et	44% (5:1) **65**
7 [a]	Bn	H	CO_2Et	21% (2:1) **66**

[a] reaction carried out in DCB at 180°C under microwave conditions; [b] reaction carried out in xylene at 140°C under microwave conditions; [c] *para*-Methoxyphenyl

Table 2.13: alkyne cycloaddition reaction of sydnones

As it appeared that only a small array of substrates underwent an efficient cycloaddition with oxetane-substituted sydnones, the potential of the alcohol group for promoting the decomposition of these mesoionic compounds was investigated. The alcohol group was therefore acetylated to give **67**, which was subjected to microwave irradiation in the presence of DMAD. These conditions furnished the corresponding pyrazole **68** in 73% yield. Unfortunately, the 49% yield over 2 steps presented no further advantage over the cycloaddition reaction with the free alcohol, as this proceeded with a yield of 92%.



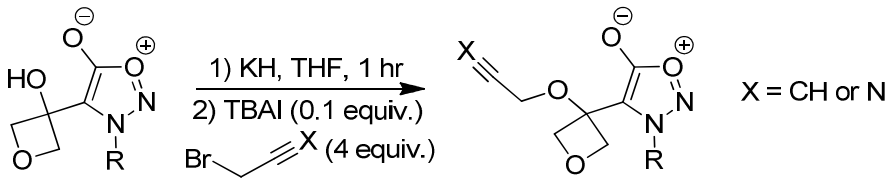
Scheme 2.37: cycloaddition of **67** with DMAD

8. Elaboration of the scope of oxetane-substituted sydnone cycloadditions

The poor yields observed in the majority of alkyne cycloadditions prompted us to explore an intramolecular variant of this reaction. Specifically, it was anticipated that the free alcohol on the oxetane ring would represent a useful handle from which to append a range of alkyne groups.

8.1. Alkylation of the alcohol group

In order to study the intramolecular cycloaddition, the preparation of a range of propargyl ethers was explored. As shown in Table 2.14, phenyl and PMP-sydnone underwent propargylation in good yield after deprotonation with potassium hydride and treatment with propargyl bromide in presence of tetrabutylammonium iodide (entries 1 and 2). The alcohol group of the *N*-Phenylsydnone derivative (**57**) also underwent propargylation with bromoacetonitrile in the presence of excess potassium hydride to furnish the corresponding nitrile (**70**) in good yield (entry 3). However, the corresponding benzylsydnone appeared to be unstable and provided the desired alkyne **72** in poor yield (entry 4). The instability of 4-substituted benzyl sydnone compared to its aryl analogues is consistent with the observations of Padwa and co-workers.[90]



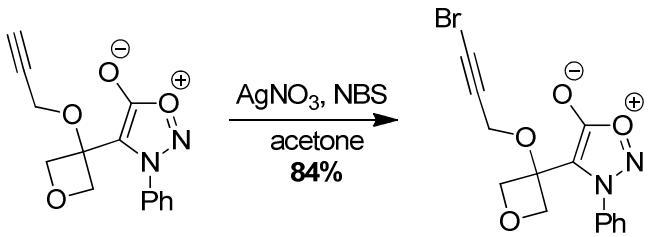
Entry	R	X	Outcome
1 [a]	Ph	CH	79% **69**
2 [a]	Ph	N	89% **70**
3 [b]	PMP [c]	CH	75% **71**
4	Bn	CH	<10% **72**

[a] using 4 equiv. of KH; [b] using 10 equiv. of KH; [c] para-Methoxyphenyl

Table 2.14: Propargylation of oxetane-sydnone derivatives

With an efficient route to access to alkynes **69** and **71**, their conversion into bromoalkynes was attempted. In fact, the intramolecular cycloaddition of these substrates could allow the synthesis of bromopyrazoles that would offer the chance for further functionalisation, via, for example cross-coupling reactions.

Wu and co-workers described a methodology to obtain bromoalkynes using silver nitrate and *N*-bromosuccinimide in acetone.[108] Pleasingly, when the alkyne **69** was treated under these conditions the corresponding bromo alkyne **73** was obtained in 84% yield.

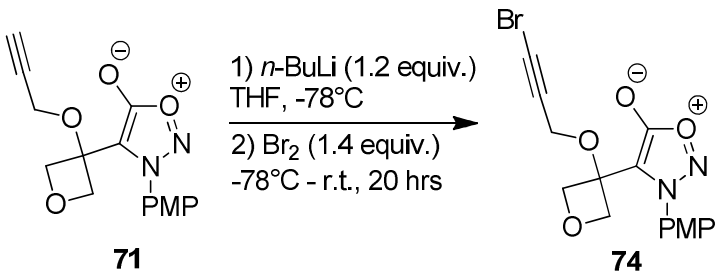


69 **73**

Scheme 2.38: Bromination of alkyne **69**

Unfortunately, when the PMP analogue was treated under the same conditions, no product was observed (entry 1). This was a surprising result and the underlying

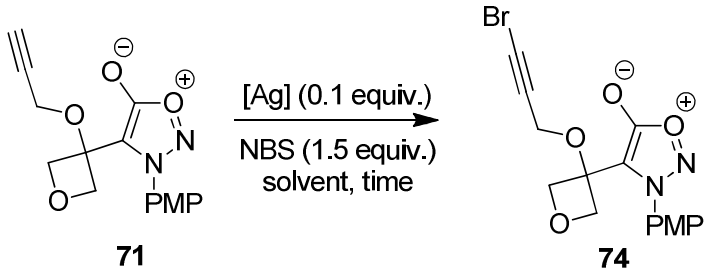
reasons for the stark difference in reactivity of these two closely related substrates are unclear. Nonetheless, alternative methods were explored. The conditions described by Vera *et al.* using *n*-butyllithium and bromine furnished a complex mixture (Scheme 2.39).[109]



71 **74**

Scheme 2.39: Bromination attempt on **71**

To our delight, when dichloromethane was used as the solvent instead of acetone, 30% of alkyne **71** was converted to the bromo analogue **74** (entry 2). The use of silver species was explored. As described by Rowan[110] and Gómez-Campillos[111] when using silver fluoride or silver acetate, the conversion and the yield of the reaction was improved (entries 3 and 4). Silver acetate was found to be the best silver salt for the reaction. The choice of the solvent was then investigated to improve the reaction (entries 4 to 7), and it was found that the reaction proceeded in good yield using silver acetate and *N*-bromosuccinimide in dichloromethane (entry 7).



71 **74**

Entry	Silver salt	Solvent	Time	Results
1	$AgNO_3$	Acetone	1 day	SM[a] recovered
2	$AgNO_3$	CH_2Cl_2	1 day	30% conversion
3	AgF	Acetone	18 hrs	32%
4	AgOAc	Acetone	1 day	69%
5	AgOAc	MeCN	3h15	91%
6	AgOAc	MeOH	4 hrs	72%
7	AgOAc	CH_2Cl_2	3 hrs	94%

[a] SM = Starting material

Table 2.15: Optimisation of bromination of **74**

The possibility of further functionalization of the alkyne was also explored, and the synthesis of the alkyne boronic ester derivatives was attempted. For this purpose, different bases were tested to deprotonate the alkyne **69** before treatment with *i*PrOBpin. Unfortunately, as shown in Table 2.6, no product was observed under any of these conditions.

69 **75**

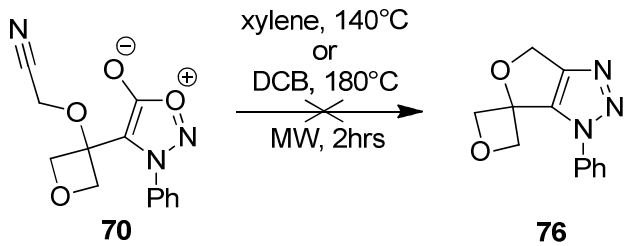
Entry	Base	Outcome
1	*n*-BuLi	RSM
2	MeMgBr	RSM
3	NaH	RSM
4	KH	RSM
5	*t*-BuLi	RSM
6	*t*-BuLi, *t*-BuOK	RSM

RSM: recovered starting material

Table 2.16: Borylation attempt of **69**

8.2. Intramolecular cycloaddition of alkynes and further transformations

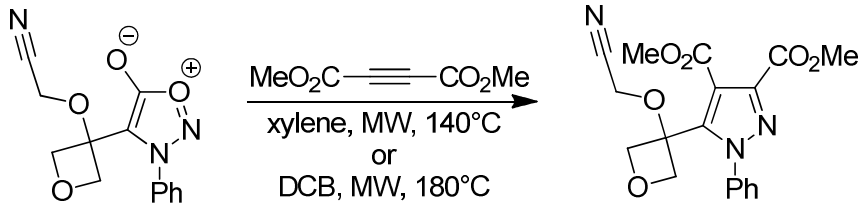
Microwave irradiation conditions were chosen to study the intramolecular cycloaddition, so that a direct comparison could be made with the intermolecular processes. First, the cycloaddition of nitrile derivative **70** was investigated. In fact, this could represent an effective synthesis of triazole compounds which are commonly found in the drug discovery sector. Unfortunately, when the nitrile derivative **70** was heated in xylene or DCB under these conditions, no reaction was observed (Scheme 2.40).



70 **76**

Scheme 2.40

As the nitrile seemed to be unreactive, the participation of this compound in intermolecular alkyne cycloaddition reactions was investigated. The nitrile **70** was heated under microwave irradiation with DMAD in xylene (entry 1) or DCB (entry 2). The cycloaddition product **77** was obtained in moderate yield and within a long reaction time. The lack of reactivity of the nitrile group can be possibly due to steric effects.



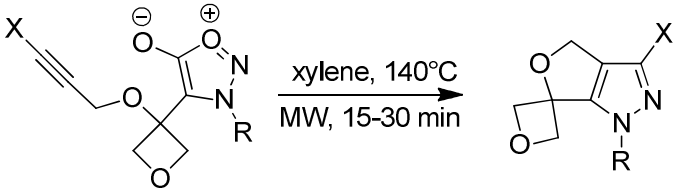
70 **77**

Entry	Time	Yield[a]
1	9 hrs	55%[b]
2	2.5 hrs	61%[c]

[a] Isolated yield; [b] reaction carried out in xylene; [c] reaction carried out in DCB.

Table 2.17

Pleasingly, all alkyne substrates **69**, **71**, **73** and **74** underwent the intramolecular cycloaddition to afford the corresponding pyrazoles in excellent yield. The results are summarized in Table 2.18. These results highlight that intramolecular cycloadditions offer a more generally efficient means for preparing highly congested pyrazoles from C4-substituted sydnones.



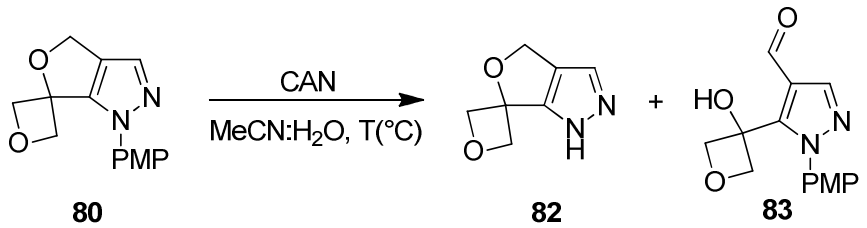
Entry	R	X	Yield
1	Ph	H	98% **78**
2	Ph	Br	94% **79**
3	PMP [a]	H	93% **80**
4	PMP [a]	Br	89% **81**

[a] *para*-Methoxyphenyl

Table 2.18

The spiro-oxetanes **79** and **81** represent an interesting intermediate for drug discovery as it has a bromide which could allow further functionalisation. Moreover, their low molecular weight and log P, and their polarity make them interesting intermediates or possible candidates for drug discovery. Compounds **80** and **81** also represent an interesting fragment as the PMP-group could be deprotected to provide the free pyrazole.

As such fragments can be interesting intermediates for the fine chemicals industry, the deprotection of the PMP-group in **80** to access the free-pyrazole was examined by using oxidation of the electron rich aromatic ring using CAN. As shown in Table 2.19, the desired product was isolated in moderate yield. Moreover, an unexpected by-product derived from oxidation and hydrolysis of the 5-membered ring containing the endocyclic oxygen was observed. The formation of this product was found to be dependent on the water concentration in the reaction mixture. After significant optimization, it was found that both pyrazoles could be selectively synthesized and isolated in moderate yield.

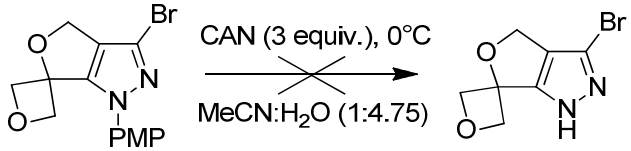


80 **82** **83**

Entry	MeCN:H_2O	T(°C)	CAN (equiv.)	82:83 (yield)
1	5:1	-15°C	3	1:0 (61%)
2	1:2	-15°C	3	45:55 (23%)
3	1:10	-15°C	3	4:6 (36%)
4	1:4.75	-15°C	3	0:1 (40%)
5	1:4.75	-78°C	3	25:75 (41%)
6	1:4.75	0°C	3	15:85 (42%)
7	1:4.75	r.t.	3	3:7 (27%)
8	1:4.75	0°C	1	20% conversion
9	1:4.75	0°C	5	0:1 (29%)

Table 2.19: Optimisation of PMP deprotection

However, on extending this study to the 3-bromo analogue **81**, it was disappointing to find that this compound seemed to be less reactive and did not provide the desired product when it was subjected to the conditions previously optimized for the pyrazole **80**. Moreover, no starting material was recovered and a complex mixture was observed on the ^{1}H NMR of the crude mixture.

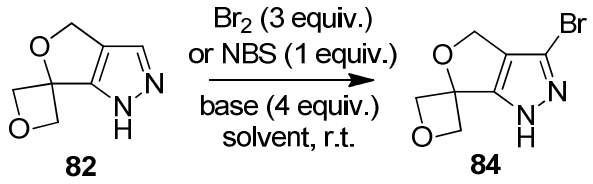


81 **84**

Scheme 2.41: deprotection attempt of **81**

As the bromopyrazole **81** seemed to be unreactive to the CAN deprotection, the bromination of the free pyrazole **82** was studied. The bromination was attempted using bromine (entries 1 and 2)[112] or *N*-bromosuccinimide in different solvents. Unfortunately as shown in Table 2.20, no trace of desired product was observed

under any of these conditions, and the pyrazole **82** appeared to degrade to provide a complex mixture.

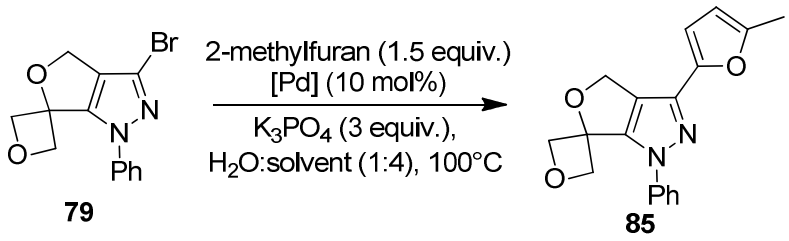


Entry	'Br' source	Base	Solvent	Outcome
1	Br_2	NaOH	H_2O	Degradation
2	Br_2	$NaHCO_3$	Et_2O	Degradation
3	NBS	-	MeCN	Degradation
4	NBS	-	DMF	Degradation
5	NBS	-	Et_2O	Degradation

Table 2.20

The bromo pyrazoles **79** and **81** can provide good intermediates for further functionalisation. Among these, the direct arylation and the Suzuki coupling was investigated.

Phenyl-substituted pyrazole **79** and 2-methylfuran were chosen to investigate and optimize the direct arylation reaction. Different palladium catalysts and solvent systems were tested, but unfortunately, traces amount of the desired compound **85** were obtained. Moreover, there appeared to be significant levels of homocoupling of the pyrazole observed in this reaction. The results are shown in Table 2.21.

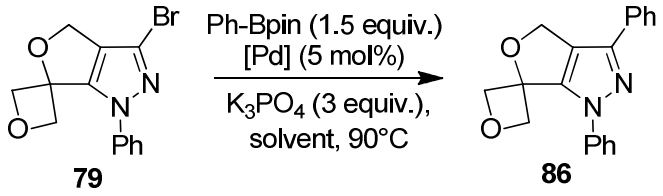


Entry	[Pd]	Solvent	Conversion
1	$PdCl_2$dppf.DCM	dioxane	28% (Homocoupled product recovered)
2	$PdCl_2(PPh_3)_2$	dioxane	19% (Homocoupled product recovered)
3	$Pd(PPh_3)_4$	DMF	RSM [a]
4	$Pd(PPh_3)_4$	toluene	RSM [a]
5	$Pd(PPh_3)_4$	dioxane	30% (Homocoupled product recovered)

[a] RSM: Recovered starting material.

Table 2.21: Direct arylation attempt

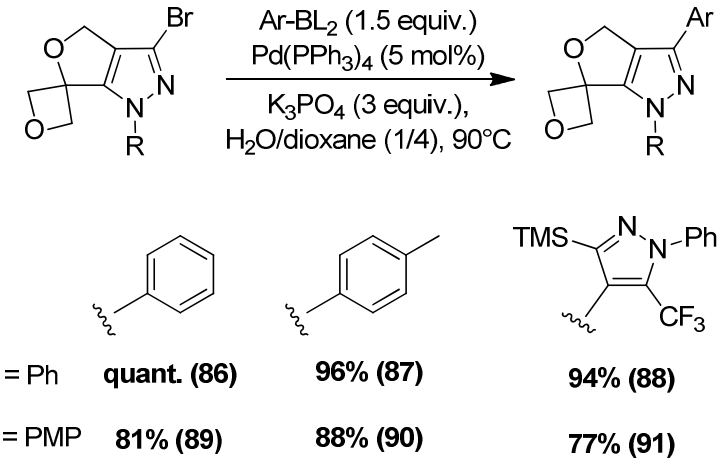
Pyrazole **79** and phenylboronic acid pinacol ester were chosen for the optimization studies on the Suzuki-Miyaura cross-coupling. Pleasingly, conditions found previously in the group for the Suzuki coupling of pyrazole with boronic acid derivatives furnished the desired compound **86** in 93% yield (Entry 1). Using the condition found by Langer and co-workers by using $PdCl_2(PPh_3)_2$ instead of $PdCl_2$dppf.DCM allowed an increase in yield to 97% (Entry 2).[113] When $Pd(PPh_3)_4$ was used in DMF and water the product **86** was obtained quantitatively (Entry 3).[114] However, to simplify the isolation of the compound, other solvent systems were investigated. In toluene-methanol a slight decrease of yield was observed (Entry 4).[115] Pleasingly, a total conversion and recovery of product **86** was obtained by using a dioxane-water mixture as solvent (Entry 5).[116]



Entry	[Pd]	Solvent	Yield
1	$PdCl_2$dppf.DCM	H_2O:dioxane (1:4)	93%
2	$PdCl_2(PPh_3)_2$	H_2O:dioxane (1:4)	97%
3	$Pd(PPh_3)_4$	H_2O:DMF (1:4)	Quant.
4	$Pd(PPh_3)_4$	MeOH:toluene (1:4)	98%
5	$Pd(PPh_3)_4$	H_2O:dioxane (1:4)	Quant.

Table 2.22: Optimisation of Suzuki-Miyaura cross-coupling reaction

For the simplicity of use and isolation, $Pd(PPh_3)_4$ in dioxane:water (1:4) was chosen as optimal reaction conditions. To highlight the scope of the reaction, *p*-tolylboronic acid, phenylboronic acid pinacol ester and a more heavily substituted pinacol ester were employed with phenyl- and PMP-substituted pyrazoles **79** and **81**. As shown in Scheme 2.42, the cross-coupling reaction was found to be very general, giving the biaryl products in excellent yield in all cases examined.



Scheme 2.42: Scope of Suzuki-Miyaura cross-coupling reaction

9. Conclusions and future outlook

In conclusion, a general strategy for the introduction of an oxetane ring in the C4 position of sydnones was developed. It was initially demonstrated that the oxetane-substituted sydnone can offer an interesting and effective intermediate for the elaboration of a range of oxetane-subsituted pyrazoles via alkyne cycloaddition reactions. However, the intermolecular cycloadditions show some limitations and this chemistry was unfortunately limited to *N*-arylsydnones. Meanwhile, the intramolecular variant proceeded in good yields and also provided an effective route to generate spiro-fused intermediates. Also, a 3-bromo pyrazole analogue that has the potential to be further elaborated via Suzuki-Miyaura cross-coupling in good yield has been developed.

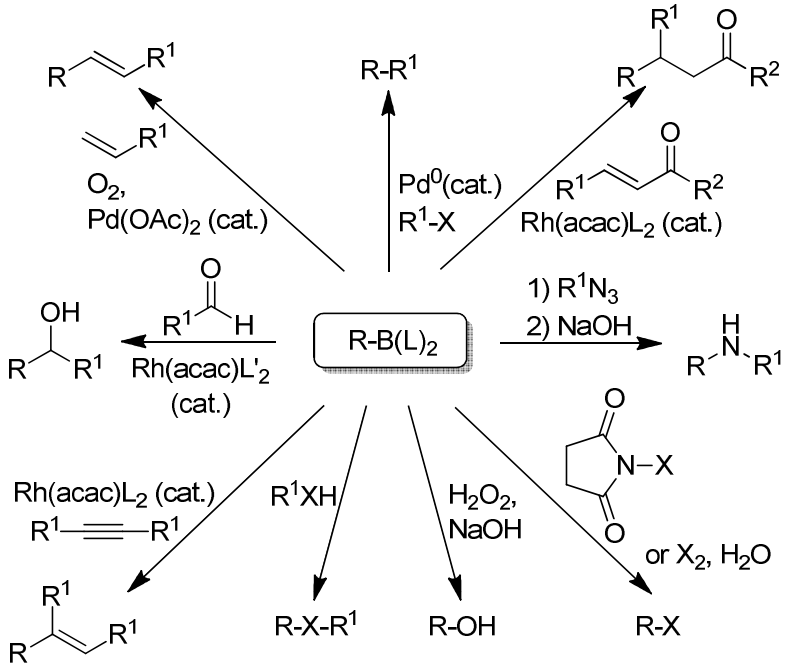
Further studies on the development of new routes of elaboration via direct arylation or other cross-coupling reactions could allow an extensive library of spiro-fused oxetane pyrazoles to be produced.

Finally, these studies highlighted that the PMP deprotection of the spiro-oxetane intermediate offered poor results. An obvious consideration for further studies in this area is to develop alternative protecting group strategies. Moreover, those that allow the 3-bromo-analogue to be prepared could be very useful indeed.

Chapter 3: Synthesis and functionalisation of azetidine and oxetane boronic acid derivatives

1. Introduction

Boronic acids were first reported in 1860 by Frankland,[117] but it is only since the early 1980's that they have been the subject of interest in the synthetic chemistry community as the versatility of the carbon-boron bond has become more established. In particular, boronic acids became an attractive class of synthetic intermediates for both academia and industry since Suzuki and Miyaura reported their utility in palladium catalyzed cross-coupling reactions with aryl halides.[118] A survey of some applications of boronic acids derivatives are shown in Scheme 3.1.[119]

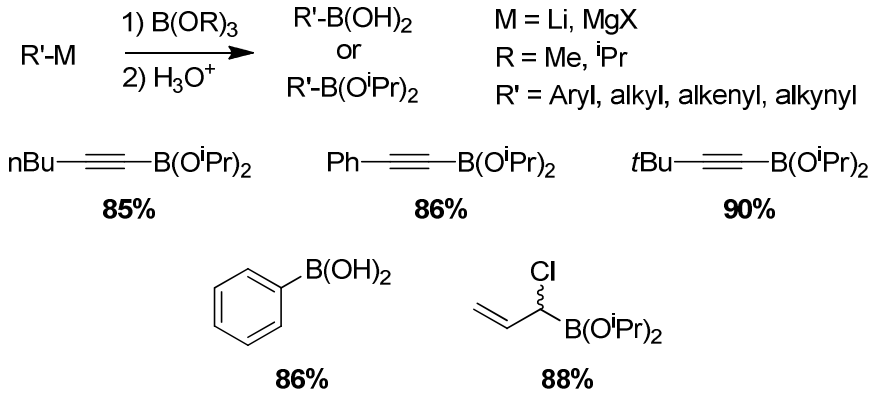


Scheme 3.1: Applications of boronic acid derivatives

2. Synthesis of boronic acid derivatives

2.1. Synthesis from organolithium or magnesium reagents

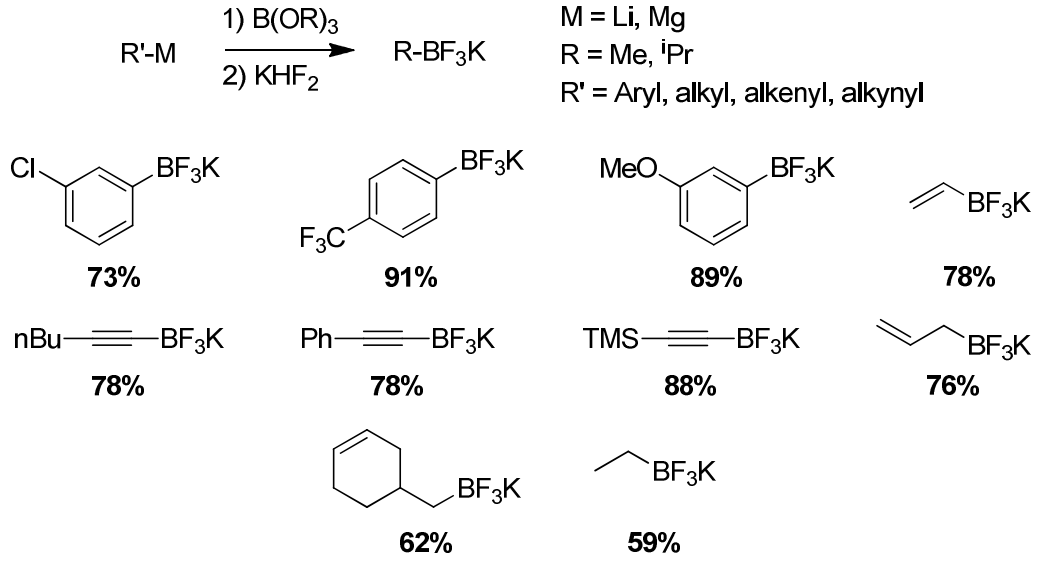
Boronic acids or esters are classically synthesized from organolithium compounds or via the corresponding Grignard reagents. These reactive organometallics are subjected to borylation and hydrolysis to furnish the desired products. This method allows the large scale and efficient synthesis of aryl, alkyl, 1-alkynyl and 1-alkenylboronic acid or esters (Scheme 3.2).[120]



Scheme 3.2: Synthesis of boronic acids and boronic esters from organometallic reagent

In the same manner, organotrifluoroborates salts are readily synthesized from organolithium or magnesium reagents. In fact, treatment of the boronic acid generated *in situ* with KHF_2 allows the formation of the potassium trifluoroborate salt.[121] This 'one pot' process allows the formation of a broad range of potassium organotrifluoroborates and avoids the isolation of the boronic acid or ester intermediates which can be unstable. Trifluoroborate salts represent a moisture and air stable class of organoboron reagents, although they maintain a high reactivity. They can be easily isolated and purified as they often precipitate and are not soluble in solvents such as petroleum ether, dichloromethane and ethyl acetate. They can however be purified by recrytallisation from acetonitrile or acetone. Using this

method, aryl,[121] allyl, [122] alkenyl, [123] alkynyl[121b, 124] and alkyl [125] potassium trifluoroborate salts can be synthesized (Scheme 3.3).

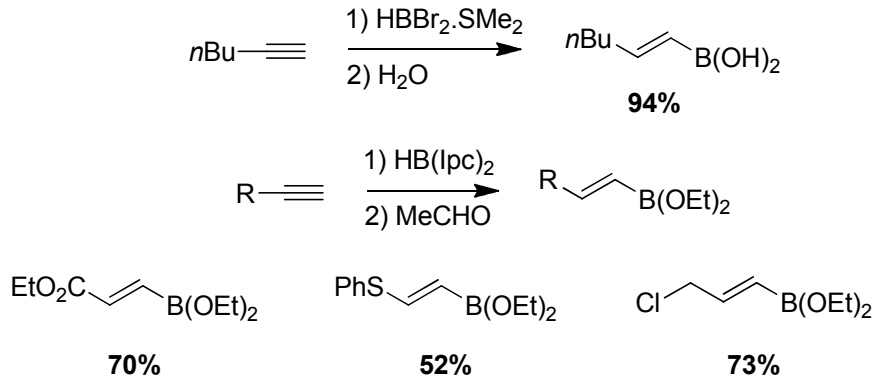


Scheme 3.3: Synthesis of trifluoroborate salts via transmetallation

Unfortunately, this method has some limitations. Indeed, in the case of substrates bearing functional groups sensitive to organolithium or Grignard reagent, an alternative route has to be found.

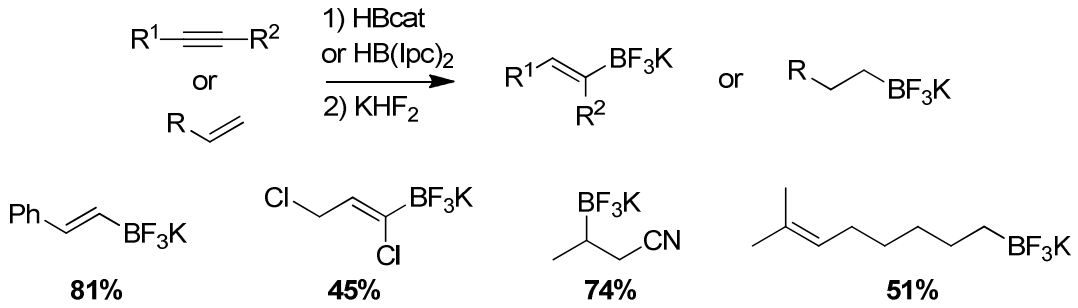
2.2. Synthesis via hydroboration process

Alternatively to the method described previously, the hydroboration of alkenes and alkynes furnishes the corresponding borylated alkyl- or alkenyl- species. Using this method, the anti-Markovnikov product is obtained in high yield (Scheme 3.4).[126]



Scheme 3.4: Synthesis of boronic acids and esters via hydroboration

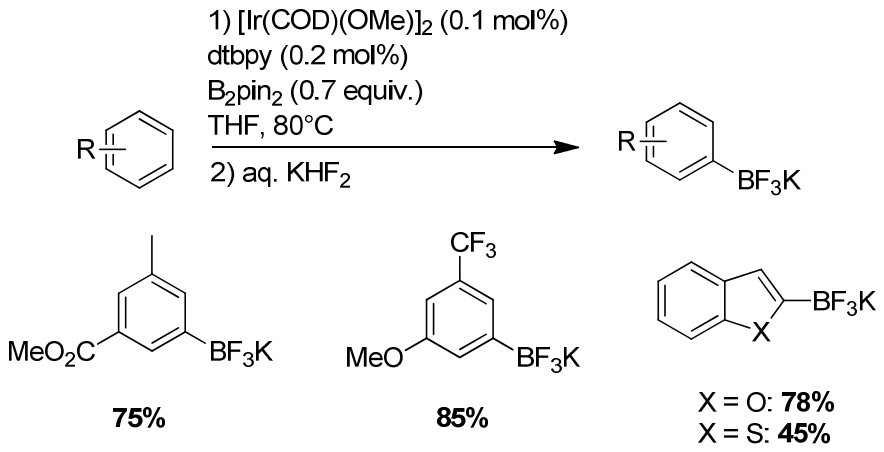
As described previously, an *in situ* treatment of the reaction mixture from the hydroboration with potassium hydrogenfluoride provides the desired alkenyl and alkyl trifluoroborates in moderate to good yield (Scheme 3.5).[125]



Scheme 3.5: Synthesis of trifluoroborate salts via hydroboration

2.3. Synthesis via C-H bond activation

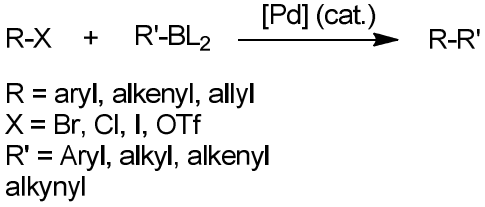
Another attractive alternative is the direct borylation of a carbon-hydrogen bond using transition metal catalysis. It has been shown that using palladium, ruthenium, rhodium or iridium catalysts and pinacolborane or bis(pinacolato)diboron, aromatic, heterocyclic and aliphatic alkanes containing oxygen, nitrogen and fluorine can be borylated in moderate to excellent yield (Scheme 3.6).[127]



Scheme 3.6: Synthesis of trifluoroborate salts via C-H bond activation

3. Applications of boronic acid derivatives

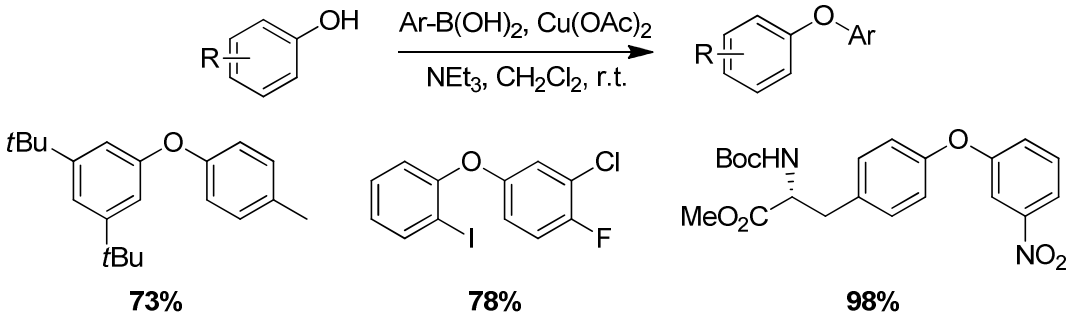
As discussed earlier, boronic acid derivatives are widely used in modern synthetic organic chemistry. In fact, organoboranes are commonly used in transition metal catalysed reactions, such as Suzuki-Miyaura cross-coupling which allows the formation of a new carbon-carbon bond, typically between two aromatic sub-units. In this reaction an organohalide reacts with an organoborane in presence of a base and a catalytic amount of palladium. This method allows the coupling between an aryl-, alkenyl- or allylhalide and a wide range of organoboranes in moderate to good yield.[118]



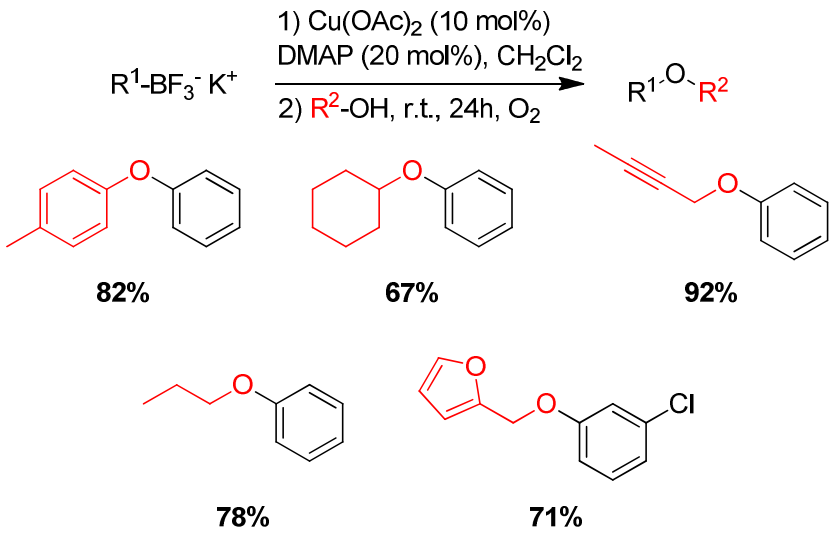
Scheme 3.7: General scheme of the Suzuki-Miyaura reaction

Boronic acid derivatives are also used to form new carbon-heteroatom bonds under copper catalysis. In 1998, Chan and Evans reported the synthesis of diaryl ethers through a copper (II) coupling of phenols and aryl-boronic acids in moderate to

excellent yield (Scheme 3.8).[128] A few years later, Batey and co-worker reported a copper (II) catalysed protocol for the etherification of alkyl- and aryl- alcohols with a range of alkenyl- and aryl-potassium trifluoroborates (Scheme 3.9).[129] They reported that boronic acids also undergo cross-coupling under the same conditions, but the yields are lower.



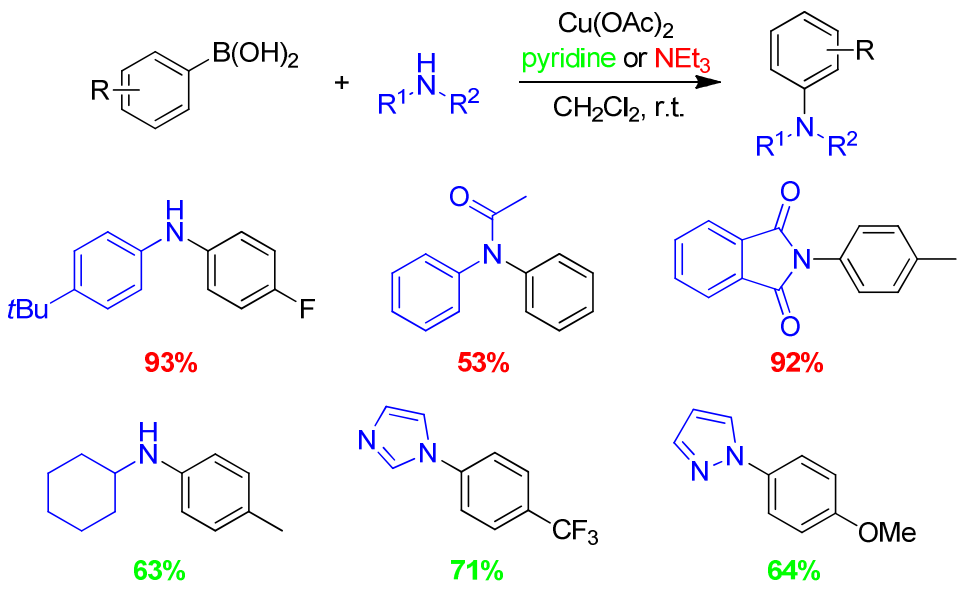
Scheme 3.8: Cross-coupling of boronic acids with phenols



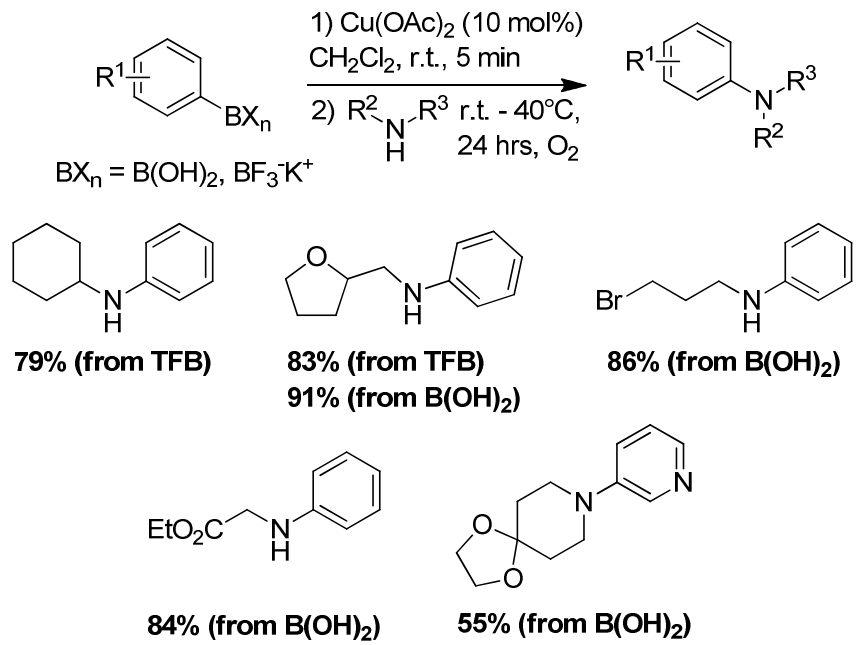
Scheme 3.9: Cross-coupling of trifluoroborate salts with alcohols

Copper (II) cross-coupling was also reported on amines. In 1998, Chan and Lam reported the arylation of N-H containing compounds using elemental copper in the presence of a tertiary amine (Scheme 3.10).[130] A few years later, Batey *et al.* described the coupling between arylboronic acids and potassium trifluoroborate salts with amines and anilines catalysed by copper in moderate to excellent yield (Scheme

3.11).[131] They observed that anilines and more hindered amines gave lower yields of products.

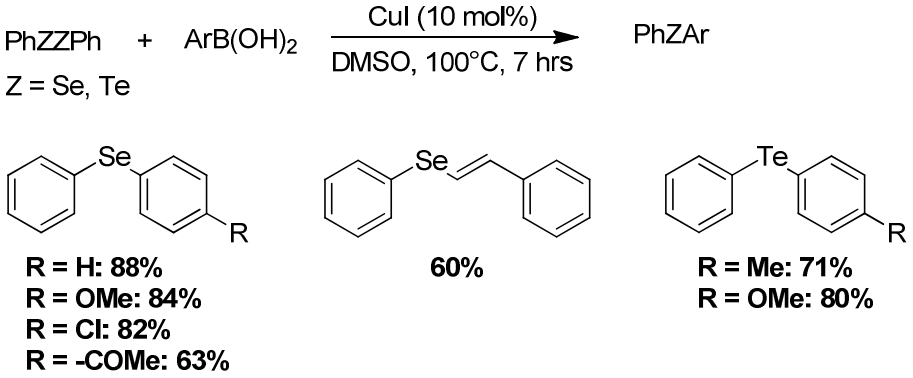


Scheme 3.10: Cross-coupling of arylboronic acids with N-H containing heterocycles



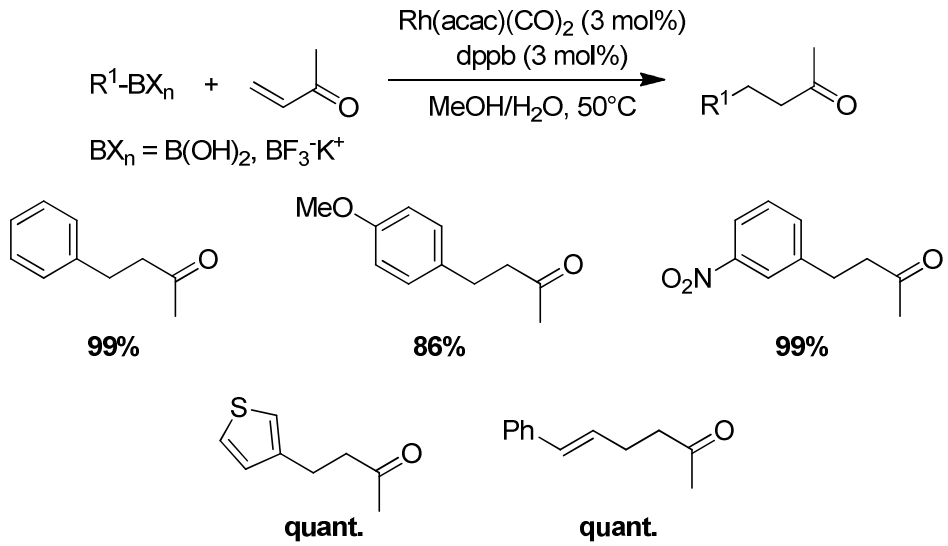
Scheme 3.11: Cross-coupling of trifluoroborate salts with anilines catalysed by copper

In 2005, it was also shown by Wang and co-workers that a range of arylboronic acids undergo cross-coupling with diphenyl ditelluride and diselenide using a catalytic amount of copper salt to furnish unsymmetrical diaryl tellurides and selenides in good to excellent yield (Scheme 3.12).[132]



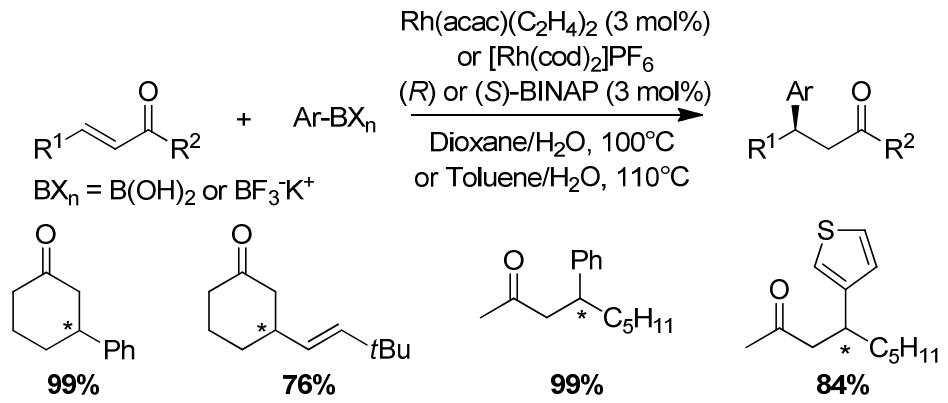
Scheme 3.12: cross-coupling of arylboronic acids with ditelluride and diselenides catalysed by copper

Organoboron reagents also participate in Rh-catalysed conjugate addition reactions. In 1997, Miyaura *et al.* reported the efficient 1,4-addition of alkenyl- and aryl-boronic acids on enones catalysed by rhodium (I) providing the β-alkylated ketones in good to excellent yield.[133] Following this communication, in 1999, Batey and co-workers reported the addition of aryl- and alkenyl-trifluoroborate salts to enones catalysed by rhodium (I).[134] They observed that the reactions using potassium trifluoroborate salts were proceeding more rapidly than their boronic acid counterparts but the main benefits resulted from the air and moisture stability of these reagents. Using these methods, aryl-, heteroaryl- and alkenyl- groups were incorporated into enones in good to excellent yield (Scheme 3.13).



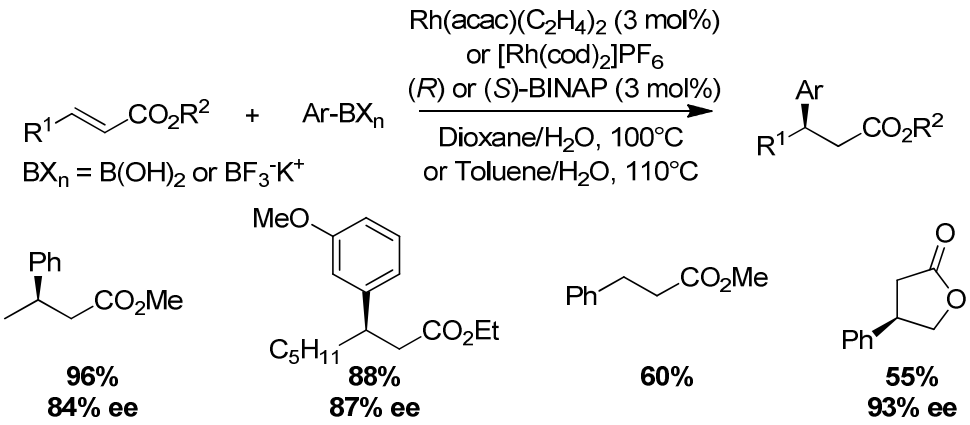
Scheme 3.13: 1,4-Addition of boronic acid derivatives to enones catalysed by rhodium

After the report of Miyaura on the rhodium catalysed conjugate addition of alkenyl- and aryl-boronic acids to enones, several reports followed on the asymmetric version of the reaction. In 1998, Hayashi and co-workers reported the asymmetric 1,4-addition of alkenyl catechol boronic esters and also the asymmetric conjugate addition of alkenyl- and aryl-boronic acids to enones.[135] In 2002, Genet and co-workers reported the use of potassium trifluoroborate salts in the enantioselective 1,4-addition to enones.[136] They observed that potassium aryl- and alkenyl-trifluoroborate salts can undergo conjugate addition to both cyclic and acyclic enones.



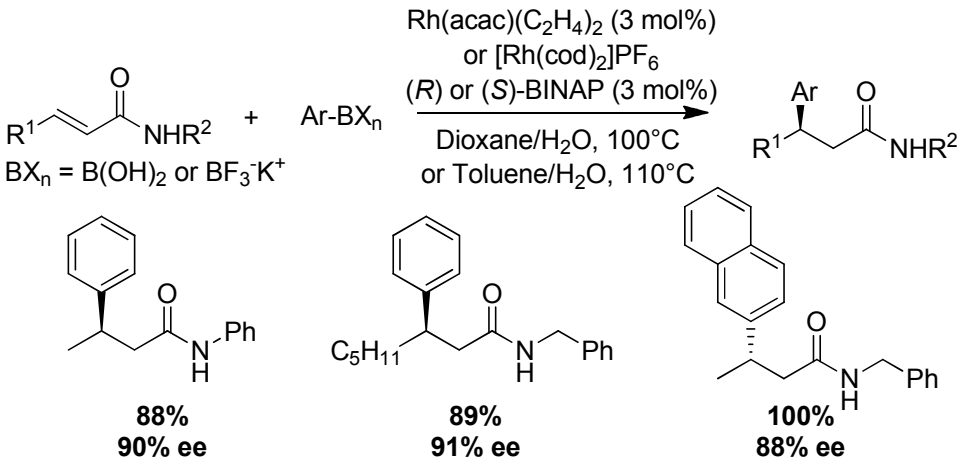
Scheme 3.14: conjugate addition of organoboron reagents to enones catalysed by rhodium

It was subsequently shown by Miyaura *et al.* that the methodology is applicable to α,β-unsaturated esters. [137] They reported that the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters proceeded in moderate to good yield and in high enantiomeric excess. Later, Genet and co-workers reported the use of potassium aryltrifluoroborate salts in conjugate addition to cyclic or acyclic α,β-unsaturated esters catalysed by rhodium in good to excellent yield and high enantioselectivity.[138139]



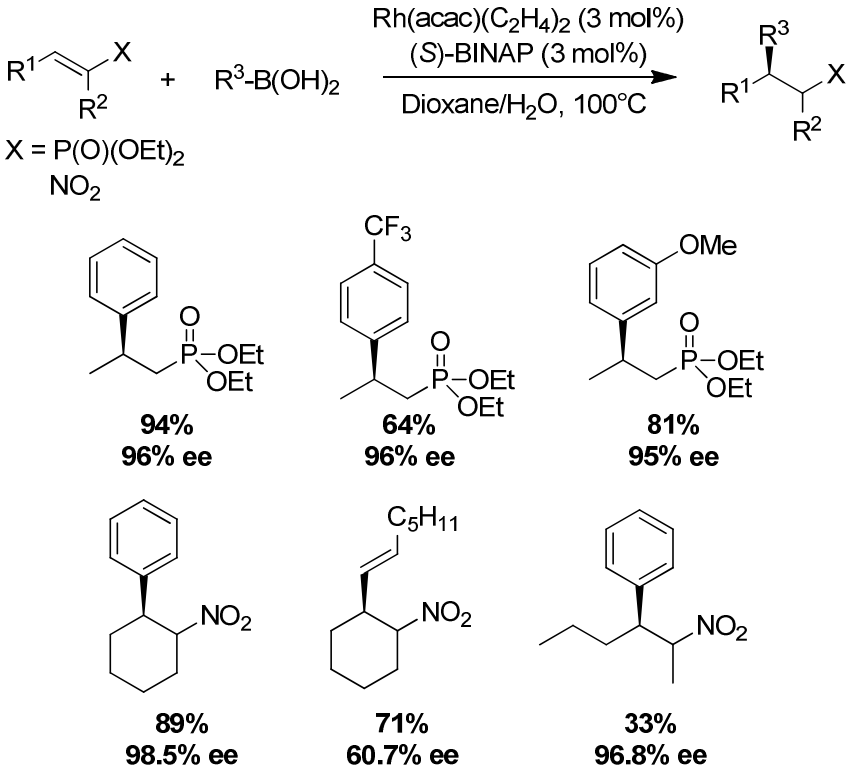
Scheme 3.15: 1,4-Addition to unsaturated esters catalysed by rhodium

In 2001, Hayashi and Miyaura *et al.* reported the enantioselective conjugate addition of arylboron reagents into cyclic and acyclic unsaturated amides in modest to good yield, and with excellent enantioselectivity. [140] A few years later, Genet and co-workers extended this methodology to the application of potassium organotrifluoroborate salts in asymmetric 1,4-addition to α,β-unsaturated amides in good to excellent yield and in high enantiomeric excess.[141]



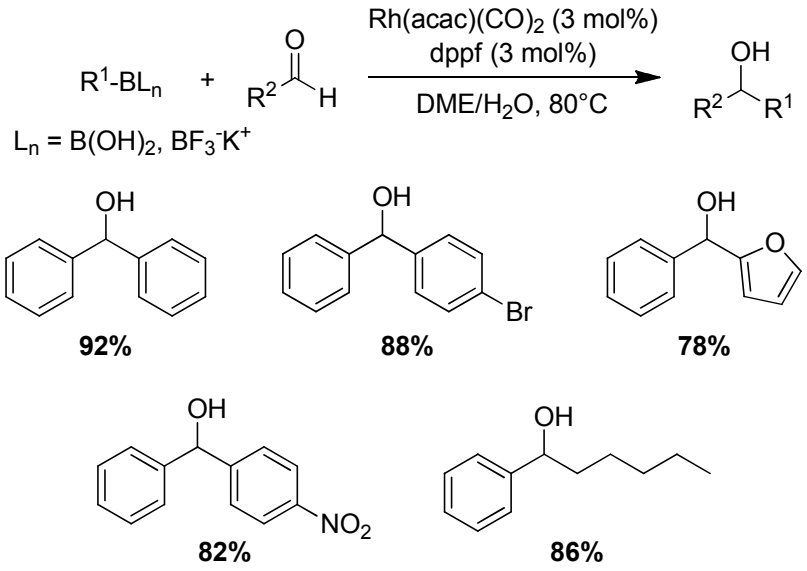
Scheme 3.16: conjugate addition of organoboron reagents to unsaturated amides catalysed by rhodium

Hayashi also described the asymmetric conjugate addition of boronic acid derivatives to alkenylphosphonates and nitroalkenes (Scheme 3.17).[142] They obtained β-arylated phosphonate and β-aryl- and alkenyl-nitro compounds in moderate to excellent yields and with high selectivity.



Scheme 3.17: 1,4-addition of organoboron reagents to alkenylphosphonate and nitroalkenes catalysed by rhodium

In 1998, Miyaura *et al.* first published the 1,2-addition of alkenyl- and aryl-boronic acids to aromatic aldehydes catalysed by rhodium in moderate to good yield.[143] They observed that the reaction was sensitive to electronic effects of substituents borne by both reacting partners. In fact, while the addition of an electron-poor aldehyde with electron-rich boronic acid was facile, the addition of an electron-rich aldehyde with an electron-poor boronic acid was relatively sluggish. They also observed that aromatic ketones were unreactive under these conditions and the reaction was specific to aromatic aldehydes. Later, Batey and co-workers and Genet *et al.* reported the 1,2-addition of alkenyl- and aryl-trifluoroborate salts to aldehydes in good yield.[134,137,144]

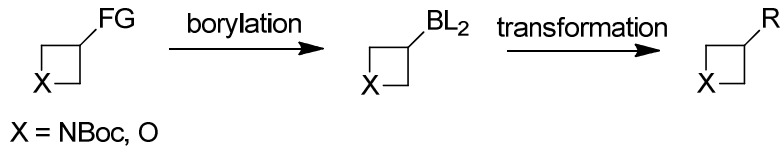


Scheme 3.18: 1,2-Addition of boronic acid derivatives to aldehydes catalysed by rhodium

4. Aims

Boronic acid derivatives have important applications in modern synthetic chemistry. It has been shown previously that the oxetane ring could be an important framework in medicinal chemistry. By synthesizing boronic acid derivatives of oxetane, useful intermediates would be provided for the introduction of small heterocyclic rings into different scaffolds of interest.

The initial aim of this project was to synthesize the boronic acid or ester and trifluoroborate salts of azetidine, then after optimization, the methodology would be applied to the oxetane moiety. After this, their application in different transformations such as Suzuki-Miyaura reaction and the addition to carbonyl containing compounds would be examined.



Scheme 3.19: Project aim

5. Synthesis of azetidine and oxetane boronic acid derivatives

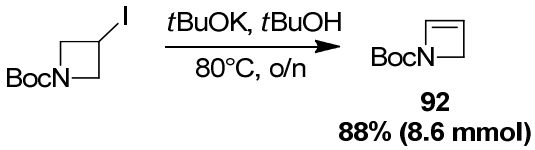
The commercially available 1-Boc-3-iodoazetidine and 3-iodooxetane were chosen as starting materials for this project. The route development and optimization studies were carried on 1-Boc-3-iodoazetidine as it is the cheaper of the two reagents.

A previous study carried out within the group showed that the transmetallation reaction between the azetidine organozinc and bromocatechol borane failed to provide the desired product. However, the dehydration of iodo-azetidine successfully provided the desired alkene in good yield thereby setting the stage for a subsequent

hydroboration reaction. The hydroboration strategy was therefore pursued in the first instance.

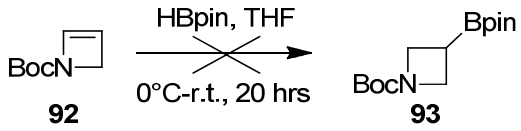
5.1. Synthesis of borylated heterocycles by hydroboration

The first attempted strategy was to dehydrate 3-iodoazetidine to form the alkene **92** which would then undergo hydroboration to furnish the boronic acid or ester derivative. The N-Boc-3-iodoazetidine was successfully dehydrated using the conditions reported by Landis *et al.*[145] 3-Iodoazetidine was treated with potassium *tert*-butoxide in *tert*-butanol at 80 °C overnight to furnish the alkene **92** 88% yield (Scheme 3.20).



Scheme 3.20: Synthesis of **92**

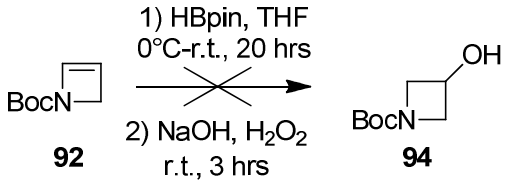
With the alkene **92** in hand, the hydroboration was then attempted. First, pinacolborane was used in THF (Scheme 3.21).[127] Unfortunately, neither the desired product **93** or starting material but decomposition and a complex mixture was observed upon crude NMR spectroscopic analysis.



Scheme 3.21: Hydroboration attempt of **92**

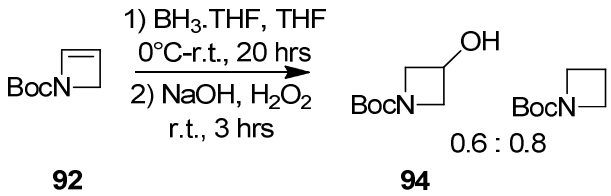
In order to demonstrate that the hydroboration occurred and to establish whether or not the desired product was unstable under the work up conditions, the hydroboration reaction was followed by an oxidation step using sodium hydroxide and hydrogen peroxide to furnish the alcohol **94** (Scheme 3.22). Unfortunately, no desired

compound **94** or starting material but a complex mixture was observed on analysis of the crude reaction mixture.



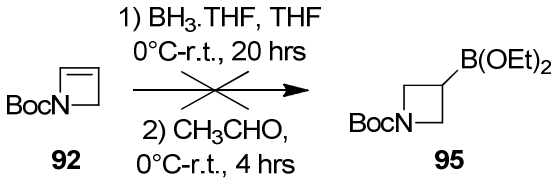
Scheme 3.22: Synthesis attempt of **92**

Borane complexed with THF was then used under the same conditions. Pleasingly, the desired alcohol product **94** was isolated but it was contaminated by *N*-Boc-azetidine, presumably generated by a protodeborylation side-reaction (Scheme 3.23).



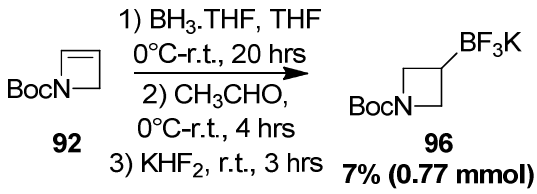
Scheme 3.23: Synthesis of **94**

These experiments suggested that borane-THF was a suitable hydroboration agent, but that the borylated intermediate might be unstable. The synthesis of the boronic ester was attempted using borane as the hydroborating agent followed by addition of acetaldehyde to form the boronic ester **95** (Scheme 3.24).[122] Unfortunately, no desired boronic ester **95** or starting material were isolated from this transformation.



Scheme 3.24: Synthesis of **95**

Given that potassium trifluoroborate salts are usually more stable than their boronic acid and ester counterparts, the synthesis of the potassium azetidine trifluoroborate salt was then attempted. The same process described previously followed by the addition of potassium bifluoride provided the desired compound **96** in 7% yield (Scheme 3.25).[126]



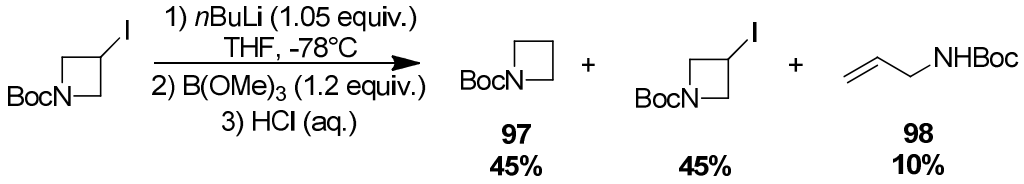
Scheme 3.25: Synthesis of the trifluoroborate salt **96**

As the desired compounds were isolated in very poor yield, the hydroboration strategy was not developed further.

5.2. Synthesis from organometallic reagents

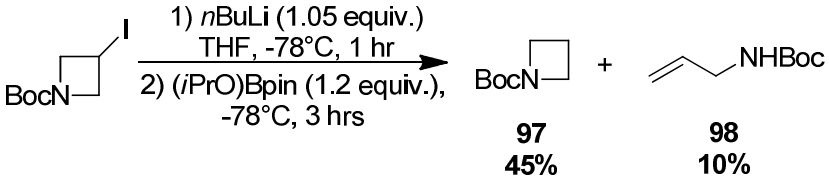
As the hydroboration strategy failed to provide a suitable method to synthesise the desired azetidine boronic ester and potassium trifluoroborate salt, another strategy was envisaged. In fact, we wanted to take advantage of the halide group to make a suitably reactive organometallic derivative.

First, the synthesis of the azetidine boronic acid was attempted using butyllithium, followed by trimethoxyborane and then by an acidic work-up. Unfortunately, the crude NMR analysis showed 45% of starting material remained, together with 45% of *N*-Boc-azetidine by-product and 10% of allylamine (Scheme 3.26).



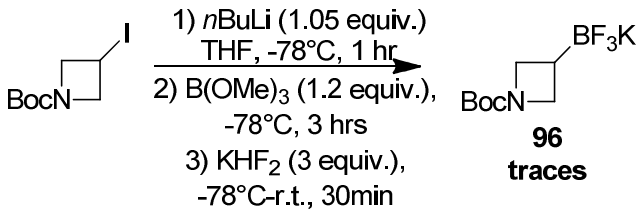
Scheme 3.26: Synthesis attempt of boronic acid

The recovery of N-Boc-azetidine suggests that transmetallation took place but that either this intermediate or the corresponding boronic ester might have been too unstable to be isolated. Accordingly the synthesis of the more stable pinacol boronic ester was then attempted. 3-Iodoazetidine was treated with *n*-butyllithium and then with (*i*PrO)Bpin to form the pinacol boronic ester of azetidine. Unfortunately, analysis of the crude mixture showed only allyamine and azetidine (Scheme 3.27).



Scheme 3.27: Synthesis attempt of boronic ester **93**

Again, the observation of the azetidine by-product could suggest that the borylation did occur but that the organolithium species was quenched during the work-up. The synthesis of the trifluoroborate salt was therefore investigated next. 3-Iodoazetidine was treated with *n*-butyllithium followed by trimethoxyborane and then potassium hydrogen fluoride. Unfortunately, only traces of product were observed (Scheme 3.28).

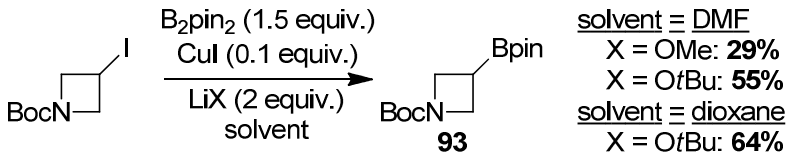


Scheme 3.28: Synthesis of potassium trifluoroborate **96**

This strategy looked promising but the desired product could only be isolated in trace amounts. It was therefore decided to try an alternative route.

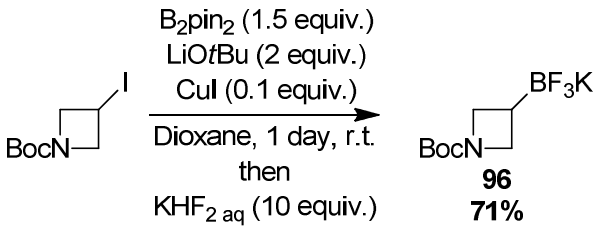
5.3. Synthesis using copper catalyzed borylation

As the strategy of metal-halogen exchange proved to be unsuitable for the synthesis of the small-strained heterocyclic boronic acid derivatives, we decided to take advantage of a transition metal catalyzed borylation methodology. Specifically, Marder *et al.* recently reported a method for the synthesis of alkylboronic esters using copper catalysed borylation of alkylhalides.[146] Pleasingly, when *N*-Boc-3-iodoazetidine was subjected to these conditions using copper iodide, lithium methoxide and bis(pinacolato)diborane in DMF, the desired boronic ester **93** was isolated in 29% yield (Scheme 3.29). Using lithium *tert*-buthoxide instead of lithium methoxide improved the reaction yield to 55%. Using dioxane instead of DMF as the reaction solvent, also increased the yield to 64%.



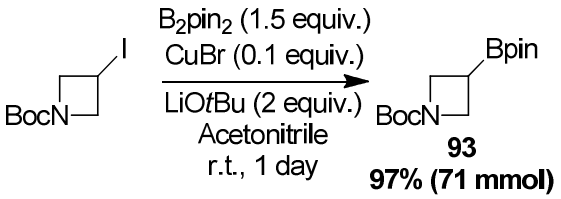
Scheme 3.29: copper catalysed synthesis of **93**

The potassium trifluoroborate salt of the azetidine was also successfully synthesised in 71% in a one-pot process by treatment of the generated pinacol boronic ester **93** with potassium bifluoride (Scheme 3.30).



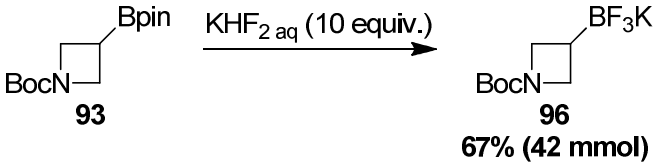
Scheme 3.30: Synthesis of **96**

Optimization studies highlighted that the best conditions found for the synthesis of **93** were the treatment of *N*-Boc-3-iodoazetidine with LiOtBu, B_2pin_2 and CuBr in acetonitrile.[147] The desired product was then isolated in 97% on 71 mmol scale (Scheme 3.31).



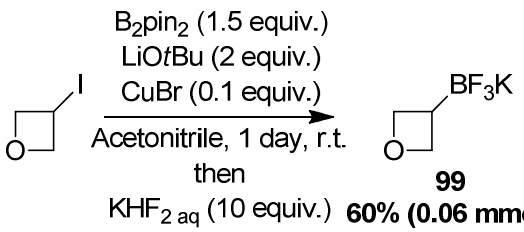
Scheme 3.31: Optimised synthesis of **93**

The trifluoroborate salt was then synthesized in 67% yield on 42 mmol scale by treatment of the pinacol boronic ester with potassium bifluoride (Scheme 3.32).



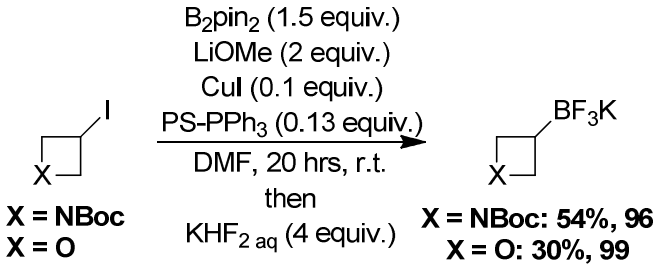
Scheme 3.32: Optimized synthesis of **96**

The methodology was then applied to 3-iodooxetane. The oxetane-pinacol ester was successfully synthesized using the best conditions found for the azetidine, but it could not be isolated in pure form. It was then decided to synthesize in a 'one-pot' process the trifluoroborate salt. Pleasingly, the potassium oxetane trifluoroborate salt **99** was isolated in 60% yield on 0.06 mmol scale (Scheme 3.33).



Scheme 3.33: copper catalysed synthesis of **99**

Unfortunately during our investigations, Molander *et al.* described the synthesis of the potassium organotrifluoroborate salt of nitrogen and oxygen saturated heterocycle in modest to good yield.[148]



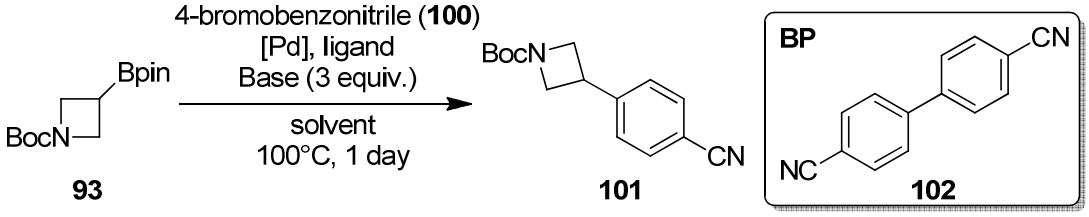
Scheme 3.34: Molander's synthesis of trifluoroborate salt **96** and **99**

6. Coupling chemistry of azetidine and oxetane boronic acid derivatives

The application of these organoboron reagents in organic synthesis were first studied on the azetidine derivatives as the starting material is more readily available and less expensive.

6.1. Suzuki-Miyaura cross-coupling reaction

With a large amount of azetidine pinacol boronic ester and potassium trifluoroborate salt in hand, the Suzuki-Miyaura cross-coupling reaction was investigated. The first attempt of the Suzuki-Miyaura cross-coupling was carried out using 4-bromobenzonitrile **100** and boronic ester **93** with various palladium catalysts, ligands, bases and solvents. The results are summarized in Table 3.1.



Entry	[Pd]	Base	Solvent	Ligand	Result
1[a]	$Pd(OAc)_2$	K_2CO_3	Toluene:H_2O (10:1)	XPhos	**93** recovered
2[a]	$Pd(OAc)_2$	Cs_2CO_3	Toluene:H_2O (10:1)	XPhos	**93** and **100** recovered
3[a]	$Pd(OAc)_2$	Cs_2CO_3	Toluene:H_2O (10:1)	SPhos	**93** and **100** recovered
4[a]	$Pd(OAc)_2$	Cs_2CO_3	Toluene:H_2O (10:1)	*n*BuPAd$_2$.HI	**93** and **100** recovered
5[a]	$Pd(OAc)_2$	Cs_2CO_3	Toluene:H_2O (10:1)	DavePhos	**93** and **102** recovered
6[b]	$Pd(dppf)Cl_2$ .CH_2Cl_2	Cs_2CO_3	Toluene:H_2O (10:1)	-	**93** and **102** recovered
7[b]	$Pd(dppf)Cl_2$ .CH_2Cl_2	Cs_2CO_3	Dioxane	-	**93** and **102** recovered
8[b]	$Pd(dppf)Cl_2$ .CH_2Cl_2	Cs_2CO_3	Ethanol	-	**93** and **102** recovered
9[c]	$Pd(PPh_3)_4$	K_3PO_4	Dioxane	-	**93** and **102** recovered

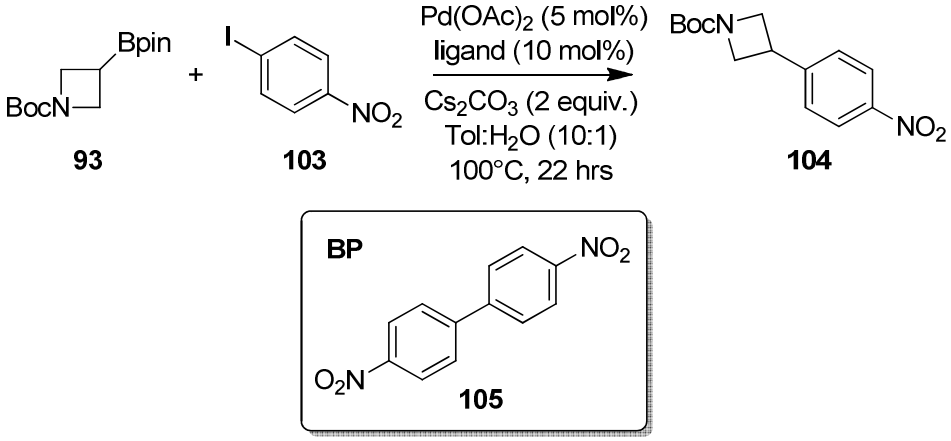
[a] Reactions were carried out with $Pd(OAc)_2$ (2 mol%) and ligand (3 mol%); [b] Reactions were carried out with $Pd(dppf)Cl_2.CH_2Cl_2$ (8 mol%); [c] Reactions were carried out with $Pd(PPh_3)_4$ (6 mol%)

Table 3.1: Suzuki-Miyaura cross-coupling attempt between **93** and aryl bromide

As shown in Table 3.1, unfortunately no cross-coupled material could be detected from any of these reactions. The use of Buchwald ligands (entries 1 to 3) returned both starting materials. Surprisingly, after using the conditions reported by Molander and co-workers[149] (entry 4) for the cross-coupling of cyclopropyl and cyclobutyl

trifluoroborates with aryl chlorides, no desired compound was observed. In many other cases, the starting pinacol boronic ester and the product arising from aryl halide homocoupling were recovered (eg entries 5-9). These results implied that the oxidative addition step occurred but the transmetalation step was very slow.

Some attempts at cross coupling were also carried out using 1-iodo-4-nitrobenzene, $Pd(OAc)_2$ and Cs_2CO_3 in toluene:water (10:1). The results are summarized in Table 3.2.

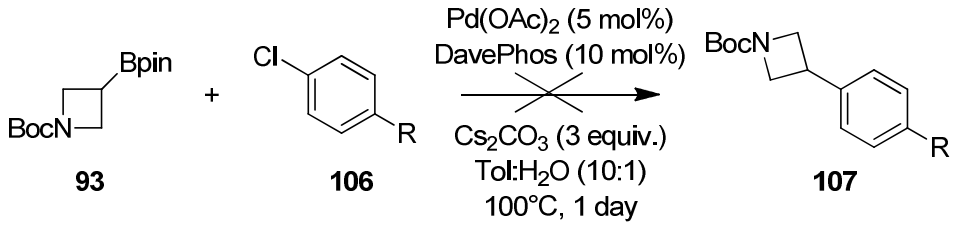


Entry	Ligand	Result
1	DavePhos	**93** and **103** recovered
2	SPhos	**93** and **103** recovered
3	RuPhos	**93** and **103** recovered
4	$nBuPAd_2$.HI	**93** and **103** recovered
5	XPhos	**93** and **105** recovered

Table 3.2: Suzuki-Miyaura cross-coupling attempt between **93** and aryl iodide

As shown in Table 3.2, no desired cross-coupled compound was isolated. In fact, only the two starting materials were recovered in most cases (entries 1 to 4). In the case when XPhos was used as the ligand, the product arising from the homocoupling reaction was again observed.

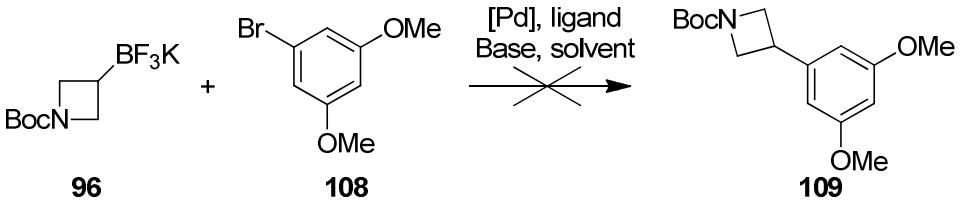
We next attempted to use a chlorobenzene coupling partner bearing different groups in order to establish if the reaction is sensitive to aryl ring electronic effects. The results are summarized in Table 3.3.



Entry	R	Result
1	-H	**93** and **106** recovered
2	$-NO_2$	**93** and **106** recovered
3	$-CONH_2$	**93** and **106** recovered
4	$-NH_2$	**93** and **106** recovered

Table 3.3: Suzuki-Miyaura cross-coupling attempt between **93** and aryl chloride

As shown in Table 3.3, both starting materials were recovered after each reaction attempted. To help with our investigations, a collaboration with AstraZeneca's catalyst screening service allowed a broader range of conditions to be employed for cross-coupling the azetidine trifluoroborate salt **96** and 1-bromo-3,5-dimethoxybenzene. The conditions attempted are summarized in Table 3.4.



		10mol% Peppsi-ipent	10mol% Pd(OAc)2/20mol%(p-CF3-Ph)3P	10mol% Pd(dppf)Cl2	10mol%Pd(OAc)2/20mol% Bretphos	10 mol% p-Trifluoro amphos	10mol% Na2PdCl4/DtBPPS (water soluble system)	10mol% Pd(OAc)2/20mol% tBu3P.HBF4	10mol% Pd(OAc)2/20mol%Mor-Dalphos	5mol% Buchwald Pd-precat/20mol%RuPhos	10mol%Pd(OAc)2/20mol% Ruphos	10 mol% Pd(OAc)2/20mol% Cataxium A	10mol% Pd(OAc)2/20mol% Jackiephos
		1	2	3	4	5	6	7	8	9	10	11	12
4M.K2CO3	n-BuOH	A											
4M.NaOH		B											
4M.K2CO3	NMP	C											
4M.NaOH		D											
4M.K2CO3	Dioxane	E											
4M.NaOH		F											
4M.K2CO3	Toluene	G											
4M.NaOH		H											

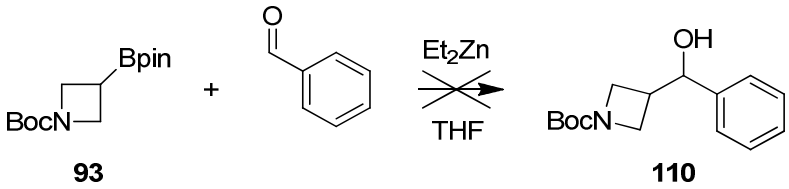
Table 3.4: Suzuki-Miyaura cross-coupling attempt between **96** and aryl bromide

Unfortunately, in all cases examined, the use of potassium trifluoroborate failed to provide any cross-coupled material.

As the Suzuki-Miyaura cross-coupling reaction of these heterocycles appeared to be unworkable, we decided to investigate another application of boronic acid derivatives.

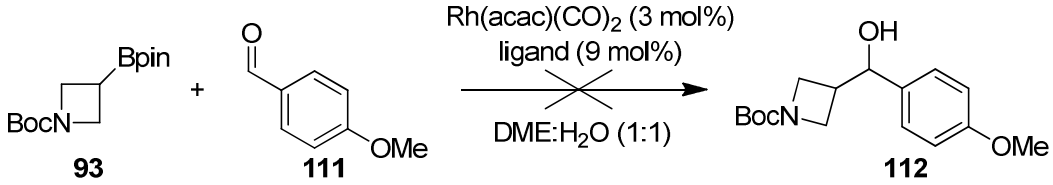
6.2. Addition to carbonyl compounds

The azetidine pinacol boronic ester was used in a 1,2-addition reaction with benzaldehyde. Following the conditions described by Fandrick,[150] we employed diethylzinc in THF but unfortunately no product arising from the 1,2-addition was observed.



Scheme 3.35: zinc catalysed 1,2-addition of **93**

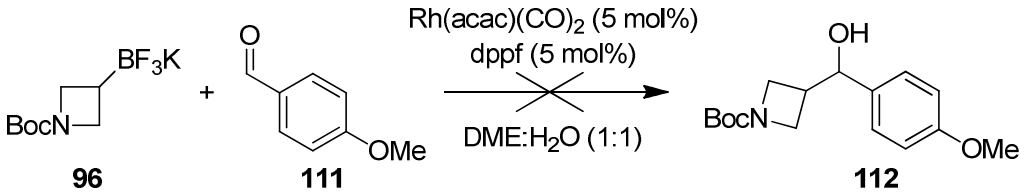
Unfortunately, the rhodium catalyzed 1,2-addition using **93** and *p*-methoxybenzaldehyde also failed to deliver the desired alcohol.



Entry	Ligand	Result
1	dppf	**93** and **111** recovered
2	PPh_3	**93** and **111** recovered
3	tBu$_3$P	**93** and **111**recovered
4	nBu$_3$P	**93** and **111** recovered

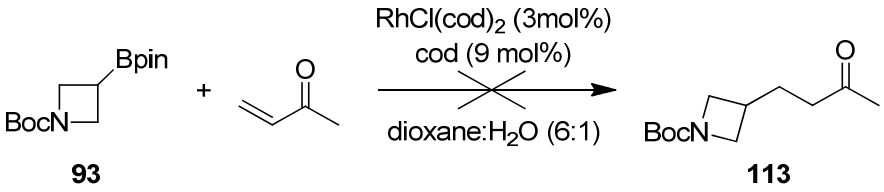
Table 3.5: 1,2-addition of **93** and **111** catalysed by rhodium

The 1,2-addition was then attempted following the conditions described by Miyaura using the azetidine trifluoroborate salt and *p*-methoxybenzaldehyde in the presence of $Rh(acac)(CO)_2$ and dppf in DME:H_2O.[143] Unfortunately, no desired compound was observed (Scheme 3.36).



Scheme 3.36: rhodium catalysed 1,2-addition of **96**

The conjugate addition of **93** to methyl vinyl ketone (MVK) was then attempted using a combination of $RhCl(cod)_2$ and cyclooctadiene in dioxane:water (Scheme 3.37). Unfortunately, no product from the 1,4-addition was observed after reaction.

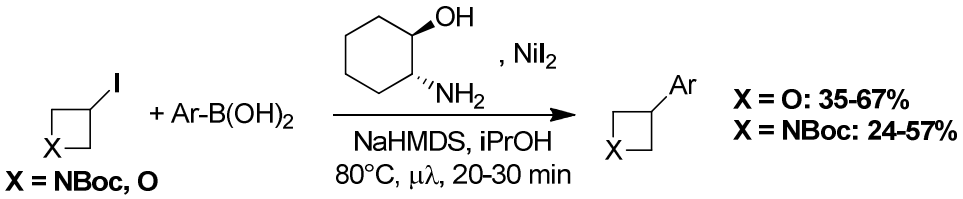


Scheme 3.37: rhodium catalysed conjugate addition of **93** to MVK

As the addition to aldehyde or α,β-unsaturated ketone did not provide any interesting results, we decided to investigate another application of these small-strained heterocyclic boronic acid derivatives.

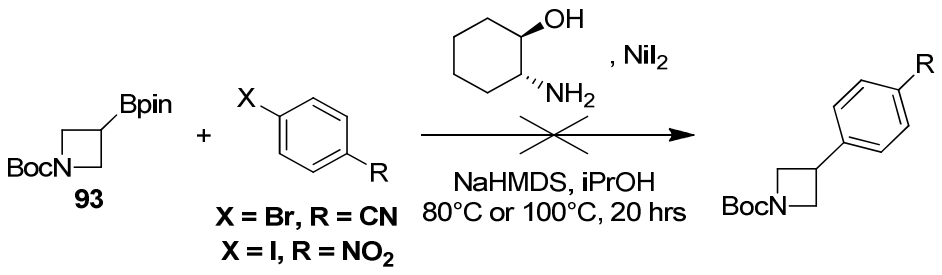
6.3. Nickel-catalysed cross-coupling

Recently, Duncton and co-workers reported a methodology to prepare aryl oxetanes and aryl azetidines using 3-iodooxetane or *N*-Boc-3-iodoazetidine and arylboronic acids catalysed by NiI_2.[49]



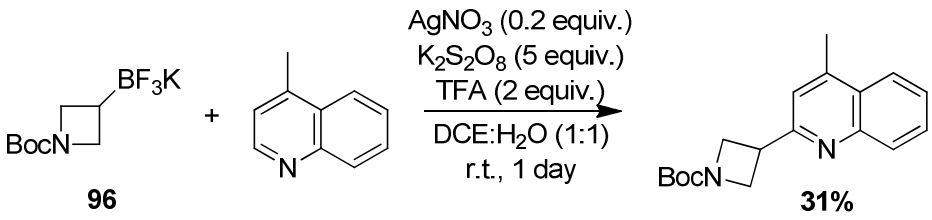
Scheme 3.38: Synthesis of aryl oxetanes and azetidines

The azetidine pinacol boronic ester **93** and *p*-bromo cyanobenzene or *p*-iodo nitrobenzene were subjected to the conditions found by Duncton. Surprisingly, no coupled compound was observed. At this point, the poor reactivity of these organoboron derivatives was suspected.



Scheme 3.39: nickel catalyzed cross-coupling of **93**

Unfortunately during our investigations, Molander *et al.* demonstrated the participation of these intermediates in the Minisci reaction.[148] As shown in this paper, potassium azetidine trifluoroborate salt **96** has poor reactivity in the Minisci reaction providing the corresponding azetidine containing heterocycles in poor yield. Moreover, Molander did not report the application of the oxetane version in this reaction.



Scheme 3.40: Minisci reaction using azetidine trifluoroborate salt **96**

7. Conclusion

The boronic acid derivatives of azetidine and oxetane were successfully synthesised in good to excellent yield using copper-catalysed borylation from their commercially available corresponding halides. Unfortunately, in our hands, their application in Suzuki-Miyaura cross-coupling was unsuccessful. We concluded that these heterocycles have a poor reactivity towards cross-coupling reactions.

This trend of reactivity was also observed by Molander *et al.* It is worth noting that our synthesis of the potassium trifluoroborate salts of azetidine and oxetane provided better yields of these species under our slightly different conditions.

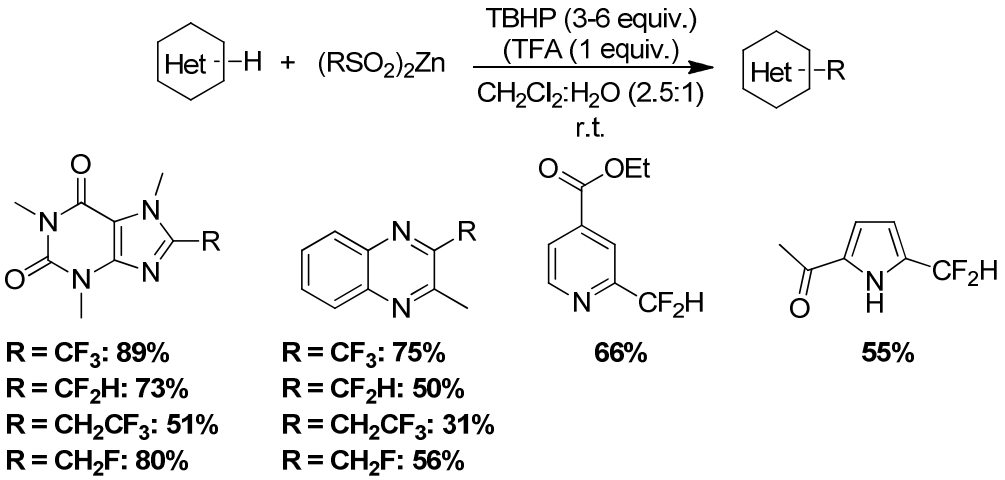
In order to pursue our efforts to introduce small strained heterocycles into functionalised scaffolds of interest for medicinal and agrochemical chemistry, we next decided to investigate the chemistry of sulfinate salts. The following section will describe our efforts in this area.

Chapter 4: Synthesis and applications of azetidine and oxetanes sulfinate salts

1. Introduction

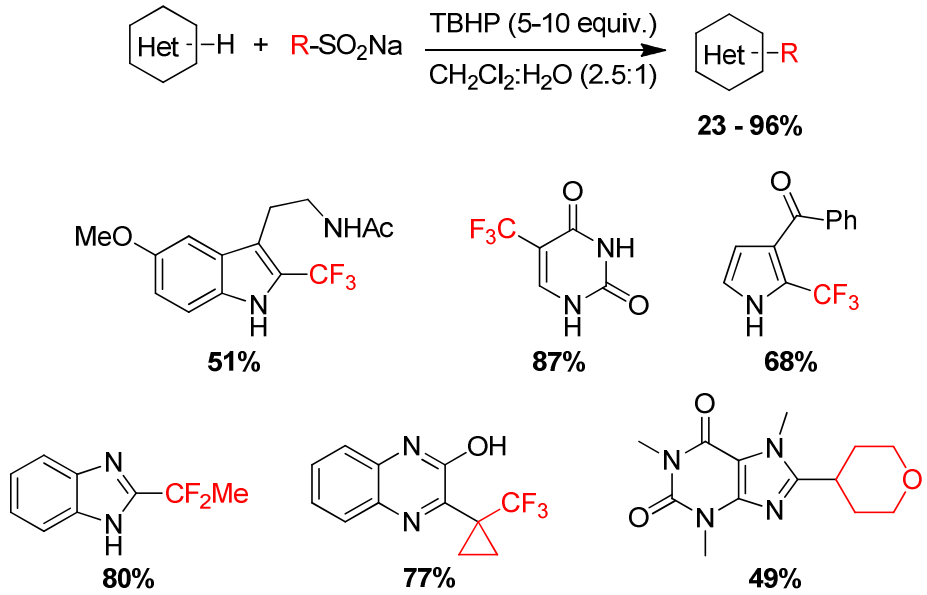
1.1. Reaction of sulfinate salts with heteroaromatic compounds

Recent studies by Baran *et al.* have focused on the development of efficient reactions for the direct introduction of a range of useful groups into heterocycles of importance in medicinal chemistry. For this purpose, they have established zinc sulfinate salts as useful reagents that allow a range of groups to be transferred under mild conditions (Scheme 4.1).[151]



Scheme 4.1: Functionalisation of heterocycles using zinc sulfinate salts

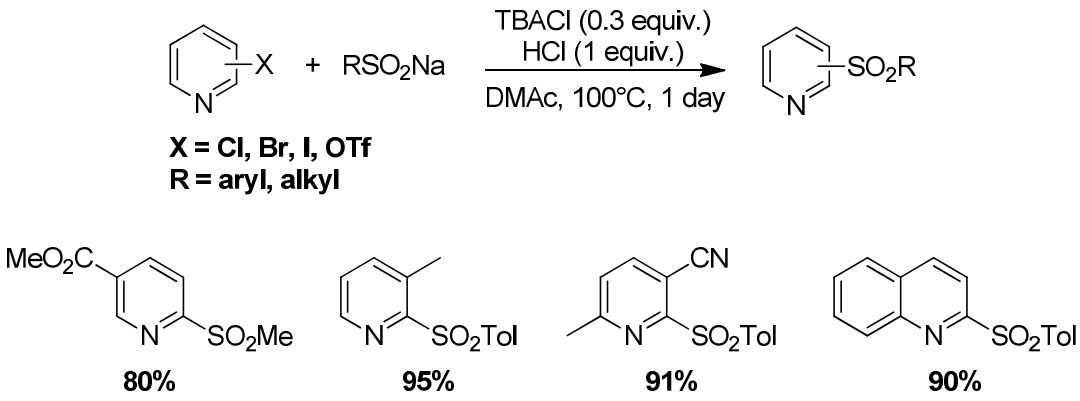
They also reported the synthesis and utilization of various sodium sulfinates in C-H functionalisation of heterocycles (Scheme 4.2).[152]



Scheme 4.2: C-H functionalisation of heterocycles

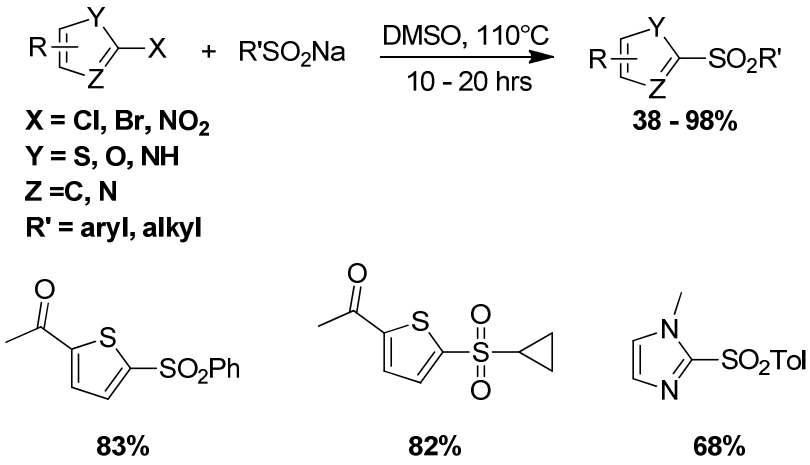
1.2. Reaction of sodium sulfinate salts with halogenated compounds

A series of related transformations whereby the sulfone group is also integrated into the product has also been developed. For example, the addition of sulfinate salts to halogenated aromatic and heteroaromatic compounds has been described. In 2011, Maloney and co-workers reported the one-pot synthesis of sulfonylated pyridines from halogenated pyridines and sodium sulfinate salts in good to excellent yield (Scheme 4.3).[153]



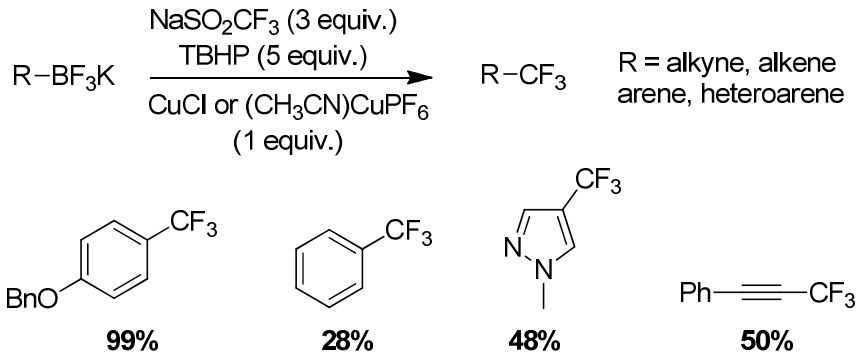
Scheme 4.3: Synthesis of sulfonylated pyridines

A few years later, Chen *et al.* reported the synthesis of sulfonylated heterocycles in moderate to excellent yield by simply heating a combination of heterocycle substrate and sulfinate salt in DMSO (Scheme 4.4).[154]



Scheme 4.4: Synthesis of sulfonylated 5-membered heterocycles

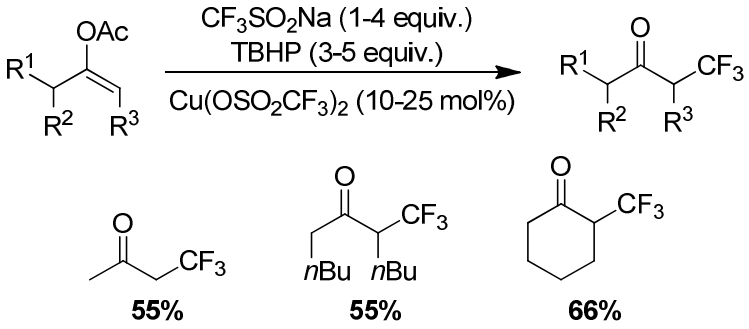
In 2013, Molander reported the synthesis of trifloromethylated aromatic and heteroaromatic compounds from the corresponding unsaturated trifluoroborate salts and Langlois's reagent in the presence of copper salts (Scheme 4.5).[155] Once again the salts undergo loss of SO_2 thereby facilitating C-C bond formation.



Scheme 4.5: Synthesis of trifluoromethylated aromatic and heteroaromatic compounds

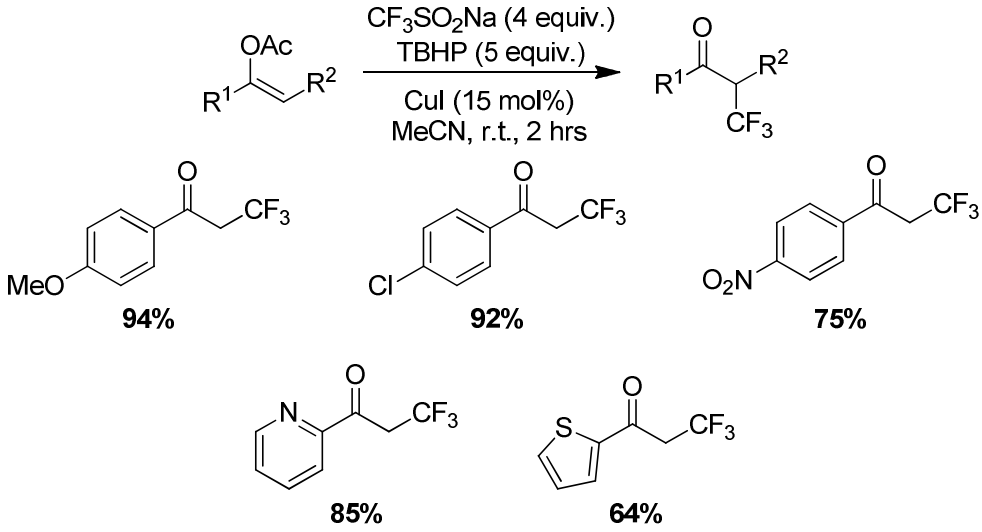
1.3. Addition of sodium sulfinate salt to alkenes

The synthesis of α-trifluoromethyl ketones from enol esters and CF_3SO_2Na catalysed by copper was first described by Langlois in 1992.[156] They observed that the reaction generally required an excess of sodium sulfinate salt to provide the trifluoromethyl product in moderate yield (Scheme 4.6).



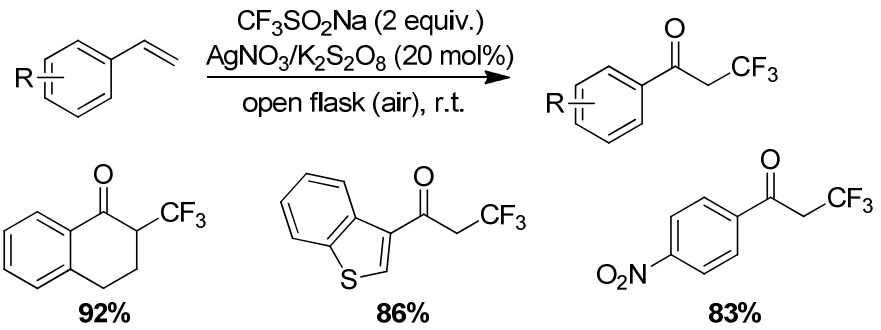
Scheme 4.6: Cu(II) catalysed addition of CF_3SO_2Na to enol esters

Recently Duan and co-workers reported the synthesis of α-trifluoromethyl ketones from acetyl enol ester and CF_3SO_2Na catalysed by copper(I) salts.[157] Aromatic and heteroaromatic α-trifluoromethyl ketones were obtained in good to excellent yield under these conditions (Scheme 4.7).



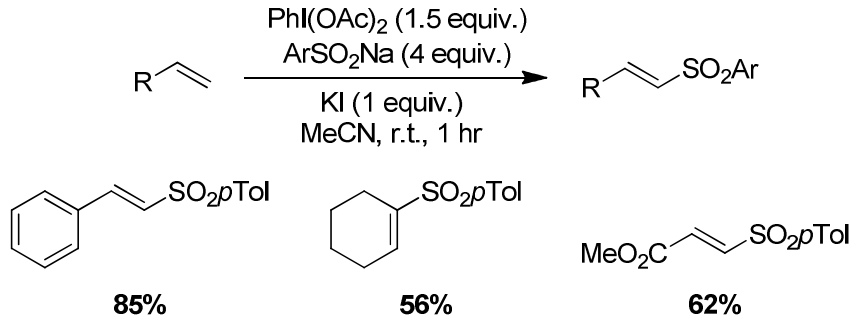
Scheme 4.7: Cu(I) catalysed addition of CF_3SO_2Na to enol esters

In 2013, Maiti described the direct synthesis of α-trifluoromethyl ketones from alkenes in excellent yields.[158] This method is compatible with a range of functional groups, such as cyano, aldehyde and ester, and also with some heterocycles (Scheme 4.8).



Scheme 4.8: addition of CF_3SO_2Na to alkenes

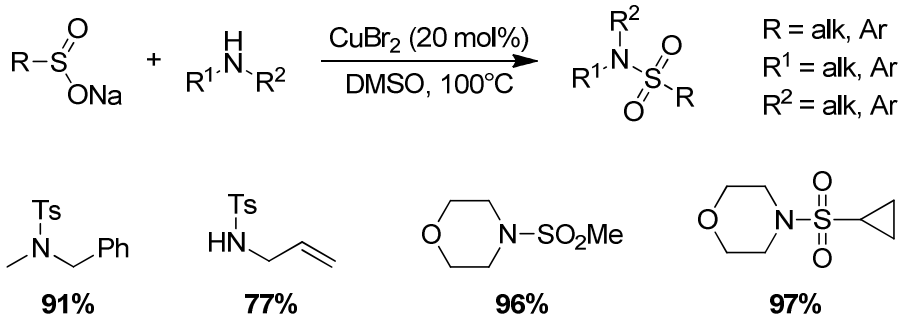
In 2010, Kuhakarn *et al.* reported the sulfonylation of alkenes using (diacetoxyiodo)benzene and sodium aryl sulfinates (Scheme 4.9).[159] Using their method, a range of sulfones could be obtained in moderate to good yield.



Scheme 4.9: addition of aryl sulfinate salts to alkenes

1.4. Addition of sodium sulfinate salts to amines

The addition of sodium sulfinate salts to amines has been recently described by Jiang and co-workers.[160] They reported the oxidative copper catalysed cross-coupling between amines and sodium sulfinate using oxygen or DMSO as the oxidant in good to excellent yield (Scheme 4.10). Various functional group were tolerated under this procedure, such as alcohol, halogen, methoxy and nitrile.



Scheme 4.10: reaction of sulfinate salts with amines

2. Aims

As discussed in this thesis, oxetanes and azetidines are important fragments in modern synthetic chemistry and medicinal chemistry. Although our efforts to employ boronic acid derivatives of azetidines and oxetanes in coupling reactions were unsuccessful, owing to the poor reactivity of these intermediates, we envisaged that we could develop methods for transferring these fragments into other compounds by exploiting the chemistry of the corresponding zinc sulfinate or sodium sulfinate salts (Figure 4.1).

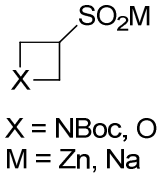
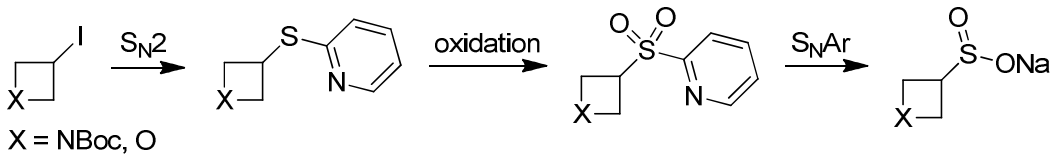


Figure 4.1: sodium and zinc sulfinate of azetidine or oxetane

3. Synthesis of oxetane and azetidine sulfinate salts

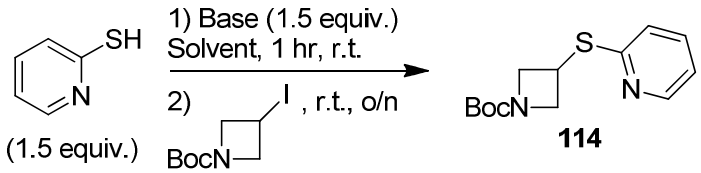
The commercially available 1-Boc-3-iodoazetidine and 3-iodooxetane were chosen as starting materials for this project. The route development and optimization studies were carried on 1-Boc-3-iodoazetidine as it is the cheaper of the two reagents.

Our strategy for the synthesis of the sulfinate salts was to realize the nucleophilic substitution of the iodide by pyridinethiol, and then to perform the oxidation of the thioether group to a sulfone. Nucleophilic aromatic substitution of the pyridine ring with a good nucleophile would then release the sulfinate salt (Scheme 4.11).



Scheme 4.11: transformation of sulfinate salts

With regard to the first step of the sequence, the deprotonation of thiolpyridine with sodium hydride in THF was carried out before addition of the 3-iodoazetidine. We were delighted to isolate the desired product **114** in 40% yield after workup and purification. The solvent and the base used in reaction were then optimized (Table 4.1). Surprisingly, when potassium hydride was used as the base in THF, no reaction was observed (entry 2). However, when the reaction was carried out in THF using NaH, *n*-BuLi and LHMDS, the thioether **114** was produced in moderate to good yields (entry 1, 3 and 4). When DMF was used instead of THF, all bases provided **114** in better yield (entry 5 to 8). However, when *n*-BuLi was used, an unidentified impurity was isolated with the desired product **114** (entry 7). Ultimately, we opted to use LHMDS in DMF as it provided clean product in excellent yield.

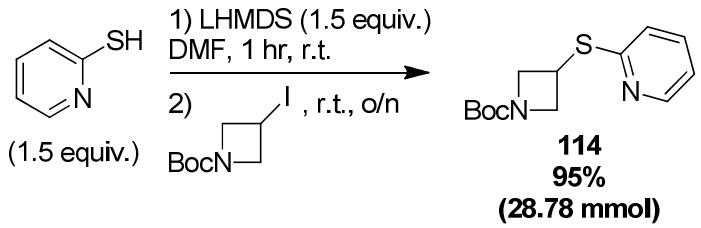


Entry	Base	Solvent	Result[a][b]
1	NaH	THF	40%
2	KH	THF	NR[c]
3	*n*-BuLi	THF	45%
4	LHMDS	THF	72%
5	NaH	DMF	70%
6	KH	DMF	61%
7	*n*-BuLi	DMF	>100%
8	LHMDS	DMF	95%

[a] Reactions were carried out on 0.353 mmol of N-Boc-3-iodoazetidine; [b] isolated yield; [c] NR = No Reaction

Table 4.1: Optimisation for the synthesis of **114**

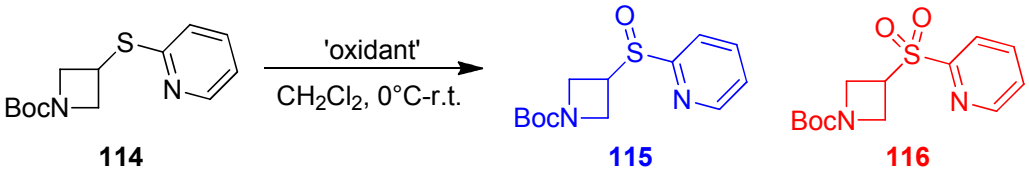
Using these optimal conditions, the reaction was carried on a larger scale (Scheme 4.12). Pleasingly, the reaction was found to be reproducible and afforded the desired product in a similar yield.



Scheme 4.12: Scale-up of the synthesis of **114**

With a large amount of the thioether **114** in hand, the oxidation step was then investigated. First, different oxidising agents were employed (Table 4.2). When hydrogen peroxide was used, the sulfoxide product was obtained as the major product of the reaction, together with a small amount of the desired sulfone (entry 1). The oxidation using sodium periodate only furnished 33% of sulfoxide **116** (entry 2).

However, the use of mCPBA provided better results. In fact, when 2.1 equivalents of mCPBA was used, a better conversion into sulfone was observed compared to H_2O_2 (entry 3). Moreover, when more equivalents of mCPBA were used, the conversion into the sulfone **116** increased (entry 4 and 5).



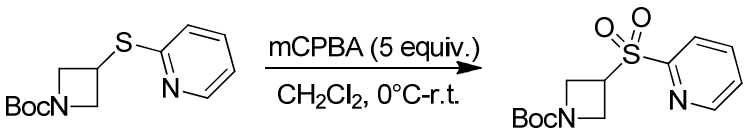
114 **115** **116**

Entry	Oxidant (n equiv.)	time	115:116 (yield[b])
1	H_2O_2 (2.1)	1 day	3 : 1
2	$NaIO_4$ (4)[a]	4 hrs	0 : 1 (33%)
3	mCPBA (2.1)	1 hr	1 : 1
4	mCPBA (4)	1hr	1 : 3
5	mCPBA (5)	5 hrs	0 : 1 (94%[c])

[a] using 0.1 equiv. of $RuCl_3$ in CH_2Cl_2:MeCN:H_2O; [b] isolated yield; [c] reaction carried on 3.7 mmol

Table 4.2: Optimisation for the synthesis of **116**

Using these optimal conditions, the reaction was carried on a larger scale (Scheme 4.13). Pleasingly, the reaction was found to be reproducible on a larger scale and afforded the desired product with the same yield.



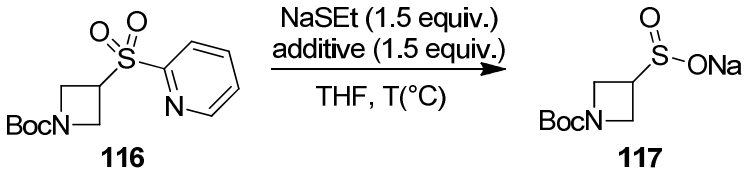
114

116
94%
(27.31 mmol)

Scheme 4.13: Scale-up of the synthesis of **116**

With a large quantity of sulfone **116** in hand, the synthesis of the sodium sulfinate salt was next investigated (Table 4.3). When the reaction was attempted using sodium ethanethiolate at room temperature or at 60 °C, no reaction was observed

(entry 1 and 2). However, when sodium hydride was added to the reaction mixture, the desired compound was isolated. Unfortunately, the product was contaminated by the remaining sodium ethanethiolate. Different methods of purification were then attempted. Trituration of the crude mixture with diethyl ether failed to provide pure product. Purification on different stationary phases was also attempted. For example, using alumina or florisil as the stationary phases, the desired product was still found to be contaminated by sodium thiosulfate. However, the purification on silica provided the desired product **117** in good yield (entry 3).



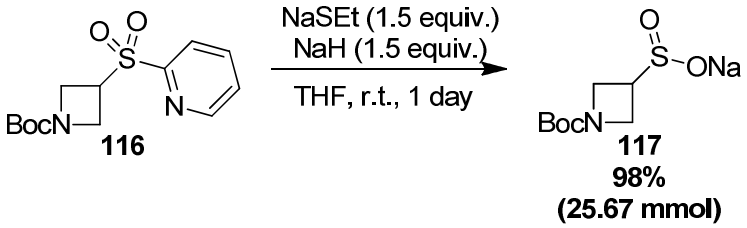
116 **117**

Entry	Additive	T(°C)	yield[a]
1	-	r.t.	NR[b]
2	-	60°C	NR[b]
3	NaH	r.t.	97%

[a] isolated yield; [b] NR = No Reaction.

Table 4.3: Optimisation for the synthesis of **117**

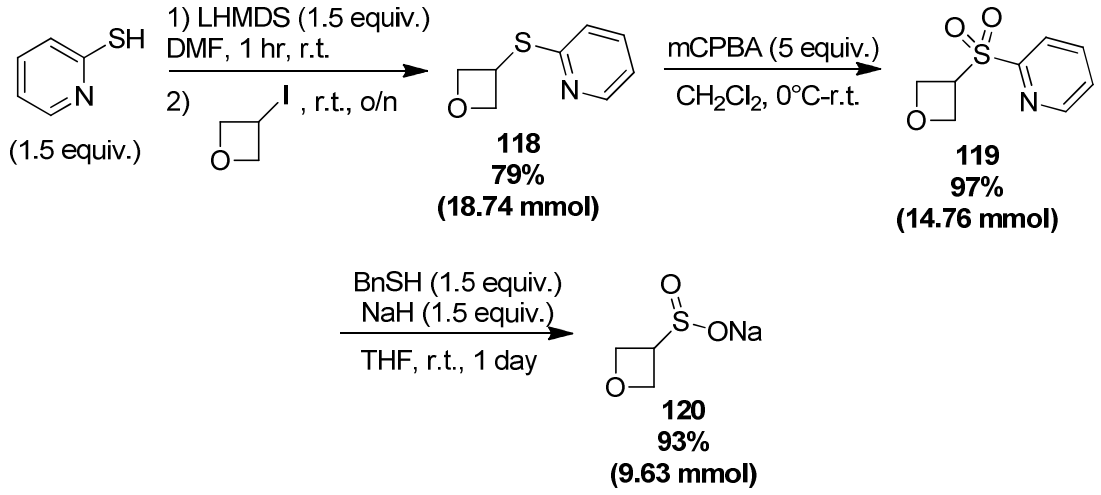
Using the best conditions found earlier, the reaction was performed on a larger scale and found to be reproducible (Scheme 4.14).



Scheme 4.14: Scale-up of the synthesis of **117**

Having optimized the route to the azetidine sulfinate salt **117**, we decided to employ these conditions to generate the oxetane derivative. Pleasingly, the thiooxetane **118** and the sulfone **119** were obtained in good yield on large scale (Scheme 4.15).

However, when the nucleophilic aromatic substitution reaction was carried out using sodium ethanethiolate, the desired product **120** could not be isolated in pure form. In order to remove the organosulfur impurities more easily, we decided to employ a less polar thiolate salt. In fact, when the reaction was carried out with benzylthiol and sodium hydride, the desired product **120** could be isolated in 93% yield after purification on a silica gel chromatography.



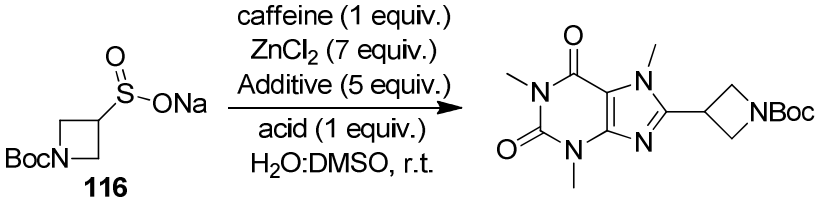
Scheme 4.15: Synthesis of **120**

With the sodium salts in hand, we decided to explore a transmetallation reaction to generate the corresponding zinc salts. However, when the azetidine sodium sulfinate salt was treated with zinc chloride, ^{1}H NMR spectroscopic analysis showed the removal of the Boc protecting group. We discontinued our studies into changing the counter ion at this stage.

4. Reaction of sulfinate salts with caffeine

As discussed at the outset of this Chapter, Baran and co-workers reported the utilization of zinc sulfinate salts for the incorporation of medicinally relevant motifs into heterocycles. As the synthesis of the zinc sulfinate by counter ion exchange was unsuccessful, the *in situ* formation of these salts was attempted (Table 4.4). Following the procedure of Baran and co-workers using $ZnCl_2$ in presence of TsOH

and TBHP, no reaction was also observed (entry 1).[151b] The use of TFA and mCPBA was also investigated, but unfortunately no desired product was observed under these conditions either (entry 2 and 3).

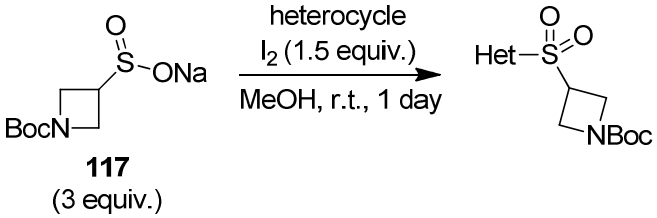


Entry	acid	Additive	Outcome
1	TsOH	TBHP	RSM[a]
2	TFA	TBHP	RSM[a]
3	TsOH	mCPBA	Boc deprotected **117**

[a] RSM = Recovered Starting Material.

Table 4.4: coupling attempts of **117** on caffeine

The scope of reacting heterocycles was investigated (Table 4.7). Unfortunately, when other heterocycles were used in place of indoles, starting material or a complex mixture was isolated. However, this preliminary study showed that reaction could work well with indoles, and so the scope of the sulfonylation process was investigated by changing the groups on the indole ring.



Entry	Heterocycle	Result
1	Quinoline	No reaction
2	Pyridine	Complex Mixture
3	Imidazole	No desired product
4	*N*-Methylimidazole	No desired product
5	2-Methylfuran	Complex mixture
6	5-Azaindole	No desired product

7	6-Azaindole	No desired product
8	Caffeine	No reaction
9	*N*-Methylindole	66%[a]

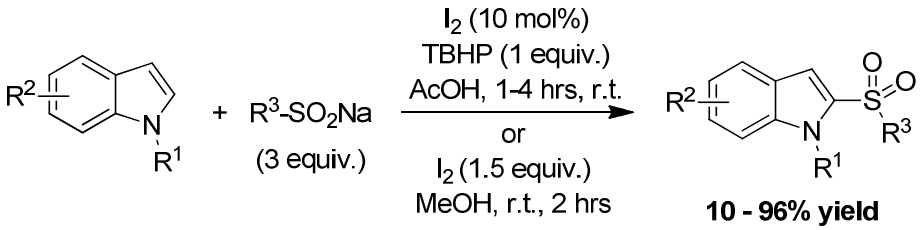
[a] isolated yield.

Table 4.5: Scope investigation

5. C2 functionalisation of indoles

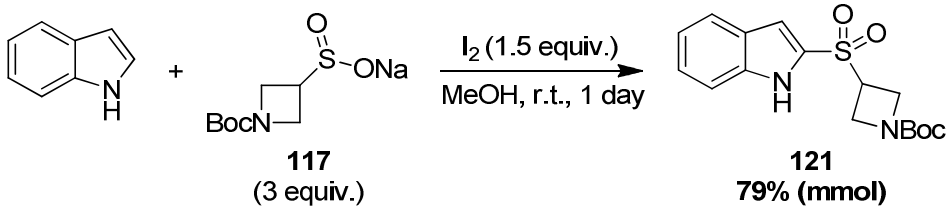
5.1. Preliminary work

During our investigation on the incorporation of azetidine into caffeine, Deng and co-workers and Kuhakarn *et al.* reported the regioselective C2-sulfonylation of indoles using sodium sulfinate salts and iodine (Scheme 4.16).[161]



Scheme 4.16: C2 functionalisation of indoles

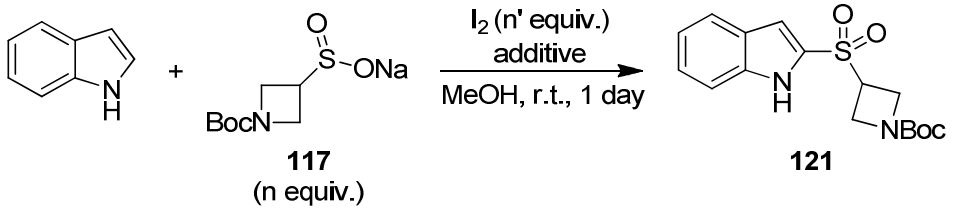
These methods appeared to be applicable for the synthesis of azetidine and oxetane derivatives. Accordingly, we applied Kuhakarn's conditions using indole and the azetidine sodium sulfinate salt **117**. Pleasingly, the desired product **121** was isolated in 79% yield (Scheme 4.17).



Scheme 4.17: C2 functionalisation of indoles

5.2. Optimisation

Deng and Kuhakarn's methodology requires 3 equivalents of sodium sulfinate salt. In our case, this salt has to be synthesized in a 3 step sequence, and so optimization was attempted in order to limit the number of equivalents required (Table 4.6). When the reaction was carried out with less than 3 equivalents of sodium sulfinate salt, the reaction required a longer time (entry 1 to 3). However, when the reaction was carried out with 3 equivalents of **117** and 1.5 of iodine, the desired product was isolated in 94% yield (entry 4). When radical precursor species, such as TBHP and mCPBA, were added to the mixture, no improvement was observed (entry 5 and 6). The solvent was also investigated. However, when the reaction was carried in THF or diethyl ether, poor conversion of starting material to **121** was observed (entry 7 and 8).



117 (n equiv.) **121**

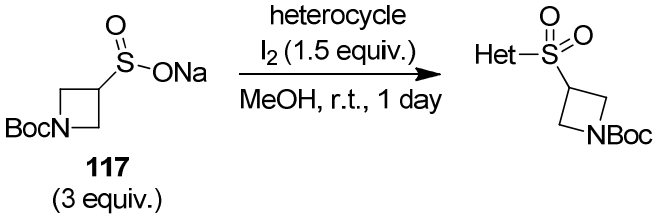
Entry	117 equivalent	Iodide equivalent	Additive	Time	Result
1	1	1	-	3 days	60% conversion
2	1	1.5	-	3 days	75% conversion
3	2	1.5	-	3 days	90% conversion
4	3	1.5	-	1 day	94%[a]
5	3	1.5	TBHP	1 day	74%[a]
6	3	1.5	mCPBA	1 day	80%[a]
7	3	1.5	-	1 day	33% conversion[b]
8	3	1.5	-	1 day	20% conversion[c]

[a] isolated yield; [b] reaction carried in THF; [c] reaction carried in Et_2O.

Table 4.6: optimization of C2 functionalisation of indole

5.3. Scope investigation

Using the best conditions found previously, the scope of reacting heterocycles was investigated (Table 4.7). Unfortunately, when other heterocycles were used in place of indoles, starting material or a complex mixture was isolated. However, this preliminary study showed that reaction could work well with indoles, and so the scope of the sulfonylation process was investigated by changing the groups on the indole ring.



117
(3 equiv.)

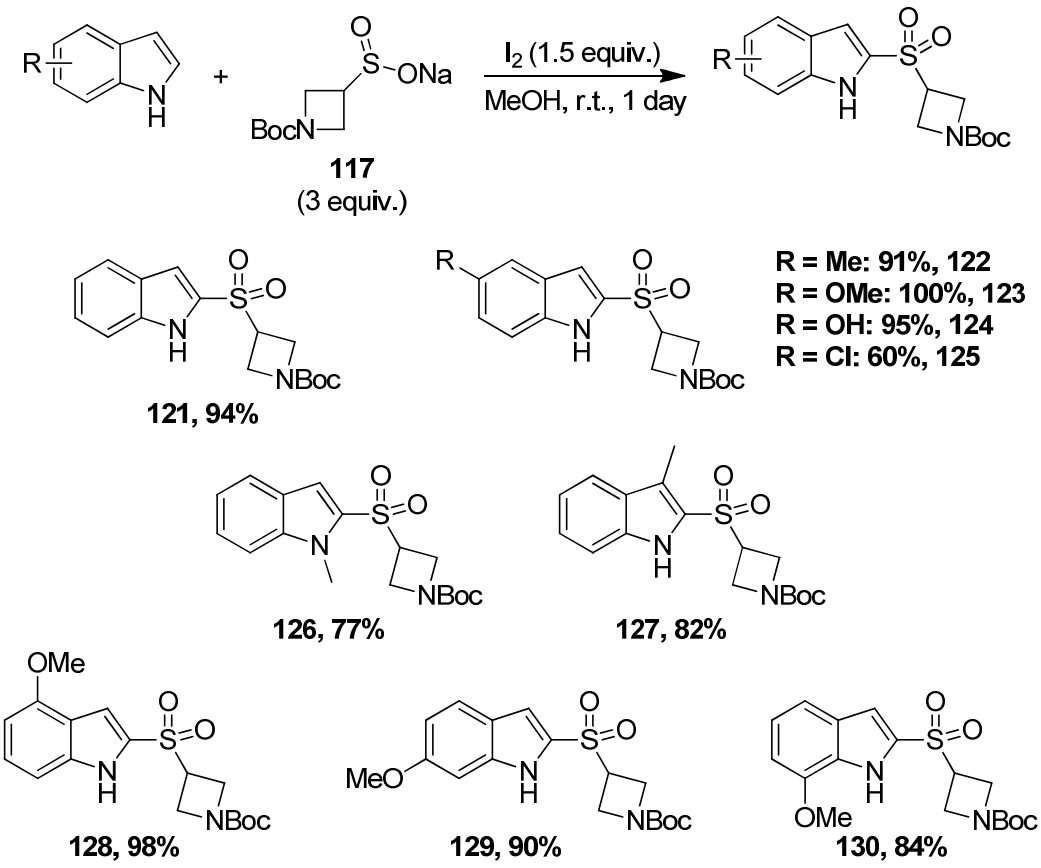
Entry	Heterocycle	Result
1	Quinoline	No reaction
2	Pyridine	Complex Mixture
3	Imidazole	No desired product
4	*N*-Methylimidazole	No desired product
5	2-Methylfuran	Complex mixture
6	5-Azaindole	No desired product
7	6-Azaindole	No desired product
8	Caffeine	No reaction
9	*N*-Methylindole	66%[a]

[a] isolated yield.

Table 4.7: Scope investigation

To investigate the scope of the reaction, indoles bearing electron-donating and electron-withdrawing groups were used. As shown in Scheme 4.18, under the optimized conditions the reaction proceeded in excellent yield with indole (**121**, 94%). A range of substituents at C5 were also well tolerated and furnished the

desired product in good to excellent yield. However, the reaction was found to be more effective with indoles bearing an electron-donating group such as an alkyl (**122**, 91%) and a methoxy group (**123**, 100%), compared to a halide (**125**, 60%). Moreover, the reaction was also effective with indoles bearing a Me-group at positions 1 and 3, furnishing the desired sulfonylated product **126** and **127** in good yield. The promoting effect of the methoxy group was also found to be effective at all positions on the benzene ring.

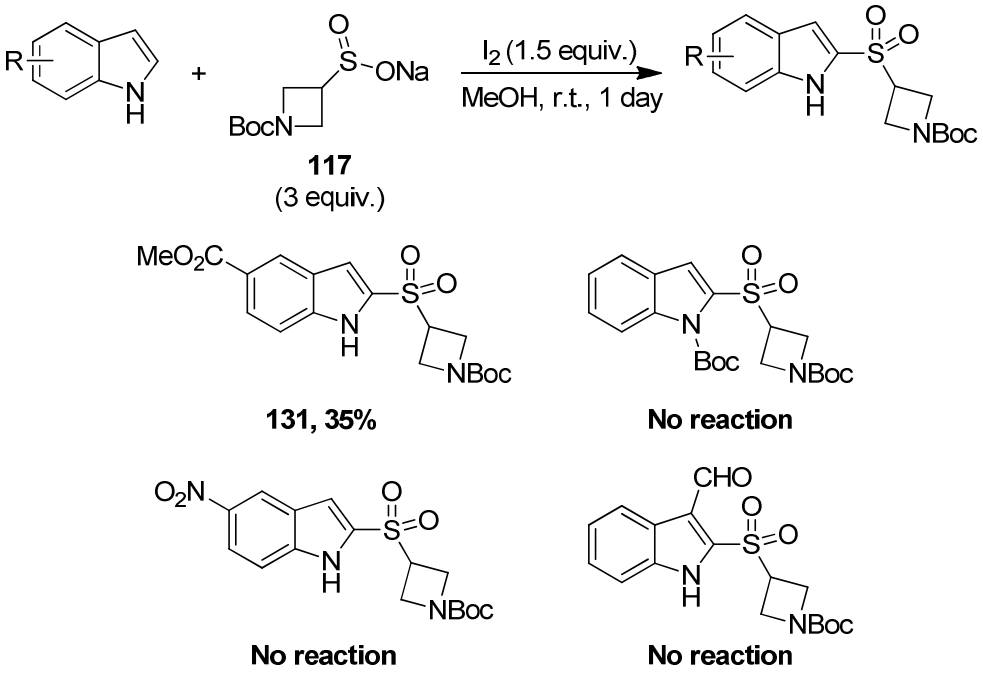


Scheme 4.18: Scope investigation using azetidine **117**

When the reaction was carried out on larger scale (1 mmol) using 5-methoxyindole, we were pleased to find that the chemistry proceeded with high efficiency. The sulfonylated indole **123** was isolated in 99% yield.

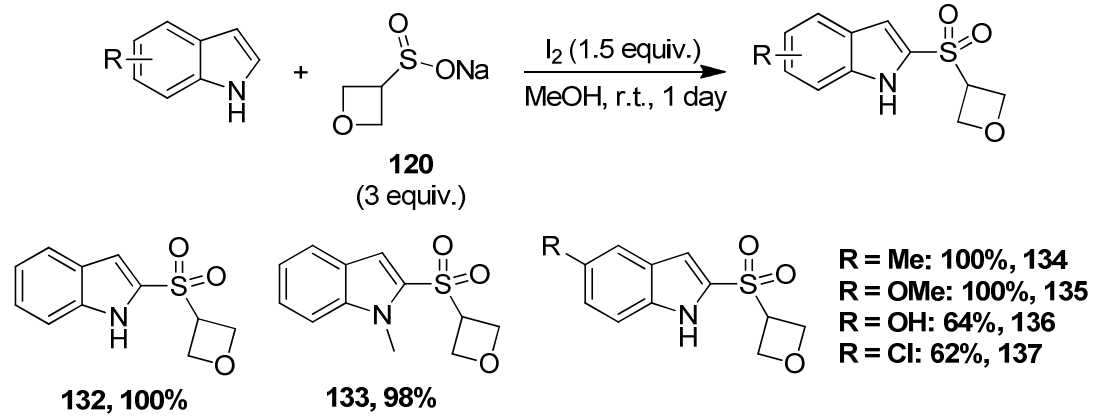
Although this reaction generated the desired products in good yield, when the indole ring incorporated an electron-withdrawing group, the reaction was less efficient (Scheme 4.19). In fact, the ester **131** was obtained in poor yield (35%). Moreover,

when the indole nitrogen included a Boc group, or the aryl ring was substituted by an aldehyde or a nitro group, no reaction was observed.



Scheme 4.19: Scope investigation using azetidine **117**

The compatibility of this chemistry was also explored with the oxetane sodium sulfinate salt. The same trends in the case of the azetidine were reproduced with the oxetane derivatives (Scheme 4.20). In fact, indole, methylated indoles and 5-methoxyindole underwent the reaction in excellent yield. However, the reaction with 5-hydroxy- and 5-chloro-indole were less effective.



Scheme 4.20: Scope investigation using oxetane **120**

5.4. Application of the method for the synthesis of an atevirdine analogue

In order to show that this methodology can be employed in the preparation of compounds of relevance to medicinal chemistry, an analogue of the marketed compound Atevirdine© was attempted (Figure 4.2). This compound is a reverse transcriptase inhibitor and is used in the treatment of HIV.[162] Our strategy was to generate a close analogue of atevirdine where the acyl ketopiperazine was replaced by a sulfonylazetidine.

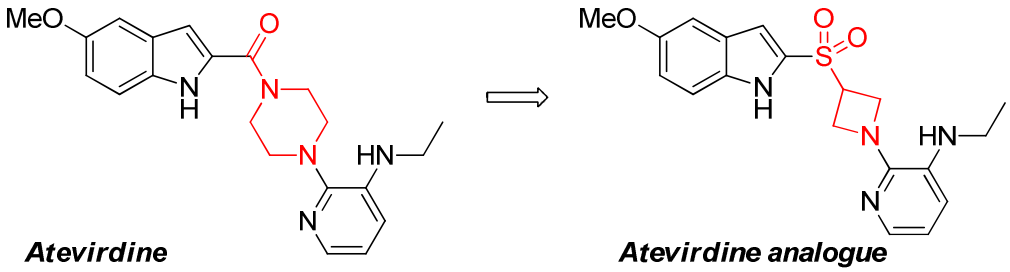
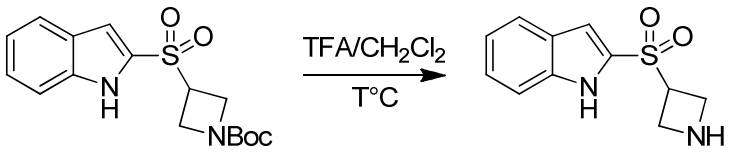


Figure 4.2: Atevirdine and its analogue structure

For this purpose, the deprotection of the Boc group on the nitrogen of the azetidine moiety was attempted (Table 4.8). When **121** was stirred in a solution of TFA:CH_2Cl_2 at room temperature, no reaction was observed (entry 1). When the temperature was increased to 40 °C, the desired amine was isolated in 73% yield (entry 2). However, when **121** was stirred in neat TFA, only degradation was observed (entry 3 and 4).



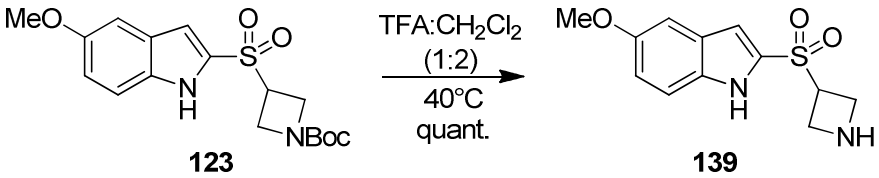
121 **138**

Entry	TFA:CH_2Cl_2 ratio	T	Result
1	1:2	r.t.	NR[a]
2	1:2	40 °C	73%[b]
3	1:0	r.t.	Degradation
4	1:0	75 °C	Degradation

[a] NR = No Reaction; [b] isolated yield.

Table 4.8: Boc deprotection of **121**

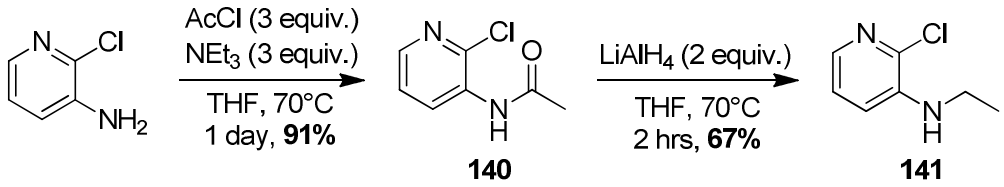
With the best conditions in hand, the deprotection was then attempted on **123**. Pleasingly, the desired amine **139** was isolated in quantitative yield (Scheme 4.21).



123 **139**

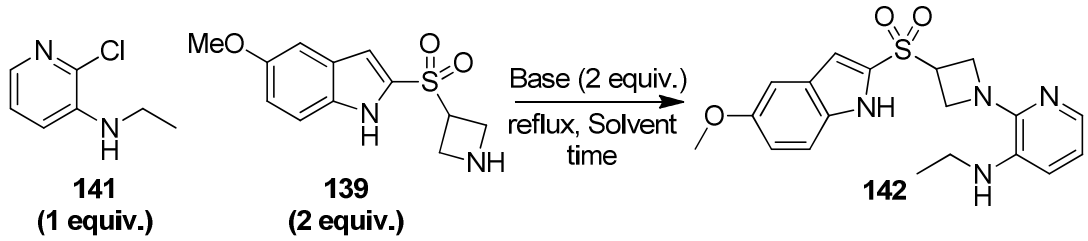
Scheme 4.21: Boc deprotection of **123**

With **139** in hand, the synthesis of the 3-aminoethyl-2-chloropyridine was investigated (Scheme 4.22). 3-Amino-2-chloropyridine was treated with acetyl chloride to furnish the desired amide **140** in excellent yield. The amide was then treated with lithium aluminium hydride to furnish the desired amine **141** in 67% yield. Notably, 3-ethylamino pyridine was observed as a by-product of this reaction. In fact, if more than 2 equivalent of LAH was used or if the reaction was stirred for longer than 2 hours, more of this dechlorinated by-product was observed.



Scheme 4.22: Synthesis of **141**

With both compounds in hand, the nucleophilic aromatic substitution was attempted. Following the procedure described for the large scale synthesis of Atevirdine, no desired compound was isolated and only starting material was recovered (entry 1).[163] As **139** was not fully soluble in toluene, the reaction was attempted in acetonitrile (entry 2) but no reaction was observed after 5 days. Using similar reaction conditions to that described by Thomas *et al.*, no reaction was observed after 2 days (entry 3).[164]



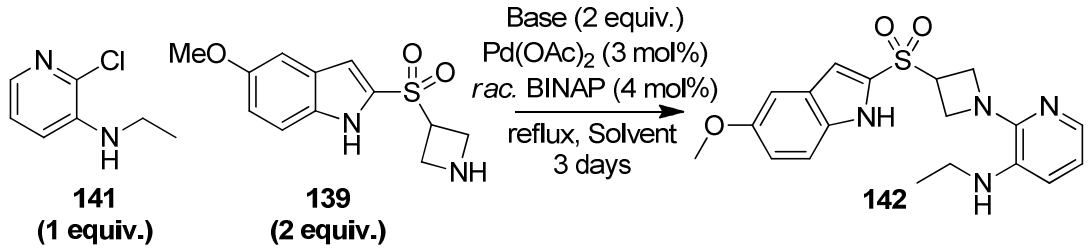
Entry	Base	Solvent	Time	Result
1	-	Toluene	1 day	NR[a]
2	-	Acetonitrile	5 day	NR[a]
3	Cs_2CO_3	Acetonitrile	2 days	NR[a]

[a] NR = No Reaction.

Table 4.9: Attempted synthesis of **142**

As the nucleophilic aromatic substitution did not afford any desired product **142**, a Hartwig-Buchwald reaction was then attempted. Following the reaction conditions of Witulski *et al.*, the reaction was attempted using 1 equivalent of chloro-pyridine **139** and 2 equivalents of azetidine **139** catalysed by $Pd(OAc)_2$ and (±)-BINAP (Table 4.10).[165] When the reaction was carried out in toluene using *t*BuONa or Cs_2CO_3 as base, no reaction was observed after 3 days (Entry 1 and 2). The poor solubility of **139** in toluene was suspected to be the cause of the low reactivity, and the reaction

was attempted in more polar solvent. However, when the reaction was carried out in DMF no desired product or starting material was isolated (Entry 3). When dioxane was used instead the crude NMR analysis showed 25% conversion (entry 4). Delighted by this result, the reaction was then carried out in acetonitrile and the desired product was isolated in 67% yield (entry 5).

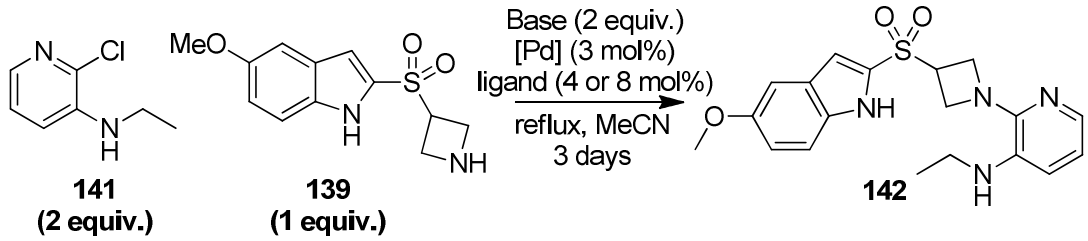


Entry	Base	Solvent	Result
1	*t*BuONa	Toluene	NR[a]
2	Cs_2CO_3	Toluene	NR[a]
3	*t*BuONa	DMF	**142** not recovered
4	*t*BuONa	Dioxane	25% conversion
5	*t*BuONa	Acetonitrile	67% [b]

[a] NR = No reaction; [b] Isolated yield

Table 4.10: Synthesis optimisation of **142**

Although we were able to conduct the cross-coupling reaction in good yield, the process required 2 equivalents of azetidine **139**. In order to decrease the required amount of this valuable substrate, the reaction was attempted using 2 equivalent of **141** and 1 equivalent of **139** in acetonitrile (Table 4.11). Bidentate ligands afforded the desired product in moderate yield (entry 1 and 2). However, when a monodentate ligand was used instead, less than 10% conversion was observed (Entry 3 to 5). When Cs_2CO_3 was used as the base, less than 10% conversion was also observed (entry 6). Unfortunately, when the reaction was attempted using a palladium (0) species or a precatalyst, no reaction was observed (entry 7 and 8).

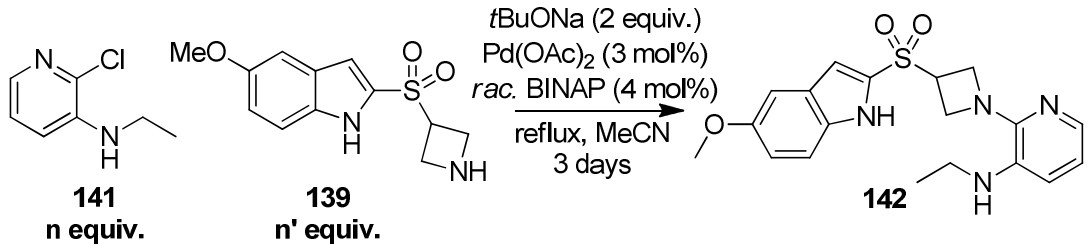


Entry	Base	[Pd]	Ligand	Result
1	*t*BuONa	$Pd(OAc)_2$	*rac.* BINAP [a]	40% [d]
2	*t*BuONa	$Pd(OAc)_2$	dppf [a]	49% [d]
3	*t*BuONa	$Pd(OAc)_2$	XPhos [b]	< 10% conversion
4	*t*BuONa	$Pd(OAc)_2$	PPh_3 [b]	< 10% conversion
5	*t*BuONa	$Pd(OAc)_2$	dppe [b]	< 10% conversion
6	Cs_2CO_3	$Pd(OAc)_2$	*rac.* BINAP [b]	< 10% conversion
7	*t*BuONa	$Pd(PPh_3)_4$	-	NR [e]
8	*t*BuONa	XPhos-precatalyst [c]		NR [e]

[a] 4 mol% used; [b] 8 mol% used; [c] Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl)]palladium(II); [d] Isolated yield; [e] NR = No reaction

Table 4.11: Synthesis optimisation of **142**

We next decided to investigate the reaction using a (1:1.1) combination of starting materials (Table 4.12). Unfortunately, no more than 14% yield was obtained.



Entry	n	n’	Result
1	1	1.1	< 10% conversion [a]
2	1.1	1	14% [b]

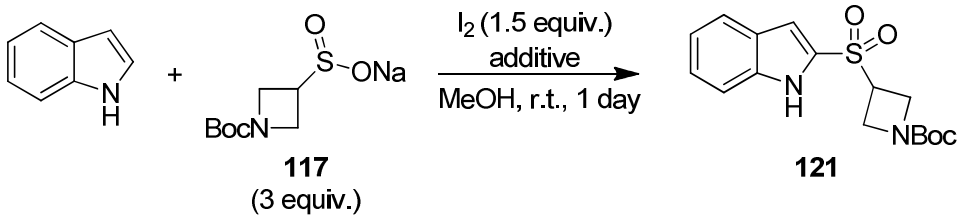
[a]observed on crude NMR analysis; [b] Isolated yield.

Table 4.12: Synthesis optimization of **142**

The atevirdine® analogue **142** was successfully synthesised. However, this compound was obtained in moderate to good yield. Its synthesis requires further investigation and optimization.

5.5. Mechanistic studies

Kuhakarn and Deng proposed that the indole sulfonylation reaction proceeds via a radical pathway. A series of experiments were then conducted to provide evidence for this hypothesis (Table 4.13). In fact, when the reaction was carried out under the standard conditions, **121** was isolated in 94% yield (entry 1). However, when the reaction was conducted in the absence of iodine, no reaction was observed (entry 2). When the reaction was carried out in the dark or under inert atmosphere, the desired product was isolated in lower yield (entry 3 and 4). These observations would suggest that the reaction requires a radical initiator. Moreover, the addition of a radical scavenger (TEMPO) had major effect on the yield. For example, when TEMPO was added in a sub-stoichiometric amount, a slight decrease in the yield was observed (entry 5). A considerable decrease was observed when 1 equivalent of TEMPO was added (entry 6), and only traces of **121** was isolated when 3 equivalents of TEMPO were added (entry 7). These experiments support the proposal that the reaction involves a radical pathway.

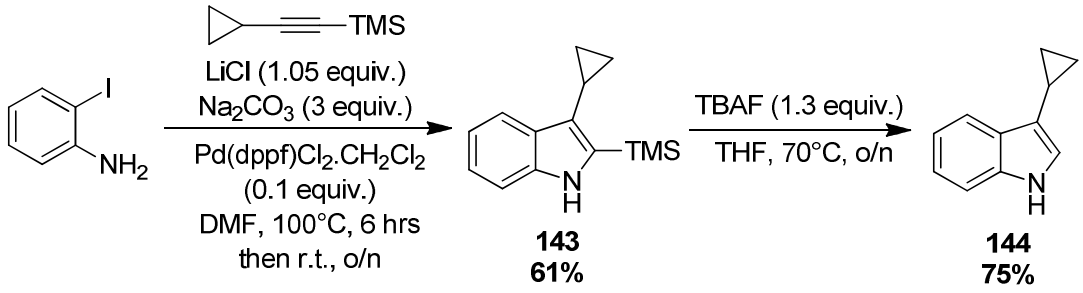


Entry	Additive	Isolated yield
1	None (Standard conditions)[a]	94%
2	None (No iodine)	NR[b]
3	None (dark)	81%
4	None (argon)	30%
5	TEMPO (0.1 equiv.)	80%
6	TEMPO (1 equiv.)	24%
7	TEMPO (3 equiv.)	Traces

[a] **117** (3 equiv.), I_2 (1.5 equiv.), MeOH, r.t., 1 day; [b] NR = No Reaction

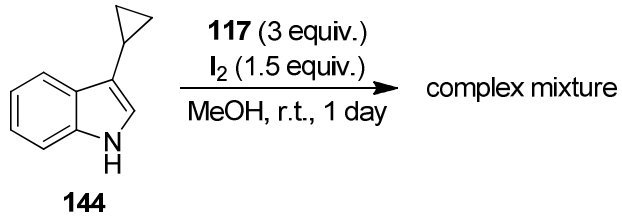
Table 4.13: Effect of conditions on the outcome of the reaction

In order to further confirm the proposed radical pathway, we were intrigued to explore the result of the reaction of 3-cyclopropylindole under our optimised conditions. To synthesize 3-cyclopropyl indole **143**, 2-iodoaniline was treated with trimethylsilyl-cyclopropylacetylene in presence of $Pd(dppf)Cl_2.CH_2Cl_2$, LiCl and sodium carbonate. The obtained indole was then treated with TBAF in THF to afford the desired product **144** (Scheme 4.23).



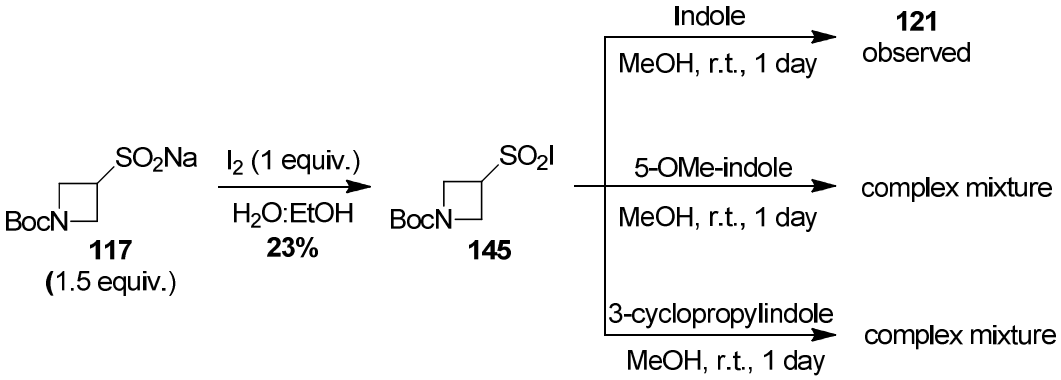
Scheme 4.23: Synthesis of 3-cyclopropylindole **144**

Unfortunately however, when 3-cyclopropylindole **144** was treated under the reaction conditions, a complex mixture was obtained from which we were unable to identify the major product (Scheme 4.24).



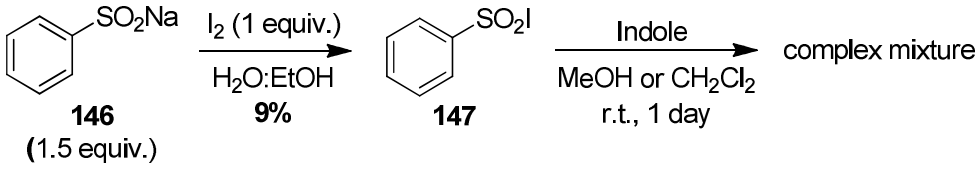
Scheme 4.24: Attempted reaction of **117** and **144**

Kuharkan and Deng also suggested that $RSO_2^{\cdot}$ was the reactive radical species formed *in situ*. In order to confirm this observation, the synthesis of **145** was attempted. In fact, if $RSO_2^{\cdot}$ is the reactive radical species, the reaction of RSO_2I with indole would provide the desired product. To form the iodosulfinate of azetidine, **117** was treated with iodine in a solution of water and ethanol. The desired product was isolated in 23% yield. When **145** was subjected to the reaction with indole, the desired product was observed but it was contaminated with 3-iodoindole. When the reaction was carried out with 5-methoxyindole or 3-cyclopropylindole, no desired product was observed in the NMR analysis of the crude mixture. These disappointing results might have been to the result of the instability of the iodosulfone substrate.



Scheme 4.25

As the azetidine required a multistep synthesis a more readily available substrate was chosen to carry out the mechanistic studies. Accordingly, sodium benzene sulfinate was treated with iodine to afford iodobenzenesulfinate in 9% yield. Sulfinate iodide **147** was then added to a solution of indole in dichloromethane or methanol. Unfortunately, no desired product was observed under these conditions.



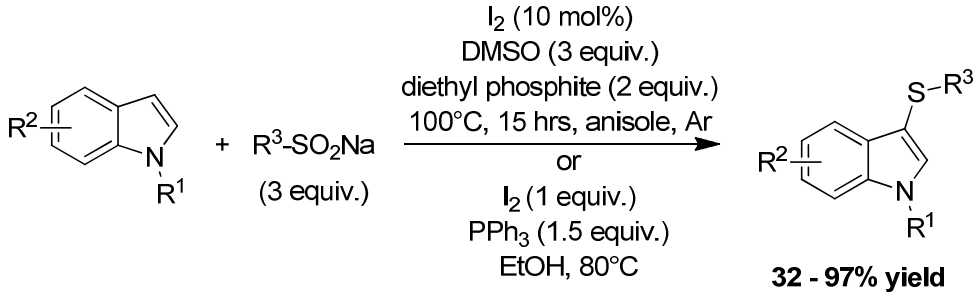
Scheme 4.26

Unfortunately, these studies did not provide any further insight into the reaction mechanism or intermediates involved in the reaction.

6. C3 functionalisation of indoles

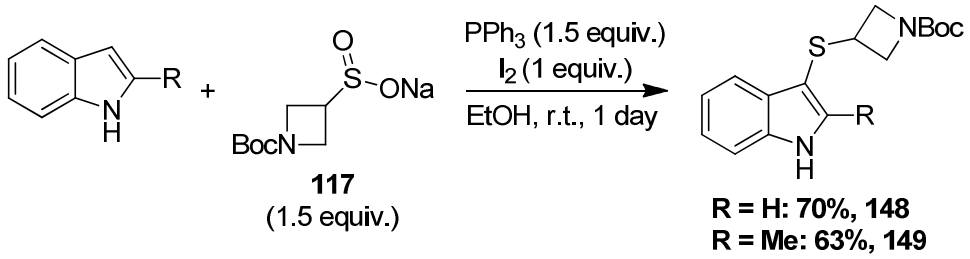
6.1. Preliminary work

Deng and Kuhakarn also reported the regioselective C3-sulfenylation of indoles using sodium sulfinate salt, iodine and triphenylphosphine (Scheme 4.27).[166]



Scheme 4.27: C3 sulfenylation of indoles

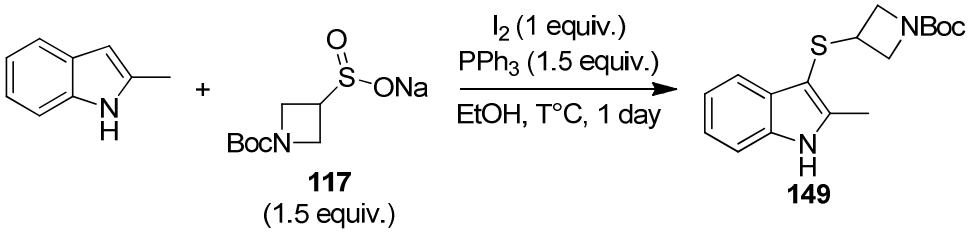
Pleasingly, when we utilized this methodology on indole and 2-methylindole using the azetidine sodium sulfinate salt **117** at room temperature, the desired products **148** and **149** were isolated in 70% and 63% yield, respectively.



Scheme 4.28: C3 functionalisation of indoles

6.2. Optimization

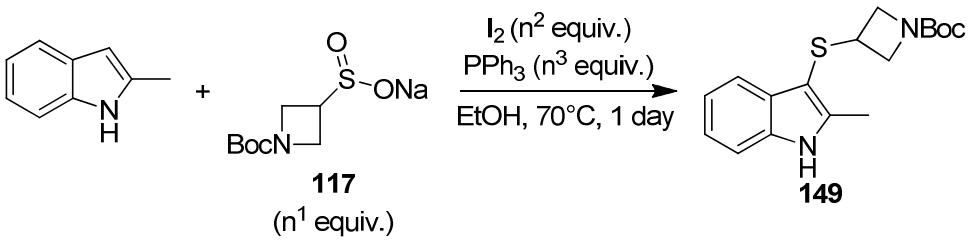
In order to optimize this process further, the reaction temperature was investigated (Table 4.14). As shown below, when the reaction was heated at reflux, a decrease in yield was observed (entry 3). However, similar results were obtained when the reaction was conducted at 70 °C, and at room temperature (entries 1 and 2).



Entry	T (°C)	Isolated yield
1	r.t.	84%
2	70 °C	83%
3	reflux	63%

Table 4.14: optimization of C3 functionalisation of indole

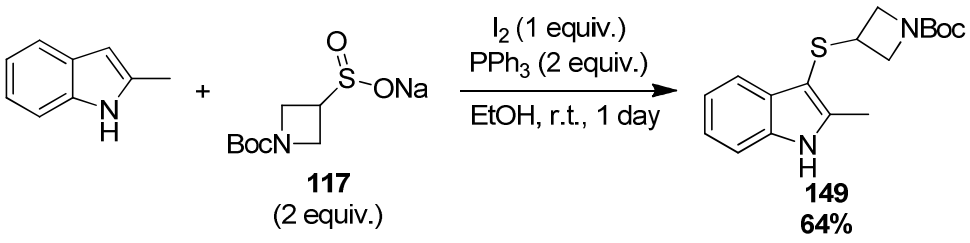
As before, we wanted to investigate the possibility of reducing the number of equivalents of sulfinate salt required in the reaction. As shown in Table 4.15, when 1 equivalent each of **117**, PPh_3 and I_2 were used, the desired product was obtained in moderate yield (entry 1). When the quantities of **117** and triphenyphosphine were increased, **149** was obtained in better yield (entry 2 and 3). However, when 3 equivalents of **117** and PPh_3 were used, no desired compound was isolated (entry 4). As using 1.5 equivalents of **117** and PPh_3 furnished a good yield, an equimolar amount of iodine was then used (entry 5). However, the product was obtained in a poorer yield.



Entry	RSO_2Na equivalent	PPh_3 equivalent	I_2 equivalent	Isolated yield
1	1	1	1	55%
2	1.5	1.5	1	83%
3	2	2	1	100%
4	3	3	1	0%
5	1.5	1.5	1.5	76%

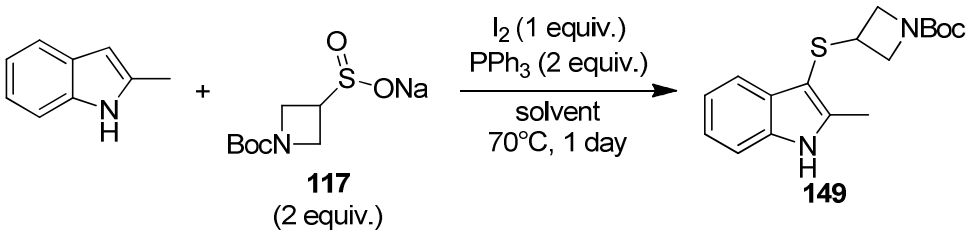
Table 4.15: optimization of C2 functionalisation of indole

To our surprise, repeating the reaction on preparative scale using the optimized conditions only produced the desired product in 64% yield (Scheme 4.29).



Scheme 4.29: Optimized conditions

We next decided to screen a range of reaction solvents at the elevated temperature of 70 °C. Surprisingly, when the reaction was carried out in methanol, no desired product was isolated (entry 1).When toluene or acetone was used, poor to moderate yield were obtained (entry 3 and 4). No reaction was observed when hexane was used (entry 5). Better results were obtained when the reaction was carried in 1,4-dioxane, dichloromethane, THF, acetonitrile or ethanol (entry 2, 6 to 9). However, an inseparable unidentified impurity was isolated with the desired product in dioxane and dichloromethane. As THF, acetonitrile and ethanol provided similar results, the more environmentally friendly solvent EtOH was chosen.



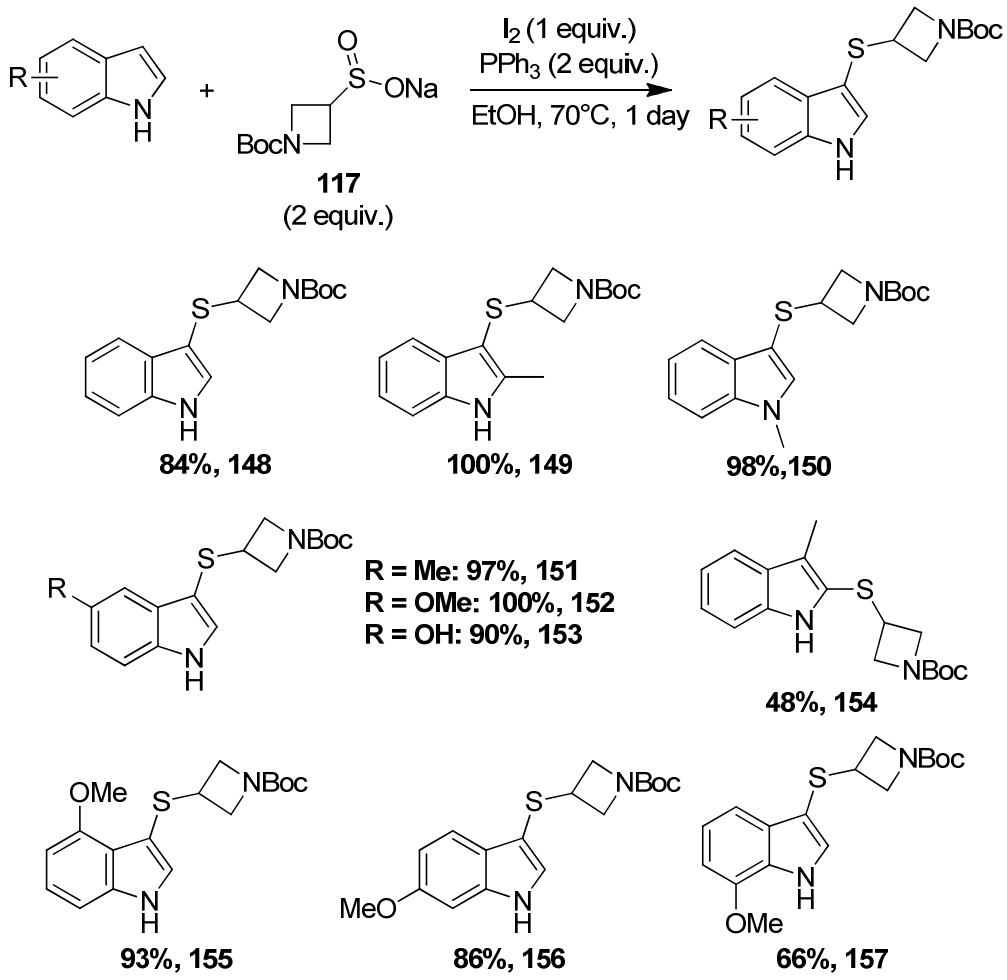
Entry	Solvent	Isolated yield
1	Methanol	0%
2	1,4-dioxane	97%[a]
3	Toluene	66%
4	Acetone	21%
5	Hexane	NR[b]
6	Dichloromethane	97%[a]
7	Tetrahydrofuran	95%
8	Acetonitrile	94%
9	Ethanol	100%

[a] purity evaluated at 70% ; [b] NR = No Reaction.

Table 4.16: optimization of C2 functionalisation of indole

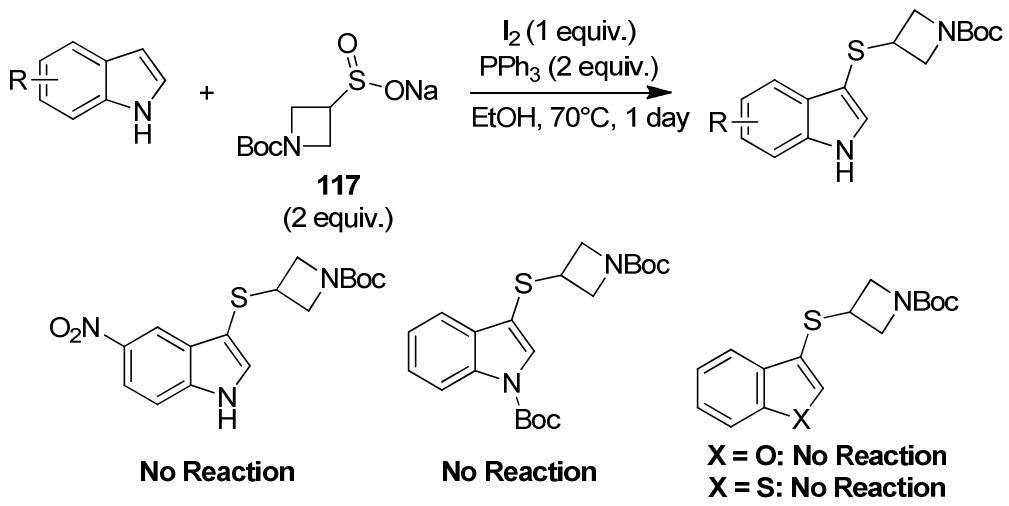
6.3. Scope of the reaction

With the optimized conditions in hand, the scope of the reaction was investigated. As shown in Scheme 4.30, indole and alkylated indole underwent the reaction to furnish the desired product in good yield. The reaction is also suitable with alcohol and methoxy groups. Moreover, 3-methylindole was also found to be suitable and furnished the desired product **154** in moderate yield, with incorporation of the sulfinate salt at C-2. The reaction also afforded 4-, 5- and 6-substituted indole in moderate to good yield.



Scheme 4.30: Scope investigation using azetidine **117**

However, the reaction seemed incompatible with indoles bearing electron-withdrawing groups, and with benzofuran and benzothiophene (Scheme 4.31).



Scheme 4.31: Scope limitation using azetidine **117**

7. Conclusion

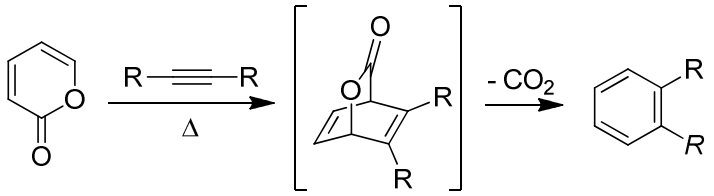
The preliminary aim of this study was to investigate the synthesis and the application of zinc sulfinate salts of azetidines and oxetane on different heterocycles using methods developed by Baran. We developed an efficient synthesis of azetidine and oxetane sodium sulfinate salts, but found these to be unreactive towards incorporation into caffeine. In contrast however, we have been successful in developing an efficient method for the regioselective synthesis of C2 and C3 azetidine and oxetane functionalized indoles. It was found that electron-rich indoles were good substrates for this reaction. We also showed that the Boc protecting group on the azetidine can be easily removed, providing the opportunity for further elaboration of this scaffold.

Other applications of these salts could also be investigated, such as the reaction with trifluoroborate, amine and halogenated heterocycles, to afford a broader range of azetidine and oxetane containing moieties. This would give the opportunity to medicinal chemist to enlarge their scope of accessible targets.

Part 2: Lewis Base directed cycloaddition of 2-pyrones with alkynylboranes

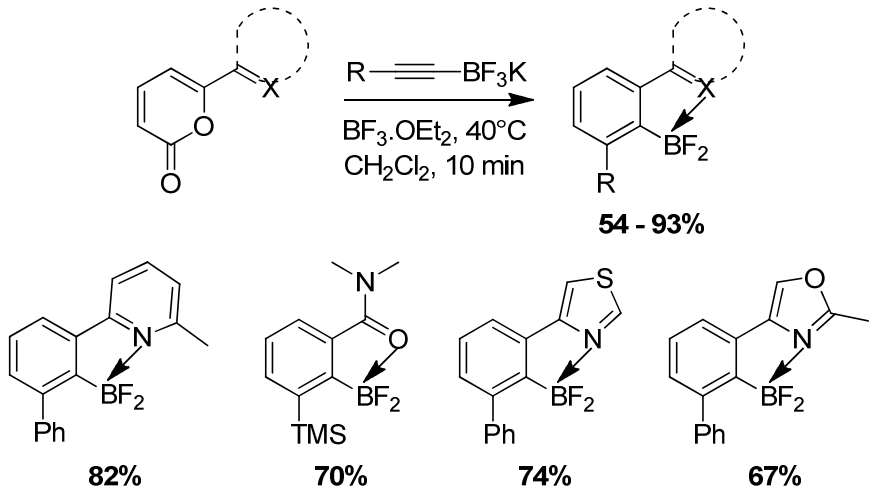
1. Introduction

The cycloaddition of 2-pyrones, first reported by Diels and Alder in 1931, allows the synthesis of functionalized cyclohexenes and aromatic compounds in 1 step.[167] When alkynes are used in the reaction with 2-pyrones, aromatic compounds are obtained. In fact, the intermediate obtained after the cycloaddition undergoes a retro-cycloaddition with expulsion of carbon dioxide (Scheme 5.1).[168]



Scheme 5.1: cycloaddition between 2-pyrones and alkynes

This process is compatible with a range of functional groups attached to the alkyne such as: silyl, [169] phosphonate, [170] stannane, [171] ester, [172] amide, [173] ketone, [174] hydrocarbon and boronate.[175] However, this reaction requires high temperatures and often long reaction times, and generally provides variable regiocontrol. In order to improve this process, studies in the Harrity group showed that the use of a Lewis acid-base complex allows the reactions to proceed at lower temperature to provide the cycloadducts with excellent regiocontrol (Scheme 5.2).[176]



Scheme 5.2: Lewis acid-base complex induced cycloaddition of 2-pyrones and alkyne trifluoroborate

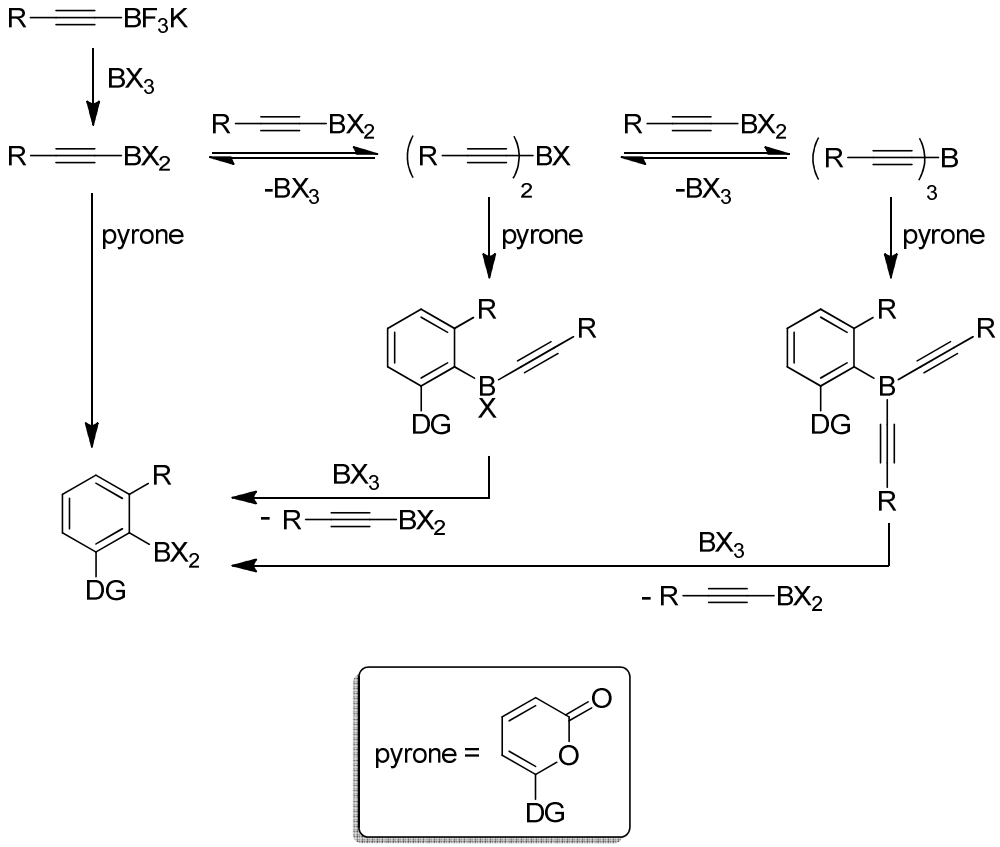
2. Aims

Computational studies carried out within the group showed that the Lewis-base directed cycloadditions of 2-pyrones involved the formation and disproportionation of alkynylboranes. The first aim of this project was to confirm some aspects of the theoretical observations experimentally.

Theoretical investigations also showed that the Lewis acid used in the reaction could have a considerable effect on the reaction. In fact, in theory, 1 equivalent of alkyne and BX_3 should promote complete conversion of the reaction. The second aim of this project was to investigate other Lewis acids that could promote the reaction in an effort to decrease the amount required in these processes.

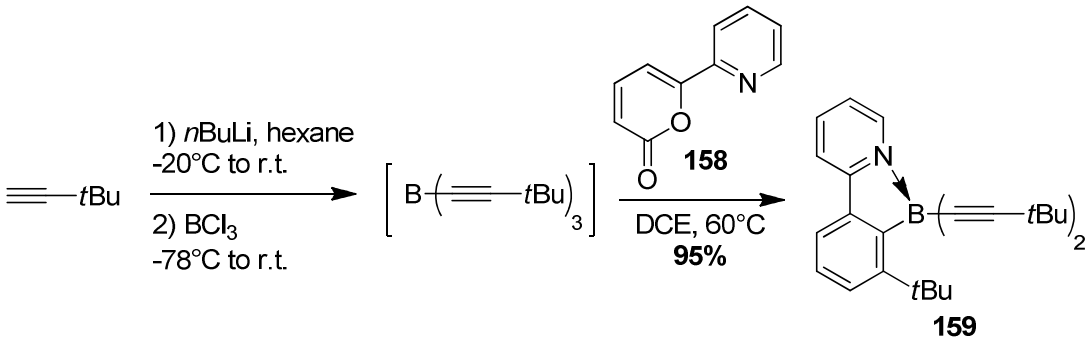
3. Mechanistic investigation

Theoretical studies carried out by Dr Julong Jiang of this department led to a proposed mechanistic scheme (Scheme 5.3).



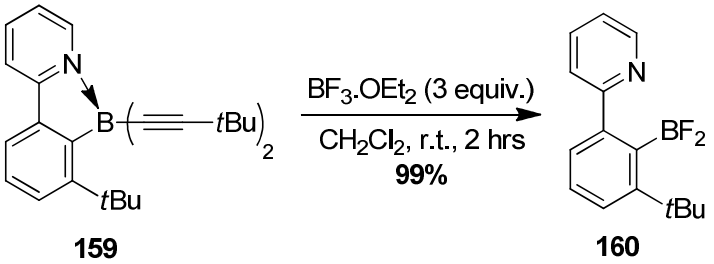
Scheme 5.3: Proposed mechanism

These computational studies suggested that tri(alkynyl)borane is formed *in situ* and reacts with the 2-pyrones to form the cycloadduct. Confirmation of the viability of this process was achieved by generating trialkynylborane following the method of Sebert.[177] Addition of this alkyne to pyrone **158** provided the corresponding cycloadduct **159** in 95% yield (Scheme 5.4). This reaction confirmed that trialkynylboranes could be competent intermediates in this reaction.



Scheme 5.4: Synthesis of **159**

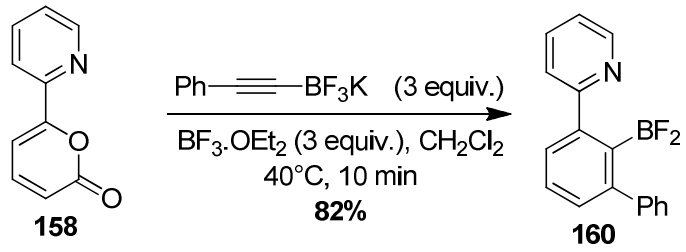
Theoretical studies also showed that disproportionation of dialkynylborane cycloadducts occurred to form difluoroboranes such as **160**. In order to gather evidence for this hypothesis, treatment of **159** with boron trifluoride was carried out and the desired difluoroborane **160** was indeed generated in 99% yield (Scheme 5.5).



Scheme 5.5: Equilibration of **159** to **160**

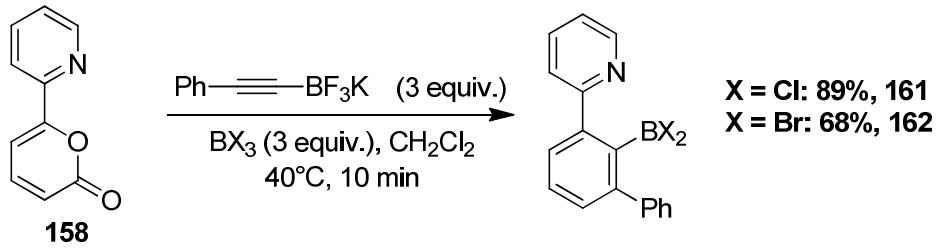
4. Extension of the methodology using boron trichloride

Previous work within the Harrity group showed that the reaction of 6-pyridine-2-pyrones with 3 equivalents of phenylethynyl trifluoroborate potassium salt and 3 equivalents of boron trichloride afforded the desired difluoroborane substituted benzene in 82% yield (Scheme 5.6).



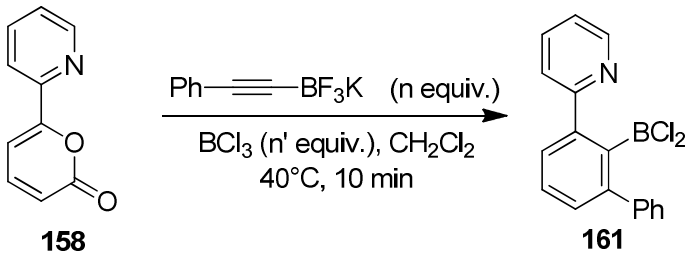
Scheme 5.6: cycloaddition of 2-pyrones using $BF_3.OEt_2$

Theoretical studies showed that other boron trihalides could catalyse the reaction and so we decided to look at these processes in more detail. The reaction using 3 equivalents of BCl_3 or BBr_3 was then attempted. Pleasingly, both desired products were isolated in good yield (Scheme 5.7). However, better results were obtained with BCl_3.



Scheme 5.7: Use of alternative boron trihalides

With respect to boron trichloride, the number of equivalents used in the reaction of alkynes or Lewis acid was then optimized (Table **5.1**). The number of equivalent of alkyne could be reduced without affecting the yield of the reaction (entries 1 to 3). The use of 2 equivalents of alkyne and borane seemed to provide a good compromise and furnished the desired product in 86% yield (entry 5). However, when the equivalents were decreased, the reaction failed to reach full conversion and furnished the desired product in moderate yield (entries 6 and 7).



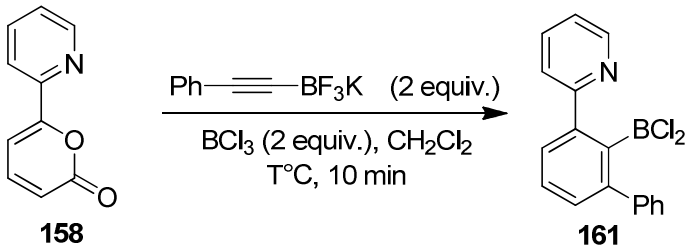
158 **161**

Entry	n	n'	Result[a]
1	3	3	89%
2	2	3	88%
3	1.5	3	89%
4	1	3	62%
5	2	2	86%
6	1	2	56%
7	1	1	33%

[a] Isolated yield.

Table 5.1: Optimisation studies for the synthesis of **161**

The temperature of the reaction was then optimized (Table 5.2). When the reaction was carried at 40 °C the product was isolated in good yield (entry 1). The reduction of the temperature to 0 °C or -15 °C did not significantly affect the yield (entries 3 and 4). However, when the reaction was carried out at room temperature, the reaction did not seem to be reproducible and gave on average the desired product in 68% yield (entry 3). A reaction temperature of 0 °C was chosen as it was both practical and efficient.

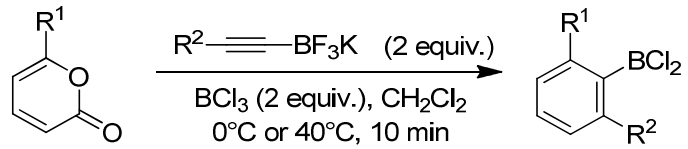


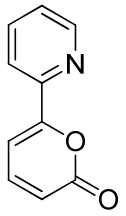
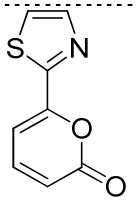
Entry	T (°C)	Isolated yield
1	40	89%
2	r.t.	68%[a]
3	0	84%
4	-15 °C	78%

[a] average yield

Table 5.2: Temperature optimization

We the best conditions in hand, the reaction scope was investigated. A series of potassium alkyne trifluoroborates and 2-pyrones were synthesized and used in the cycloaddition. The pyridine or thiazole substituted pyrones underwent the cycloaddition reaction in good to excellent yield under mild conditions using phenyl, *n*-butyl, *t*-butyl, cyclohexenyl or trimethylsilyl substituted alkynes (Table 5.3). However, the reaction between thiazole pyrone and trimethylsilyl alkynes was slower and required an elevated temperature.

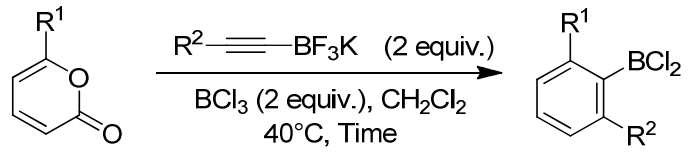


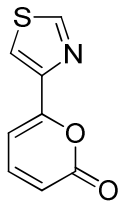
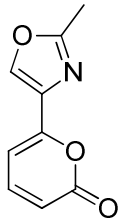
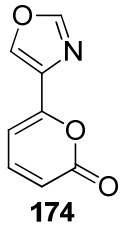
Entry	R^1	R^2	T(°C)	Isolated yield
1		Ph-	0	84% (**161**)
2		nBu-	0	89% (**164**)
3		tBu-	0	70% (**165**)
4		1-cyclo hexenyl-	0	54% (**166**)
5	**158**	TMS-	0	47% (**167**)
6		Ph-	0	83% (**168**)
7		nBu-	0	97% (**169**)
8		1-cyclo hexenyl-	0	84% (**170**)
9	**163**	TMS-	40	51%[a] (**171**)

[a] The product of protodesilylation was isolated in 18% yield.

Table 5.3: Scope investigation

The reaction between 4-thiazole **172** and oxazole **173** substituted pyrones with phenyl, *n*-butyl and 1-cyclohexenyl alkyne trifluoroborates afforded the desired products in moderate to good yield. However, the reaction of oxazole substituted pyrones **174** proved to be less reactive to cycloaddition and required a longer reaction time than its 2-methyloxazole counterpart. Importantly however, this pyrone **174** was found to be completely unreactive towards cycloaddition in the presence of $BF_3.OEt_2$.



Entry	R^1	R^2	Time	Isolated yield
1	 **172**	Ph-	10 min	77% (**175**)
2		nBu-	10 min	75% (**176**)
3		1-cyclo hexenyl-	10 min	67% (**177**)
4	 **173**	Ph-	10 min	76% (**178**)
5		nBu-	10 min	78% (**179**)
6		1-cyclo hexenyl-	10 min	48% (**180**)
7	 **174**	Ph-	3 d.	55% (**181**)
8		nBu-	3 d.	53%[a] (**182**)
9		1-cyclo hexenyl-	3 d.	42%[a] (**183**)

[a] The reaction did not reach full conversion.

Table 5.4: Scope investigation

5. Conclusion

To conclude, experiments in support of the proposed reaction mechanism of the directed cycloaddition have been carried out. It has been proposed that rapid equilibration between alkynyldifluoroborane, bis- and tris-alkynylboranes takes place and that the latter undergoes cycloaddition followed by disproportionation. We have carried our experiments that show that these steps are viable. We have also shown that other Lewis acid, BX_3 could catalysed the reaction. Moreover, the reaction using boron trichloride allows the cycloaddition of a range of alkyne trifluoroborate and 2-pyrones, and improves the scope of substrates that participate in this process.

Part 3: Experimental

1. General experimental

All reactions were conducted in flame-dried glassware under ambient conditions and inert atmosphere (nitrogen or argon) unless otherwise stated. Microwave promoted reactions were conducted in a CEM discover SP Microwave Reactor.

Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, Elmer Spectrum 100 spectrophotometer or Thermo Nicolet Avatar 370 FT-IR, ν_{max} in cm^{-1}. Samples were recorded neat or as thin films using sodium chloride plates, as a CH_2Cl_2 or MeOH solution. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Bruker AC-250 (250 MHz), AMX-400 (400 MHz) or Avance-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in ppm from trimethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm) unless otherwise stated. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration and assignment). ^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz), AMX-400 (100.6 MHz), Avance-400 (101 MHz) or Avance-700 (176 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from trimethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm) unless otherwise stated. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+), a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode, or on a ThermoScientific LTQ-FT.

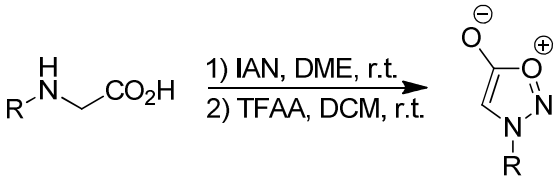
Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) or pre-coated glass plates with silica (Merck DC Kieselgel 60 F_{254}) which were developed using

standard visualizing agents: Ultraviolet light or potassium permanganate. Flash chromatography was performed on silica-gel (BDH Silica Gel 60 43-60 or Davisil 60A). Melting points, performed on recrystallized solids, were recorded on a Gallenkamp melting point apparatus or on a Büchi Melting point B-545 and are uncorrected.

All solvents and reagents were purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego and Perrin (Pergamon Press, 1966). Grignard reagents were titrated against menthol using 1,10-phenantroline as an indicator and dry THF as solvent. Unless otherwise stated, all other solvents and materials were used as supplied.

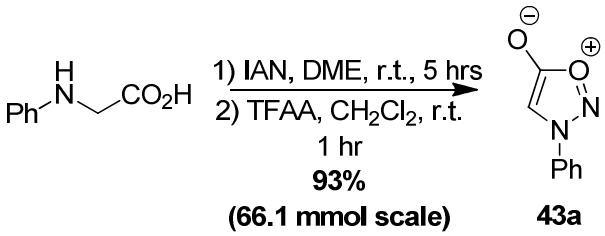
2. Synthesis of sydnones

General procedure 1:



IAN (1.1 equiv.) was added to a solution of the desired amino acid (1 equiv.) in DME [0.5 – 1.5 M] under stirring. The resulting mixture was stirred at r.t. for the designated time before concentrated *in vacuo* to form a thick oil. A mixture of petroleum ether and diethyl ether (15:1) (50 mL for 10.00 g) was added to allow the formation of a solid. The liquor was then decanted, the supernatant was removed and the solid was dried *in vacuo* and used in the following step without further purification. (CAUTION: These nitrosamine intermediates are suspected carcinogens). TFAA (2 equiv.) was added to a suspension of the solid in CH_2Cl_2 [1 M] under nitrogen atmosphere and the mixture was allowed to stir at r.t. for 1 hour. A small amount of water was then added and the solution was neutralized to pH=7 with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was then extracted with CH_2Cl_2 (3x 150 mL for 10.00 g). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired sydnone which was then recrystallised with EtOH (100 mL for 10.00 g).

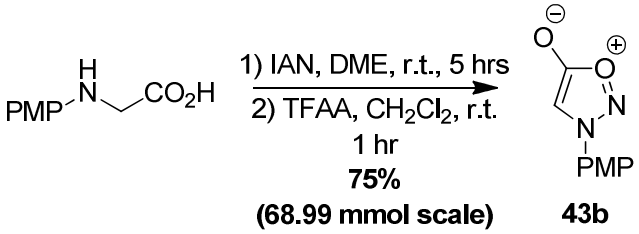
Synthesis of *N*-Phenylsydnone (43a)[73]



Following general procedure 1 using *N*-phenylglycine (10.00 g, 66.1 mmol), DME (40 mL), stirring for 5 hrs, *N*-phenylsydnone (**43a**) was isolated as a beige solid (10.02 g, 93%).

M.p. = 128 - 130 °C (lit. 131 – 134 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H, Ar***H***), 7.70 – 7.59 (m, 3H, Ar***H***), 6.74 (s, 1H, Ar***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 134.9, 132.6, 130.4, 121.4, 93.8; FTIR: 3423 (br), 3124 (m), 1758 (s), 1439 (m), 1362 (w), 1226 (w), 1082 (m), 943 (s), 753 (s), 719 (s); HRMS: m/z $[M+H]^+$ calcd. for $C_8H_7N_2O_2$: 163.0508, found: 163.0500.

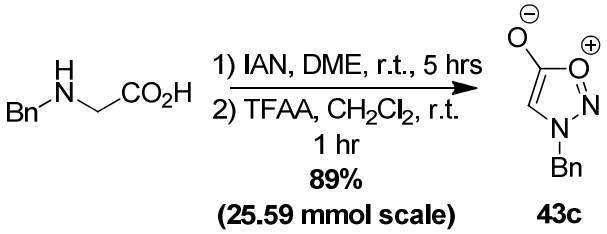
Synthesis of *N*-paramethoxyphenylsydnone (43b)[178]



Following procedure 1 using 2-((*para*-methoxyphenyl)amino)acetic acid (12.50 g, 68.99 mmol), DME (100 mL), stirring for 3 hrs, *N*-(*para*-methoxyphenyl)sydnone (**43b**) was isolated as a brown solid (9.91 g, 75%).

M.p. = 122 - 124 °C (lit.125-126°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.08 (d, *J* = 9.0 Hz, 2H, Ar***H***), 6.73 (s, 1H, Ar***H***), 3.90 (s, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 162.8, 127.7, 122.9, 115.4, 94.0, 56.0; FTIR: 3420 (br), 3116 (w), 1760 (s), 1610 (m), 1513 (m), 1450 (m), 1263 (m), 1176 (m), 1023 (w), 826 (m), 723 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_9H_9N_2O_3$: 193.0613, found: 193.0610.

Synthesis of *N*-Benzylsydnone (43c)[179]

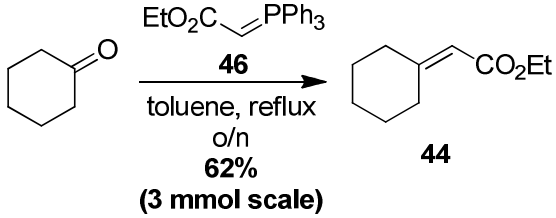


Following general procedure 1 using *N*-benzylglycine (4.23 g, 25.59 mmol), DME (50 mL), stirring 5 hrs, *N*-benzylsydnone (**43c**) was isolated as a white solid (4.03 g, 89%).

M.p. = 64 - 66 °C (lit. 67 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 3H, Ar***H***), 7.37 (dt, *J* = 4.5, 3.5 Hz, 2H, Ar***H***), 6.17 (s, 1H, Ar***H***), 5.35 (s, 2H, C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 130.6, 130.3, 129.7, 128.8, 94.7, 57.4; FTIR: 3463 (br), 3153 (m), 1730 (s), 1473 (m), 1180 (m), 1063 (w), 936 (w), 696 (s); HRMS: m/z $[M+H]^+$ calcd. for $C_9H_9N_2O_2$: 177.0664, found: 177.0658.

3. Investigation on the introduction of an oxetane ring into a sydnone

Synthesis of ethyl 2-cyclohexylideneacetate (44)[180]

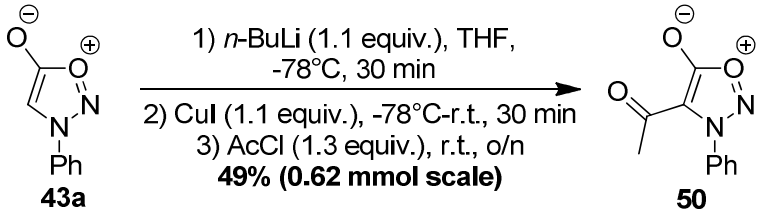


(Carbethoxymethylene)triphenylphosphorane (**46**) (1.254 g, 3.6 mmol, 1.2 equiv.) was added to a solution of cyclohexanone (0.310 mL, 3 mmol, 1 equiv.) in toluene (2 mL). The resulting mixture was heated at reflux o/n before being concentrated *in vacuo*. The residue was then diluted with petroleum ether (20 mL) and filtrated. The filtrate was concentrated *in vacuo* and purified via flash column chromatography on silica gel eluting with a gradient from 0 to 10% ethyl acetate in petroleum ether to afford ethyl 2-cyclohexylideneacetate (**44**) as a pale yellow oil (0.314 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (s, 1H, C***H***), 4.13 (q, *J* = 7.0 Hz, 2H, C***H***$_2$-CH_3), 2.85 – 2.78 (m, 2H, C***H***$_2$), 2.22 – 2.14 (m, 2H, C***H***$_2$), 1.62 (tt, *J* = 7.0, 6.0 Hz, 6H, C***H***$_2$), 1.26 (t, *J* = 7.0 Hz, 3H, CH_2-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 163.7, 113.1, 59.6, 38.1, 29.9, 28.7, 27.9, 26.4, 14.4; FTIR: 2980 (s), 2933 (s), 2856 (s), 1713 (s), 1646 (s), 1446 (s), 1380 (s), 1310 (m), 1273 (s), 1236 (s), 1206 (s),

1160 (s), 1040 (s), 993 (w), 850 (s); HRMS: m/z [M+H]+ calcd. for $C_{10}H_{17}O_2$: 169.1229, found: 169.1235. Analysis are in accordance with those reported in the literature.

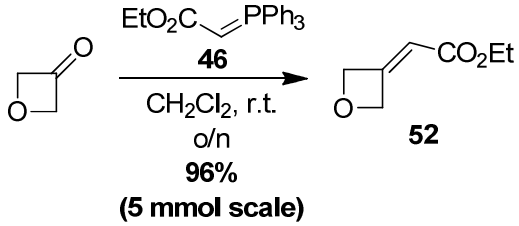
Synthesis of 4-acetyl-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (50)[181]



A solution of *n*-BuLi (2.5 M in THF, 0.27 mL, 0.68 mmol, 1.1 equiv.) was added to a cooled solution of *N*-Phenylsydnone (**43a**) (0.100 g, 0.62 mmol, 1 equiv.) in THF (1 mL) at -78°C under argon to form a red solution. The resulting mixture was stirred at -78°C for 30 min. Copper (I) iodide (0.129 g, 0.68 mmol, 1.1 equiv.) was then added and the mixture was allowed to warm to r.t. over 30 min before acetyl chloride (0.06 mL, 0.80 mmol, 1.3 equiv.) was added dropwise. The resulting mixture was then stirred at r.t. o/n. A 1 M solution of HCl (5 mL) was then added and the solution was extracted with CH_2Cl_2 (3x 5 mL). The combined organic layer were then dried over magnesium sulfate, filtered and concentrated. The crude material was then purified via flash column chromatography on silica gel eluting with 20% ethyl acetate in petroleum ether to afford 4-acetyl-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**50**), as a pale yellow solid (0.062 g, 49%).

M.p. = 146 – 148 °C (lit. 143-145 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 1H, Ar***H***), 7.61 – 7.55 (m, 2H, Ar***H***), 7.49 – 7.44 (m, 2H, Ar***H***), 2.51 (s, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3, 166.3, 135.0, 132.4, 129.5, 124.9, 106.1; FTIR: 3443 (br), 3063 (w), 2920 (w), 2850 (w), 1666 (s), 1426 (s), 1053 (m), 990 (m), 770 (s); HRMS: m/z [M+H]+ calcd. for $C_{10}H_9N_2O_3$: 169.1229, found: 169.1235.

Synthesis of ethyl 2-(oxetan-3-ylidene)acetate (52)[20]



(Carbethoxymethylene)triphenylphosphorane (**46**) (1.910 g, 5.5 mmol, 1.1 equiv.) was added to a solution of 3-oxetanone (0.3 mL, 5 mmol, 1 equiv.) in CH_2Cl_2 (5 mL). The resulting mixture was heated at reflux o/n before being concentrated *in vacuo*. The residue was then diluted with petroleum ether (50 mL) and filtrated. The filtrate was concentrated *in vacuo* and purified via flash column chromatography on silica gel eluting with 10% ethyl acetate in petroleum ether to afford ethyl 2-(oxetan-3-ylidene)acetate (**52**) as a pale yellow oil (0.682 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.60 (m, 1H, C***H***), 5.51 – 5.47 (m, 2H, C***H***$_2$), 5.31 – 5.27 (m, 2H, C***H***$_2$), 4.15 (q, *J* = 7.0 Hz, 2H, C***H***$_2$-CH_3), 1.26 (t, *J* = 7.0 Hz, 3H, CH_2-C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 159.3, 111.2, 81.2, 78.6, 60.5, 14.4; FTIR: 2983 (m), 2930 (m), 2860 (m), 1720 (s), 1696 (s), 1443 (w), 1370 (s), 1346 (s), 1300 (s), 1266 (s), 1206 (s), 1100 (s), 1036 (s), 963 (s), 870 (m), 836 (m); HRMS: m/z [M+H]+ calcd. for $C_{10}H_{11}O_3$: 143.0708, found: 143.0714. Analysis are in accordance with those reported in the literature.

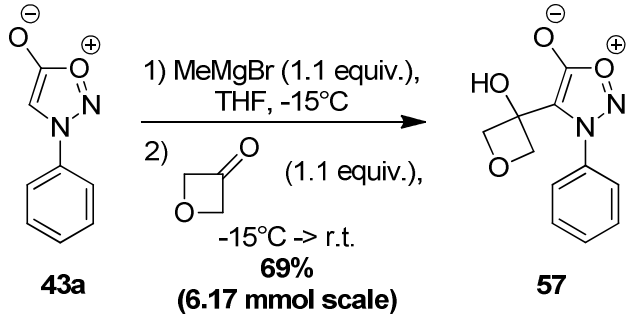
4. Synthesis of 3-hydroxyoxetan-3-yl)-*N*-aryl-sydnone

General procedure 2: Synthesis of 4-(3-hydroxyoxetan-3-yl)-*N*-aryl-sydnone

A 3 M solution of methyl magnesium bromide in hexane (1.1 equiv.) was added dropwise to a solution of sydnone (1 equiv.) in dry THF (10 mL for 1.00 g) under argon at -15 °C. The resulting mixture was left to stir at -15 °C for 1 hour. 3-Oxetanone (1.1 equiv.) was then added at -15 °C, and the resulting mixture was allowed to warm to room temperature and left to stir for 5 hours. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL for 1.00

g), and the volatiles were removed *in vacuo*. The residue was extracted with CH_2Cl_2 (3x 20 mL for 1.00 g) and, the combined organic fractions were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resulting oil was then triturated with ethanol (20 mL for 1.00 g) and filtered to afford the title product.

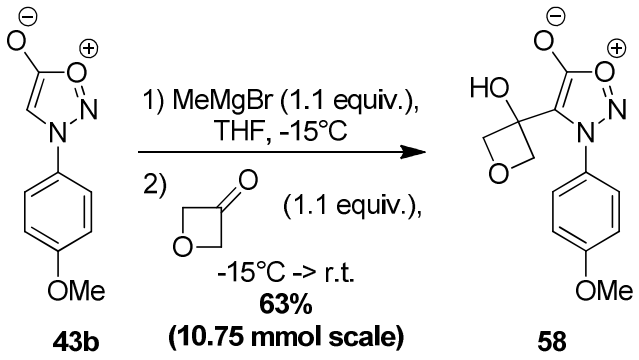
Synthesis of 4-(3-hydroxyoxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (57)



Using general procedure 1 with *N*-phenylsydnone (**43a**) (1.00 g, 6.17 mmol) in THF (10 mL), 4-(3-hydroxyoxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**57**) was isolated as a yellow solid (1.01 g, 69%).

M.p. = 126 - 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.84 (m, 2H, Ar***H***), 7.76 – 7.70 (m, 1H, Ar***H***), 7.69 – 7.63 (m, 2H, Ar***H***), 4.90 (s, 1H, O***H***), 4.75 (d, *J* = 7.5 Hz, 2H, C***H*****$_2$**), 4.61 (d, *J* = 7.5 Hz, 2H, C***H*****$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 134.4, 132.9, 130.2, 124.1, 108.5, 80.6, 67.8; FTIR: 3289 (br), 2950 (w), 2882 (w), 1721 (s), 1476 (m), 1267 (m), 1187 (m), 1140 (w), 1156 (w), 1018 (m), 982 (m), 773 (m), 690 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{11}H_{10}N_2O_4$: 235.0719, found: 235.0709.

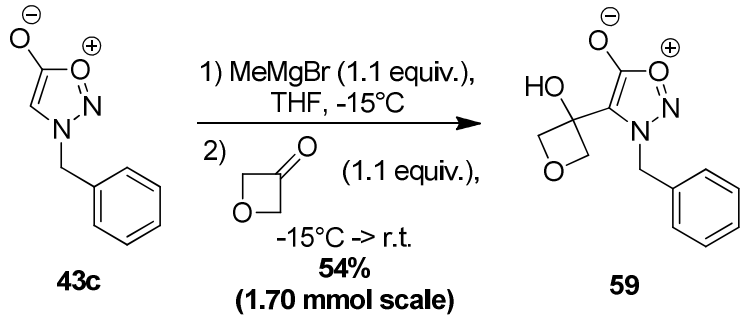
Synthesis of 4-(3-hydroxyoxetan-3-yl)-3-(4-methoxyphenyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (58)



Using general procedure 1 with *N*-*p*-methoxyphenylsydnone (**43b**) (2.07 g, 10.75 mmol) in THF (20 mL), 4-(3-hydroxyoxetan-3-yl)-3-(4-methoxyphenyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**58**) was isolated as a beige solid (1.80 g, 63%).

M.p. = 126 - 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.10 (d, *J* = 9.0 Hz, 2H, Ar***H***), 4.86 (s, 1H, O***H***), 4.77 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.62 (d, *J* = 7.5 Hz, 2H, C***H₂***), 3.93 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.7, 127.0, 125.5, 115.2, 108.3, 80.7, 67.8, 55.8; FTIR: 3343 (m), 2878 (w), 1721 (s), 1606 (m), 1512 (s), 1469 (m), 1306 (w), 1256 (s), 1173 (m), 1115 (w), 1021 (m), 982 (m), 837 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{12}H_{12}N_2O_5$: 265.0824, found: 265.0819.

Synthesis of 3-benzyl-4-(3-hydroxyoxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (59)



Using general procedure with *N*-benzylsydnone (**43c**) (0.300 g, 1.70 mmol) in THF (5 mL), 3-benzyl-4-(3-hydroxyoxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**59**) was isolated as a beige solid (0.228 g, 54%).

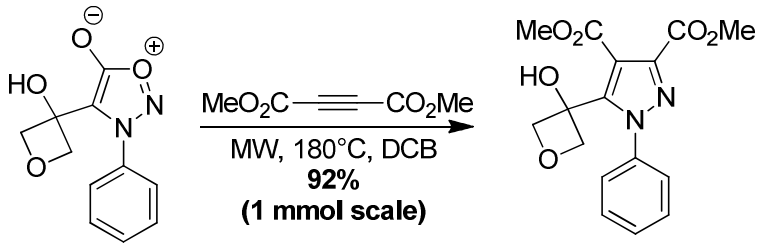
M.p. = 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 3H, Ar***H***), 7.33 (d, *J* = 3.5 Hz, 2H, Ar***H***), 5.60 (s, 2H, C***H*****$_2$**), 4.93 – 4.63 (m, 3H, C***H*****$_2$** and O***H***), 4.40 (d, *J* = 6.0 Hz, 2H, C***H*****$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 130.4, 130.0, 129.4, 128.2, 106.1, 80.8, 69.2, 56.5; FTIR: 3317 (m), 2955 (w), 2881 (w), 1724 (s), 1495 (m), 1456 (m), 1328 (w), 1185 (m), 980 (m), 868 (w), 737 (m), 700 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{12}H_{12}N_2O_4$: 249.0864, found: 249.0875.

5. Synthesis of 4-oxetanylsydnone cycloadducts

General procedure 3: Cycloaddition of 4-(3-hydroxyoxetan-3-yl)-*N*-aryl-sydnone with alkynes

An alkyne (2 equiv.) was added to a mixture of the appropriate 4-(3-hydroxyoxetan-3-yl)-*N*-aryl-sydnone (1 equiv.) in solvent (2 mL for 0.500 g) in a sealed microwave vial. The vial was then placed in a CEM Microwave Explorer Reactor and heated at the stated temperature for the required time. The reaction mixture was directly purified by flash chromatography on silica gel to afford the title compounds.

Synthesis of dimethyl 5-(3-hydroxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (60)

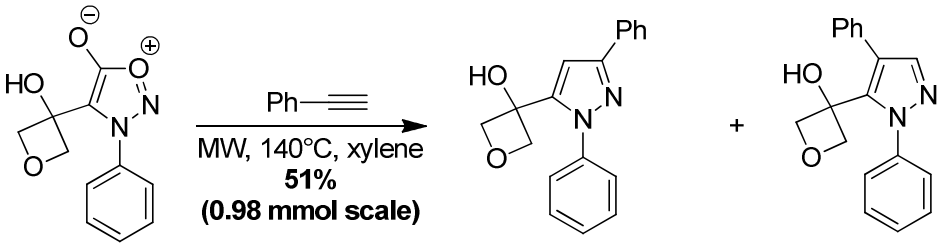


57 **60**

Using general procedure 3 with (**57**) (0.234 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.25 mL, 2 mmol), the mixture was stirred for 5 minutes and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), dimethyl 5-(3-hydroxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (**60**) was isolated as a beige solid (0.306 g, 92%).

M.p. = 114 - 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H, Ar***H***), 7.54 – 7.47 (m, 3H, Ar***H***), 4.55 – 4.47 (m, 4H, C***H₂***), 4.16 (s, 1H, O***H***), 3.97 (s, 3H, C***H₃***), 3.91 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 162.1, 147.4, 143.9, 138.7, 130.0, 129.6, 124.8, 112.7, 81.0, 70.7, 52.8, 52.6; FTIR: 3399 (br), 2955 (w), 2880 (w), 1722 (s), 1542 (w), 1482 (m), 1316 (m), 1225 (s), 1080 (m), 988 (w), 769 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{16}H_{16}N_2O_6$: 333.1074, found: 333.1087.

Synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-5-yl)oxetan-3-ol (61a)

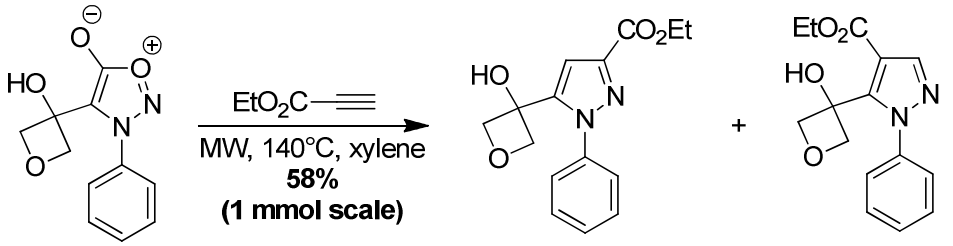


57 **61a** **61b**

Using general procedure 3 with (**57**) (0.230 g, 0.98 mmol) and phenylacetylene (0.22 mL, 1.96 mmol), the mixture was stirred for 5 minutes and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), 3-(1,3-diphenyl-1*H*-pyrazol-5-yl)oxetan-3-ol (**61a**) was isolated as a beige solid (0.142 g, 51%; >98:2).

M.p. = 33 - 35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 2H, Ar***H***), 7.64 – 7.55 (m, 2H, Ar***H***), 7.51 – 7.34 (m, 6H, Ar***H***), 6.59 (s, 1H, pyr-***H***), 4.72 (d, *J* = 7.0 Hz, 2H, C***H₂***), 4.60 (d, *J* = 7.0 Hz, 2H, C***H₂***), 3.62 (s, 1H, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 144.6, 140.0, 132.5, 129.2, 128.8, 128.5, 128.4, 125.8, 124.6, 103.6, 82.9, 70.5; FTIR: 3393 (br), 2949 (m), 2881 (m), 1640 (m), 1597 (m), 1550 (w), 1500 (s), 1460 (m), 1364 (m), 1270 (w), 1227 (w), 1138 (w), 1080 (w), 980 (m), 872 (w), 768 (m), 696 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{18}H_{16}N_2O_2$: 293.1291, found: 293.1290.

Synthesis of ethyl 5-(3-hydroxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate (62)



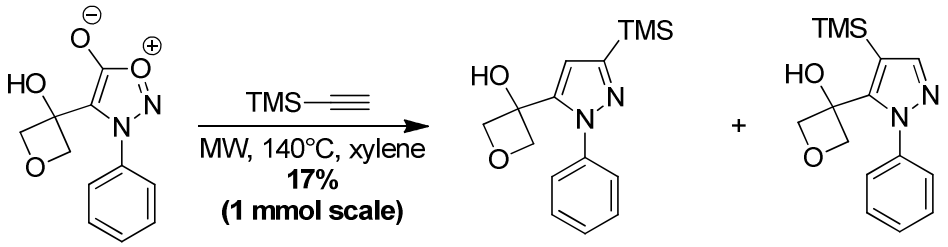
57 **62a** **62b**

Using general procedure 3 with (**57**) (0.234 g, 1 mmol) and ethyl propiolate (0.21 mL, 2 mmol), the mixture was stirred for 30 min and purified by flash chromatography on silica gel (eluting with a gradient from 20 to 30% ethyl acetate in dichloromethane), 5-(3-hydroxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate (**62a**) was isolated as a brown oil (167 mg, 58%) and ethyl 5-(3-hydroxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-4-carboxylate (**62b**) as a brown oil (25 mg, 8%).

(**62a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H, Ar***H***), 7.45 – 7.36 (m, 3H, Ar***H***), 6.78 (s, 1H, pyr-***H***), 4.64 (d, *J* = 7.0 Hz, 2H, C***H₂***), 4.57 (d, *J* = 7.0 Hz, 2H, C***H₂***), 4.40 (q, *J* = 7.0 Hz, 2H, C***H₂***), 1.40 (t, *J* = 7.0 Hz, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 145.4, 143.5, 139.4, 129.21, 129.25, 124.9, 108.5, 82.6, 69.9, 61.4, 14.3; FTIR: 3365 (br), 3074 (w), 2981 (m), 2949 (m), 2877 (m), 1719 (s), 1593 (m), 1496 (m), 1453 (m), 1371 (m), 1238 (s), 1177 (m), 1123 (m), 1077 (w), 1023 (m), 987 (m), 919 (w), 876 (w), 836 (w), 775 (m), 732 (m), 689 (m), 646 (w); HRMS: m/z $[MH]^+$ calcd. for $C_{15}H_{16}N_2O_4$: 289.1182, found: 289.1188.

(**62b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, pyr-***H***), 7.59 – 7.48 (m, 5H, Ar***H***), 4.61 (d, *J* = 8.5 Hz, 2H, C***H₂***), 4.55 (d, *J* = 8.5 Hz, 2H, C***H₂***), 4.36 (q, *J* = 7.0 Hz, 2H, C***H₂***), 4.01 (s, 1H, O***H***), 1.42 (t, *J* = 7.0 Hz, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 146.5, 141.8, 139.3, 129.6, 129.5, 124.7, 112.8, 81.3, 70.9, 61.0, 14.3; FTIR: 3415 (br), 2981 (w), 2942 (w), 2873 (w), 1711 (s), 1597 (w), 1550 (m), 1500 (m), 1399 (m), 1381 (m), 1281 (m), 1238 (s), 1134 (m), 1087 (m), 1034 (w), 987 (m), 876 (w), 764 (m); HRMS: m/z $[MH]^+$ calcd. for $C_{15}H_{16}N_2O_4$: 289.1175, found: 289.1188.

Synthesis of 3-(1-phenyl-3-(trimethylsilyl)-1*H*-pyrazol-5-yl)oxetan-3-ol (63a)

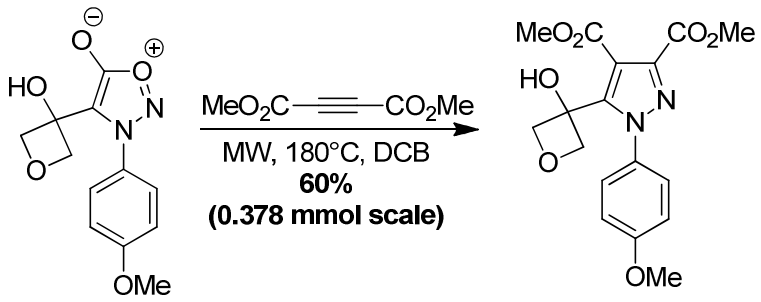


57 **63a** **63b**

Using general procedure 3 with (**57**) (0.234 g, 1 mmol) and (trimethylsilyl)acetylene (0.29 mL, 2 mmol), the mixture was stirred for 3.5 hrs and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), 3-(1-phenyl-3-(trimethylsilyl)-1*H*-pyrazol-5-yl)oxetan-3-ol (**63a**) was isolated as a brown foam (51 mg, 17%, >98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2H, Ar***H***), 7.48 – 7.38 (m, 3H, Ar***H***), 6.48 (s, 1H, pyr-***H***), 4.75 (d, *J* = 7.0 Hz, 2H, C***H₂***), 4.61 (d, *J* = 7.0 Hz, 2H, C***H₂***), 0.34 (s, 9H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 143.2, 140.3, 129.2, 128.4, 124.8, 112.3, 83.2, 70.6, -1.0; FTIR: 3365 (br), 2956 (m), 2881 (w), 1733 (w), 1600 (m), 1503 (m), 1410 (w), 1320 (m), 1249 (m), 1199 (w), 1141 (w), 1073 (w), 983 (m), 912 (w), 840 (s), 757 (m), 729 (m), 696 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{15}H_{20}N_2O_2Si$: 289.1368, found: 289.1372.

Synthesis of dimethyl 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3,4-dicarboxylate (64)



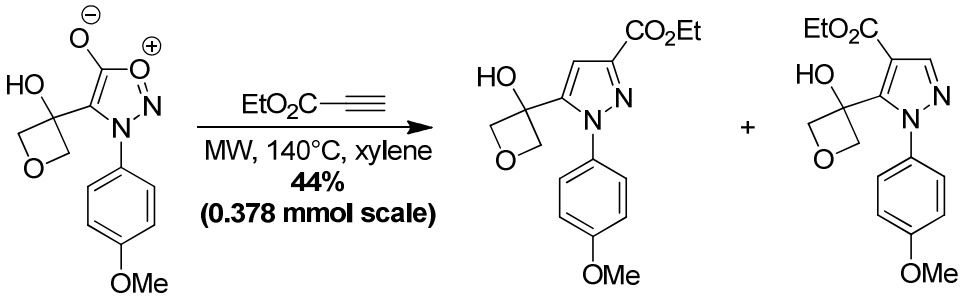
58 **64**

Using general procedure 3 with (**58**) (0.100 g, 0.378 mmol) and dimethyl acetylenedicarboxylate (0.09 mL, 0.756 mmol), mixture was stirred for 20 minutes

and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), dimethyl 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3,4-dicarboxylate (**64**) was isolated as a beige solid (0.082 g, 60%).

M.p. = 135 - 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 2H, Ar***H***), 6.99 (d, *J* = 9.0 Hz, 2H, Ar***H***), 4.53 (s, 4H, C***H₂***), 3.97 (s, 3H, C***H₃***), 3.92 (s, 3H, C***H₃***), 3.87 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 162.1, 160.7, 147.3, 143.6, 131.6, 126.2, 114.7, 112.3, 80.9, 70.8, 55.6, 52.8, 52.6; FTIR: 3396 (br), 2952 (m),2878 (w), 2839 (w), 1724 (s), 1608 (m), 1514 (s), 1483 (m), 1303 (m), 1255 (s), 1178 (m), 1078 (m), 1029 (m), 986 (m), 880 (w), 840 (m), 798 (w), 734 (w); HRMS: m/z $[M+H]^+$ calcd. for $C_{17}H_{18}N_2O_7$: 363.1190, found: 363.1192.

Synthesis of ethyl 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (65)



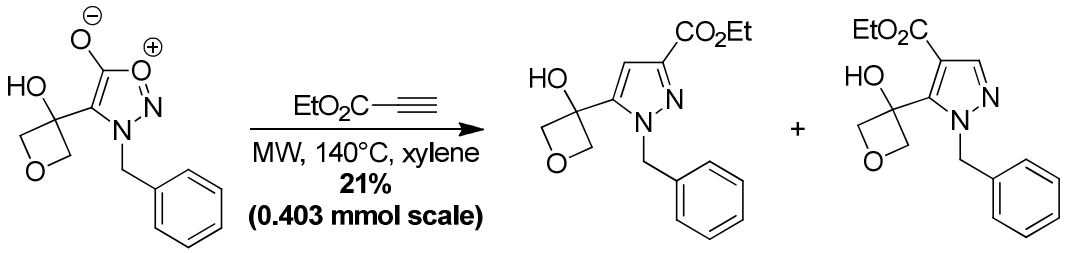
58 **65a** **65b**

Using general procedure 3 with (**58**) (0.100 g, 0.378 mmol) and ethyl propiolate (0.08 mL, 0.756 mmol), mixture stirred for 1 hour and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), ethyl 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (**65a**) and 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (**65b**) were isolated as an inseparable mixture (5:1) as a brown oil (53 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 0.2H, pyr-***H***), 7.74 (d, *J* = 9.0 Hz, 0.4H, Ar***H***), 7.56 – 7.50 (m, 2H, Ar***H***), 7.47 (d, *J* = 9.0 Hz, 0.4H, Ar***H***), 6.98 – 6.94 (m, 2H, Ar***H***), 6.92 (s, 1H, pyr-***H***), 5.32 (s, 1H, O***H***), 4.83 – 4.75 (m, 2.4H, C***H₂***), 4.64 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.59 (d, *J* = 4.5 Hz, 0.4H, C***H₂***), 4.45 (q, *J* = 7.0 Hz, 2H,

C***H₂***), 4.35 (q, *J* = 7.0 Hz, 0.2H, C***H₂***), 3.93 (s, 0.6H, C***H₃***), 3.87 (s, 3H, C***H₃***), 1.43 (t, *J* = 7.0 Hz, 3.6H, C***H₃***); data reported only for the major isomer (**65a**): ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 160.0, 145.1, 143.3, 132.4, 126.5, 114.2, 108.2, 82.7, 81.3, 61.3, 55.5, 14.4; FTIR: 3360 (br), 2955 (w), 2876 (w), 2840 (w), 1720 (s), 1608 (w), 1517 (s), 1467 (m), 1380 (m), 1301 (m), 1250 (s), 1174 (m), 1124 (m), 1030 (m), 986 (w), 838 (m), 780 (w), 733 (w); HRMS: m/z $[M+H]^+$ calcd. for $C_{16}H_{18}N_2O_5$: 319.1281, found: 319.1294.

Synthesis of ethyl 1-benzyl-5-(3-hydroxyoxetan-3-yl)-1*H*-pyrazole-3-carboxylate (66)

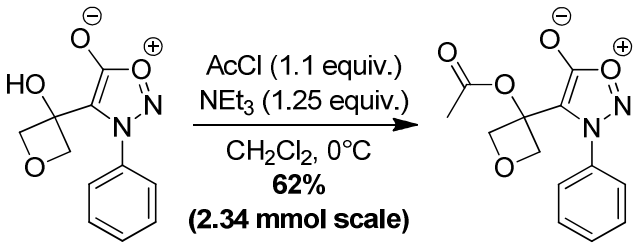


59 **66a** **66b**

Using general procedure 3 with (**59**) (0.100 g, 0.403 mmol) and ethyl propiolate (0.08 mL, 0.806 mmol), the mixture was stirred for 30 min and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane), ethyl 1-benzyl-5-(3-hydroxyoxetan-3-yl)-1*H*-pyrazole-3-carboxylate (**66a**) and ethyl 1-benzyl-5-(3-hydroxyoxetan-3-yl)-1*H*-pyrazole-4-carboxylate (**66b**) were isolated as an inseparable mixture (2:1) as a brown oil (26 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 0.5H, pyr-***H***), 7.39 – 7.29 (m, 4.5H, Ar***H***), 7.17 – 7.11 (m, 3H, Ar***H***), 6.85 (s, 1H, pyr-***H***), 5.52 (s, 2H, C***H₂***), 5.26 (s, 1H, C***H₂***), 5.00 (d, *J* = 8.0 Hz, 1H, C***H₂***), 4.83 (d, *J* = 8.5 Hz, 1H, C***H₂***), 4.52 (s, 4H, C***H₂***), 4.44 (q, *J* = 7.0 Hz, 2H, C***H₂***), 4.30 (q, *J* = 7.0 Hz, 1H, C***H₂***), 1.43 (t, *J* = 7.0 Hz, 3H, C***H₃***), 1.37 (t, *J* = 7.0 Hz, 1.5H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 160.4, 146.1, 143.8, 141.6, 138.2, 136.0, 129.0, 128.8, 128.3, 128.2, 127.2, 126.7, 108.2, 102.3, 96.9, 82.9, 82.2, 71.0, 70.7, 61.2, 61.0, 55.5, 54.3, 14.4, 14.3; FTIR: 3394 (br), 2979 (m), 2878 (w), 1717 (s), 1556 (m), 1456 (m), 1384 (m), 1223 (s), 1030 (m), 983 (m), 911 (w), 875 (w), 840 (w), 779 (m), 728 (s), 700 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{16}H_{18}N_2O_4$: 303.1331, found: 303.1345.

Synthesis of 4-(3-acetoxyoxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (67)

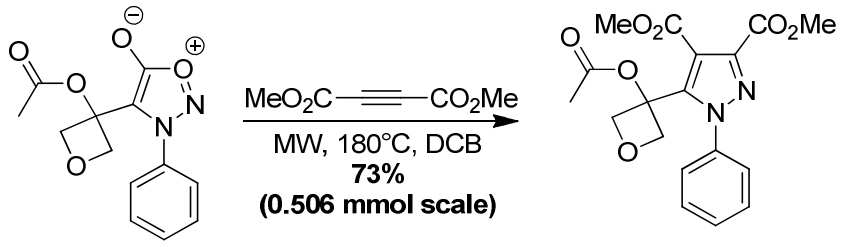


57 **67**

Acetyl chloride (0.17 mL, 2.34 mmol, 1.1 equiv.) was added to a mixture of 4-(3-hydroxyoxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**57**) (0.500 g, 2.13 mmol, 1 equiv.) and triethylamine (0.37 mL, 2.67 mmol, 1.25 equiv.) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was then warmed to 45 °C and left to stir for 2 days. The reaction mixture was then concentrated and purified by flash chromatography on silica gel (eluting with 20% ethyl acetate in dichloromethane) to afford 4-(3-acetoxyoxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**67**) as a pale brown solid (0.366 g, 62%).

M.p. = 150 - 152°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 1H, Ar***H***), 7.71 – 7.64 (m, 2H, Ar***H***), 7.59 – 7.54 (m, 2H, Ar***H***), 5.05 (dd, *J* = 8.0, 1.0 Hz, 2H, C***H₂***), 4.68 (dd, *J* = 8.0, 1.0 Hz, 2H, C***H₂***), 2.09 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 165.6, 134.2, 132.9, 130.2, 124.6, 105.1, 78.1, 72.6, 20.8; FTIR: 2959 (w), 2880 (w), 1763 (s), 1470 (w), 1373 (w), 1304 (w), 1236 (m), 1174 (w), 1113 (m), 1040 (w), 990 (m), 914 (w), 824 (w), 780 (w), 693 (w); HRMS: m/z $[M+H]^+$ calcd. for $C_{13}H_{12}N_2O_5$: 277.0834, found: 277.0824.

Synthesis of dimethyl 5-(3-acetoxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (68)



67 **68**

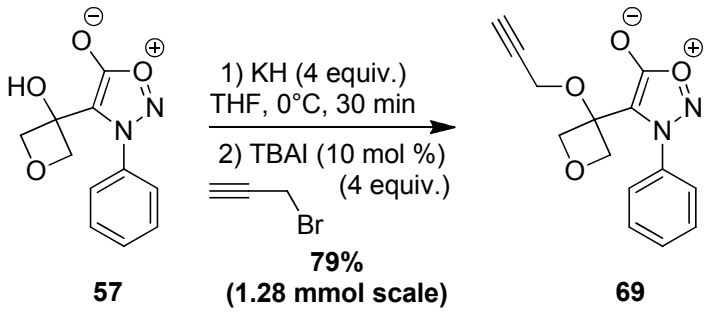
Dimethyl acetyelene dicarboxylate (0.072 mL, 0.506 mmol, 2 equiv.) was added to a mixture of (**67**) (70 mg, 0.253 mmol, 1 equiv.) in 1,2-dichlorobenzene (1 mL) in a sealed microwave vial. The vial was then placed in a CEM Microwave Explorer Reactor and heated at 180 °C for 30 min. The reaction mixture was directly purified by flash chromatography on silica gel (eluting with a gradient from 10 to 20% ethyl acetate in CH_2Cl_2) to afford dimethyl 5-(3-acetoxyoxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (**68**) as a brown foam (70 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 5H, Ar***H***), 4.96 (d, *J* = 9.0 Hz, 2H, C***H₂***), 4.55 (d, *J* = 9.0 Hz, 2H, C***H₂***), 3.94 (2 x s, 6H, C***H₃***), 2.12 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 163.9, 161.5, 142.4, 140.4, 138.9, 130.4, 129.4, 126.5, 94.6, 78.9, 75.7, 52.7, 52.6, 21.1; FTIR: 3359 (br), 2953 (m), 2918 (m), 2850 (w), 1735 (s), 1547 (w), 1470 (m), 1371 (m), 1317 (w), 1231 (s), 1080 (m), 989 (m), 907 (s), 839 (w), 765 (w), 728 (s); HRMS: m/z $[M+H]^+$ calcd. for $C_{18}H_{18}N_2O_7$: 375.1174, found: 375.1192.

General procedure 4: Synthesis of alkynes 69 - 72

To an ice-cooled suspension of potassium hydride (30 wt % dispersion in mineral oil) (4 equiv.) in THF (0.5 mL for 0.500 g) was added a solution of the appropriate oxetane sydnone (1 equiv.) in THF (0.5 mL for 0.500 g). After 30 min of stirring, tetrabutylammonium iodide (10 mol%) and propargyl bromide (80% vw in toluene) (4 equiv.) were then added. The reaction mixture was then allowed to warm to room temperature and stirred for 1 day. The reaction was concentrated, quenched with a saturated aqueous solution of ammonium chloride (10 mL for 0.500 g), and extracted with CH_2Cl_2 (3x 10 mL for 0.500 g). The organic fractions were combined, dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in CH_2Cl_2) to afford the title products.

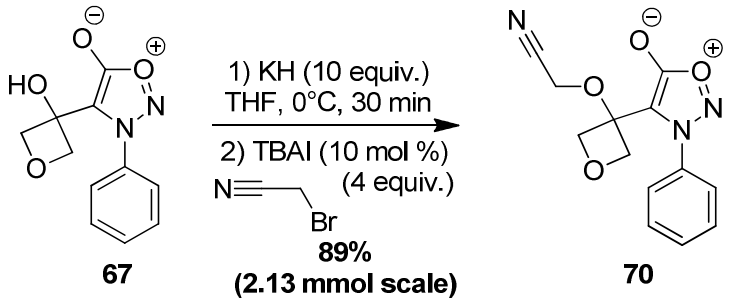
Synthesis of 3-phenyl-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (69)



Using general procedure 4 with (**57**) (300 mg, 1.28 mmol), 3-phenyl-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**69**) was isolated as a beige solid (274 mg, 79%).

M.p. = 122 - 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 2H, Ar***H***), 7.75 – 7.69 (m, 1H, Ar***H***), 7.68 – 7.62 (m, 2H, Ar***H***), 4.71 (dd, *J* = 7.5, 1.0 Hz, 2H, C***H*****$_2$**), 4.60 (dd, *J* = 7.5, 1.0 Hz, 2H, C***H*****$_2$**), 4.33 (d, *J* = 2.5 Hz, 2H, C***H*****$_2$**), 2.45 (t, *J* = 2.5 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 134.3, 132.8, 130.2, 124.1, 105.1, 79.2, 78.1, 75.0, 73.3, 53.2.; FTIR: 3246 (w), 2947 (w), 2882 (w), 1743 (s), 1479 (m), 1447 (w), 1277 (w), 1126 (m), 1043 (m), 1021 (m), 985 (m), 769 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{12}N_2O_4$: 273.0881, found: 273.0875.

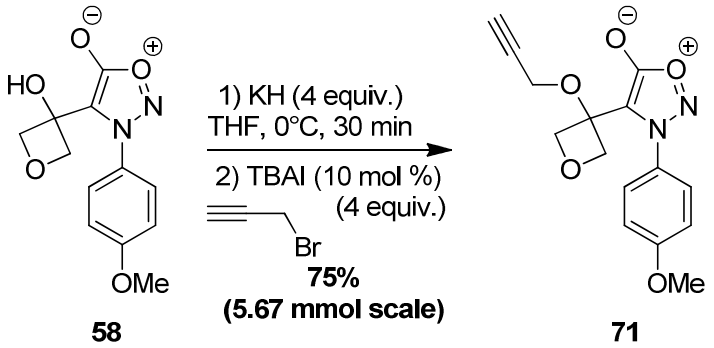
Synthesis of 4-(3-(cyanomethoxy)oxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (70)



Using general procedure 4 with (**67**) (0.500 g, 2.13 mmol, 1 equiv.) but with potassium hydride (30 wt % dispersion in mineral oil) (2.845 g, 21.30 mmol, 10 equiv.), 4-(3-(cyanomethoxy)oxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**70**) was isolated as a grey solid (0.518 g, 89%).

M.p. = 150 - 152°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 5H, Ar***H***), 4.70 (dd, *J* = 8.0, 1.0 Hz, 2H, C***H₂***), 4.60 (dd, *J* = 8.0, 1.0 Hz, 2H, C***H₂***), 4.42 (s, 2H, C***H₂***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 134.0, 133.3, 130.5, 123.7, 115.8, 102.8, 77.4, 74.7, 50.8.; FTIR: 2947 (w), 2882 (w), 1739 (s), 1476 (m), 1447 (w), 1277 (w), 1187 (w), 1119 (m), 1058 (m), 1036 (m), 985 (m), 888 (w), 769 (m), 737 (w), 690 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{13}H_{11}N_3O_4$: 274.0829, found: 274.0828.

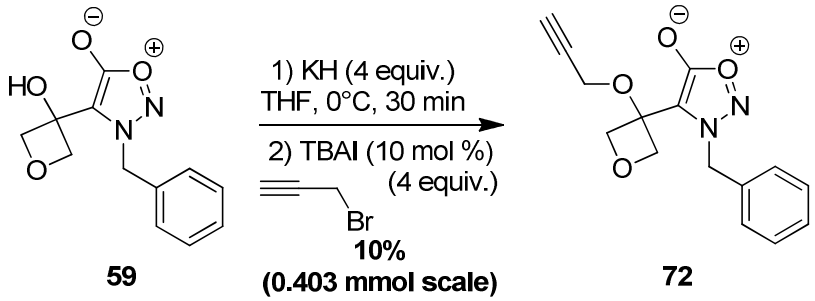
Synthesis of 3-(4-methoxyphenyl)-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (71)



Using general procedure 4 with (**58**) (1.50 g, 5.67mmol), 3-(4-methoxyphenyl)-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**71**) was isolated as a pale yellow solid (1.29 g, 75%).

M.p. = 96 - 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H, Ar***H***), 7.12 – 7.07 (m, 2H, Ar***H***), 4.75 – 4.71 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.62 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.31 (d, *J* = 2.5 Hz, 2H, C***H₂***), 3.93 (s, 3H, C***H₃***), 2.44 (t, *J* = 2.5 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 162.7, 127.0, 125.5, 115.2, 104.7, 79.2, 78.2, 74.9, 73.4, 55.8, 53.1.; FTIR: 3289 (m), 3084 (w), 2947 (m), 2878 (m), 1735 (s), 1606 (s), 1512 (s), 1469 (s), 1389 (m), 1259 (s), 1169 (m), 1126 (m), 1021 (s), 935 (m), 837 (s), 737 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_5$: 303.0983, found: 303.0981.

Synthesis of 3-benzyl-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (72)



59 **72**

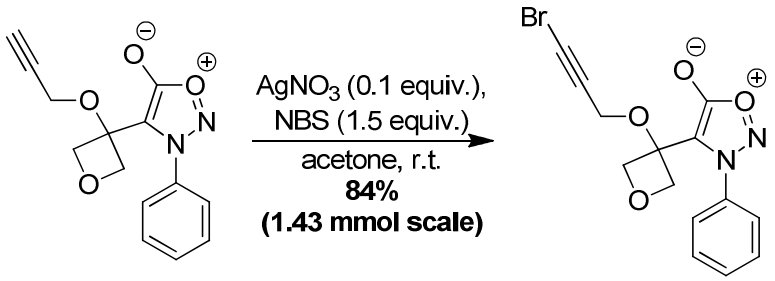
Using general procedure 4 with (**59**) (0.100 g, 0.403 mmol), 3-benzyl-4-(3-(prop-2-ynyloxy)oxetan-3-yl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**72**) was isolated as a pale yellow oil (12 mg, 10%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 5H, Ar***H***), 5.45 (s, 2H, C***H***$_2$), 4.74 (dd, *J* = 7.5, 1.0 Hz, 2H, C***H***$_2$), 4.53 (dd, *J* = 7.5, 0.5 Hz, 2H, C***H***$_2$), 4.10 (d, *J* = 2.5 Hz, 2H, C***H***$_2$), 2.44 (t, *J* = 2.5 Hz, 1H, C***H***). HRMS: m/z $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_4$: 287.1025, found: 287.1032. The compound was too unstable to generate sufficient quantities of pure material for further characterization.

<u>General procedure 5:</u> Synthesis of 1-Bromoalkynes

NBS (1.5 equiv.) was added to a solution of alkyne (1 equiv.) and silver salt (0.1 equiv.). The resulting mixture was then stirred at room temperature for the desired time before volatiles were removed *in vacuo*. Crude material was purified by flash chromatography on silica gel to afford the title product.

Synthesis of 4-(3-(3-bromoprop-2-ynyloxy)oxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (73)

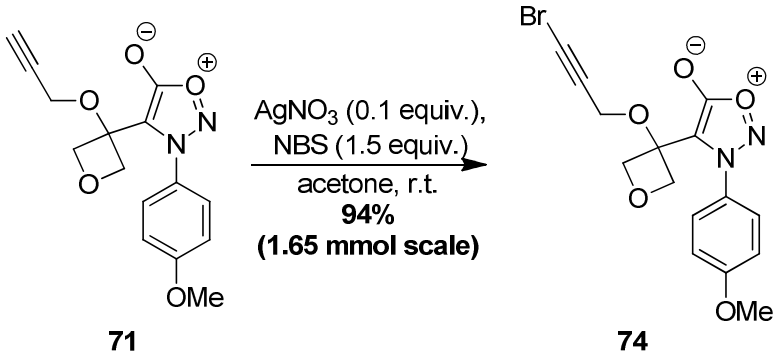


69 **73**

Using general procedure 5 with (**69**) (0.390 g, 1.43 mmol) in acetone (8 mL), the mixture was stirred for 1 hr and purified by flash chromatography on silica gel (eluting with a gradient from 5 to 10% of ethyl acetate in CH_2Cl_2), 4-(3-(3-bromoprop-2-ynyloxy)oxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**73**) was isolated as a yellow solid (422 mg, 84%).

M.p. = 102 - 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H, Ar***H***), 7.74 (t, *J* = 7.5 Hz, 1H, Ar***H***), 7.69 – 7.64 (m, 2H, Ar***H***), 4.70 (d, *J* = 7.5 Hz, 2H, C***H*****$_2$**), 4.59 (d, *J* = 7.5 Hz, 2H, C***H*****$_2$**), 4.34 (s, 2H, C***H*****$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 134.3, 132.9, 130.3, 124.0, 104.6, 78.1, 75.5, 73.3, 54.1, 47.2.; FTIR: 3069 (w), 2947 (w), 2878 (w), 2211 (w), 1743 (s), 1476 (m), 1274 (m), 1187 (m), 1122 (m), 1047 (m), 993 (m), 938 (w), 888 (w), 769 (m), 733 (m), 690 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{11}{}^{79}BrN_2O_4$: 350.9970, found: 350.9980.

Synthesis of 4-(3-(3-bromoprop-2-ynyloxy)oxetan-3-yl)-3-(4-methoxyphenyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (74)

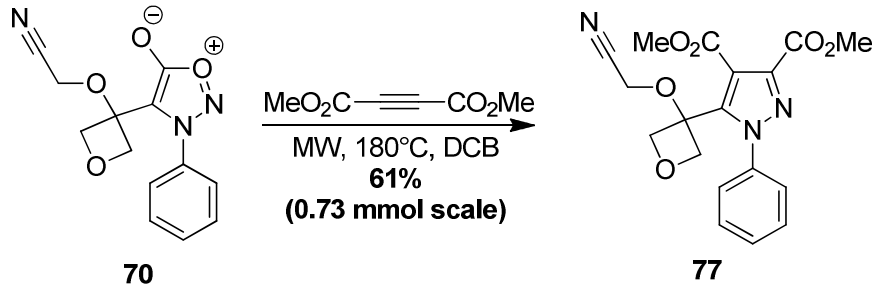


71 **74**

Using general procedure 5 with (**71**) (0.500 g, 1.654 mmol) in dichloromethane (10 mL), the mixture was stirred for 4 hrs and purified by flash chromatography on silica gel (eluting with 10% of ethyl acetate in dichloromethane), 4-(3-(3-bromoprop-2-ynyloxy)oxetan-3-yl)-3-(4-methoxyphenyl)-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**74**) was isolated as a pale brown solid (0.595 g, 94%).

M.p. = 81 - 82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.10 (d, *J* = 9.0 Hz, 2H, Ar***H***), 4.71 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.60 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.31 (s, 2H, C***H₂***), 3.92 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 162.7, 126.9, 125.4, 115.3, 104.2, 78.1, 75.5, 73.4, 55.9, 54.1, 47.2; FTIR: 3083 (w), 2945 (w), 2881 (w), 2211 (w), 1742 (s), 1602 (m), 1514 (s), 1465 (m), 1261 (s), 1172 (m), 1124 (m), 1023 (m), 993 (m), 932 (w), 840 (m), 740 (w); HRMS: m/z $[M+H]^+$ calcd. for $C_{15}H_{13}{}^{79}BrN_2O_5$: 381.0072, found: 381.0086.

Synthesis of dimethyl 5-(3-(cyanomethoxy)oxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (77)



70 **77**

Dimethyl acetylene dicarboxylate (0.09 mL, 0.732 mmol, 2 equiv.) was added to a mixture of 4-(3-(cyanomethoxy)oxetan-3-yl)-3-phenyl-3*H*-1,2,3-oxadiazol-1-ium-5-olate (**70**) (0.100 g, 0.366 mmol, 1 equiv.) in 1,2-dichlorobenzene (0.5 mL) in a sealed microwave vial. The vial was then placed in a CEM Microwave Explorer Reactor and heated at 180 °C for 2.5 hrs. The reaction mixture was directly purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in CH_2Cl_2) to afford dimethyl 5-(3-(cyanomethoxy)oxetan-3-yl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate (**77**) as a beige solid (74.5 mg, 61%).

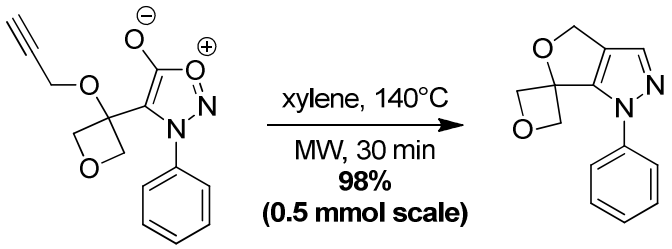
M.p. = 124 - 126°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H, Ar***H***), 7.56 – 7.51 (m, 3H, Ar***H***), 4.72 (s, 2H, C***H₂***), 4.56 (d, *J* = 9.0 Hz, 2H, C***H₂***), 4.48 (d, *J* = 9.0 Hz, 2H, C***H₂***), 3.99 (s, 3H, C***H₃***), 3.94 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ

163.3, 161.9, 144.1, 140.9, 138.2, 130.5, 129.5, 125.7, 116.0, 115.7, 78.1, 76.6, 52.9, 52.9, 51.1; FTIR: 2953 (m), 2881 (w), 1722 (s), 1596 (w), 1542 (m), 1477 (m), 1314 (m), 1228 (s), 1130 (m), 1083 (s), 1054 (m), 993 (m), 942 (w), 831 (w), 766 (m), 697 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{18}H_{17}N_3O_6$: 372.1199, found: 372.1196.

General procedure 6: Intramolecular cycloaddition

Xylene (1 mL for 0.500 g) was added to the alkyne (1 equiv.) in a sealed microwave vial under nitrogen. The vial was then placed in a CEM Microwave Explorer Reactor and heated at 140 °C for 15-30 min. The reaction mixture was directly purified by flash chromatography on silica gel to afford the title compounds.

Synthesis of 1-phenyl-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (78)

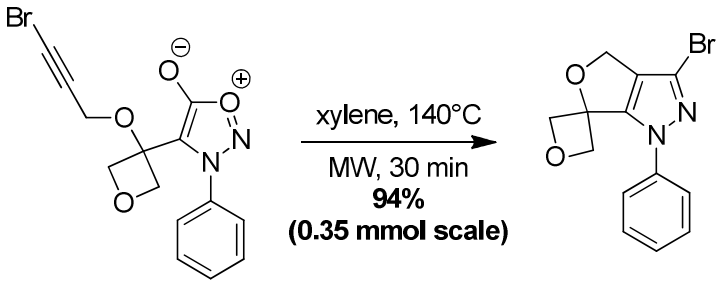


69 **78**

Using general procedure 6 with (**69**) (0.136 g, 0.5 mmol), mixture stirred for 30 min and purified by flash chromatography (eluting with 10% ethyl acetate in CH_2Cl_2), 1-phenyl-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (**78**) was isolated as a yellow solid (112 mg, 98%).

M.p. = 104 - 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 2H, Ar***H***), 7.55 (t, *J* = 7.5 Hz, 2H, Ar***H***), 7.44 (s, 1H, Pyr-***H***), 7.39 (t, *J* = 7.5 Hz, 1H, Ar***H***), 5.07 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.97 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.93 (s, 2H, C***H₂***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 139.4, 131.9, 129.6, 128.6, 127.3, 120.8, 82.7, 81.3, 65.7.; FTIR: 2959 (w), 2923 (w), 2879 (m), 1565 (w), 1511 (m), 1489 (w), 1381 (w), 1046 (w), 970 (s), 819 (m), 751 (s), 693 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{13}H_{12}N_2O_2$: 229.0983, found: 229.0977.

Synthesis of 3-bromo-1-phenyl-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (79)

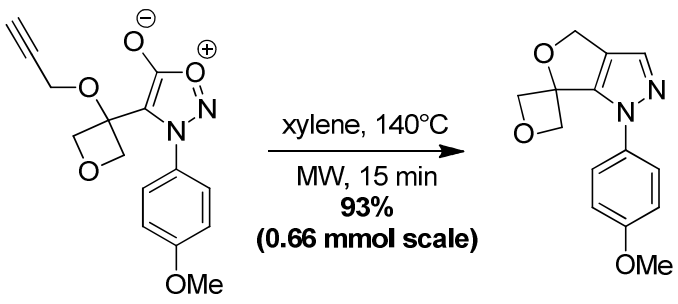


73 **79**

Using general procedure 6 with (**73**) (100 mg, 0.35 mmol), the mixture was stirred for 30 min and purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in petroleum ether), 3-bromo-1-phenyl-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (**79**) was isolated as a white solid (82 mg, 94%).

M.p. = 142 - 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H, Ar***H***), 7.57 – 7.51 (m, 2H, Ar***H***), 7.44 – 7.38 (m, 1H, Ar***H***), 5.05 (d, *J* = 8.5 Hz, 2H, C***H*****$_2$**), 4.93 (d, *J* = 8.5 Hz, 2H, C***H*****$_2$**), 4.88 (s, 2H, C***H*****$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 138.7, 129.7, 128.6, 127.8, 120.7, 118.5, 82.4, 81.9, 65.4.; FTIR: 2925 (w), 2885 (w), 1598 (w), 1551 (w), 1512 (w), 1458 (m), 1332 (w), 1155 (w), 971 (s), 902 (w), 823 (s), 755 (s), 690 (m); HRMS: m/z $[M+H]^+$calcd. for $C_{13}H_{11}{}^{79}BrN_2O_2$: 307.0083, found: 307.0082.

Synthesis of 1-(4-methoxyphenyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (80)

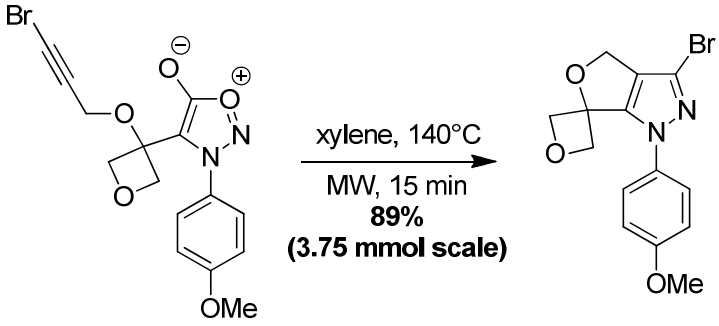


71 **80**

Using general procedure 6 with (**71**) (0.200 g, 0.66 mmol), the mixture was stirred for 15 min and purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in dichloromethane), 1-(4-methoxyphenyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**80**) was isolated as a beige solid (158 mg, 93%).

M.p. = 100 - 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H, Ar***H***), 7.40 (s, 1H, pyr-***H***), 7.07 – 7.02 (m, 2H, Ar***H***), 5.04 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.93 (s, 2H, C***H₂***), 4.91 (d, *J* = 8.0 Hz, 2H, C***H₂***), 3.88 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 145.8, 132.6, 131.4, 127.8, 123.1, 114.6, 82.7, 81.0, 65.9, 55.5.; FTIR: 2947 (w), 2875 (w), 2835 (w), 1519 (s), 1443 (m), 1303 (m), 1249 (s), 1209 (w), 1155 (m), 1072 (w), 1032 (m), 978 (m), 931 (w), 834 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{14}N_2O_3$: 259.1091, found: 259.1083.

Synthesis of 3-bromo-1-(methoxyphenyl)-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (81)



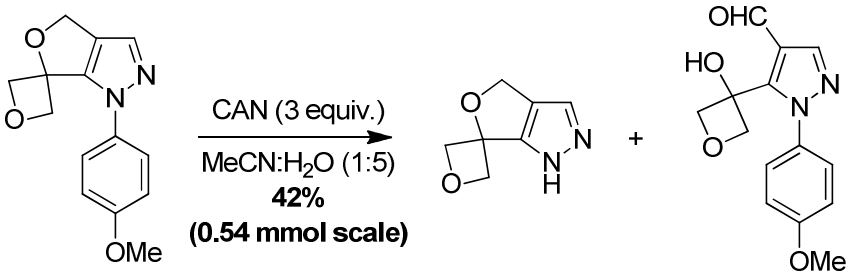
74 **81**

Using general procedure 6 with (**74**) (1.430 g, 3.75 mmol), the mixture was stirred for 15 min and purified by flash chromatography on silica gel (eluting with a gradient from 10 to 20% ethyl acetate in petroleum ether), 3-bromo-1-(methoxyphenyl)-1,4-dihydrospiro(furo[3,4-c]pyrazole-6,3'-oxetane) (**81**) was isolated as a beige solid (1.125 g, 89%).

M.p. = 149 - 151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.03 (d, *J* = 9.0 Hz, 2H, Ar***H***), 5.01 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.90 – 4.84 (m, 4H, C***H₂***), 3.88 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 147.6, 131.9, 127.8, 123.1, 117.8, 114.7, 82.5, 81.6, 65.5, 55.6.; FTIR: 3415 (br), 2945 (w), 2878 (w), 1742 (w), 1520 (s), 1447 (m), 1328 (m), 1300 (m), 1252 (s), 1157 (m), 1032 (m), 977

(m), 831 (m), 615 (w); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{13}{}^{79}BrN_2O_3$: 337.0199, found: 337.0188.

Synthesis of 1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (82)



80 **82** **83**

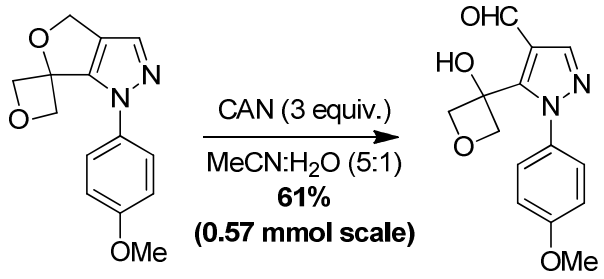
A solution of ceric ammonium nitrate (0.296 g, 0.54 mmol, 3 equiv.) in H_2O (4.75 mL) was added to a solution of (**80**) (46.5 mg, 0.18 mmol, 1 equiv.) in acetonitrile (1 mL) at 0 °C. The resulting mixture was then warmed to room temperature and stirred for 15 min. The reaction mixture was concentrated and extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (eluting with a gradient from 50% to 100% ethyl acetate in CH_2Cl_2) to afford 1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**82**) as a pale yellow solid (12 mg, 42%) and 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**83**) as a pale yellow solid (3 mg, 6%).

(**82**): M.p. = 118 - 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H, pyr-***H***), 5.09 (d, *J* = 7.5 Hz, 2H, C***H₂***), 4.98 (m, 4H, C***H₂***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 121.7, 120.9, 83.9, 79.7, 66.2; FTIR: 3143 (s), 3111 (s), 3064 (m), 2912 (s), 2872 (s), 1590 (w), 1431 (m), 1329 (m), 1239 (m), 1160 (m), 1127 (m), 1080 (m), 1051 (m), 983 (s), 928 (m), 881 (m), 838 (m), 798 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_7H_8N_2O_2$: 153.0661, found: 153.0664.

(**83**): M.p. = 147 - 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H, C***H***O), 8.12 (s, 1H, pyr-***H***), 7.49 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.02 (d, *J* = 9.0 Hz, 2H, Ar***H***), 4.62 (d, *J* = 9.0 Hz, 2H, C***H₂***), 4.53 (d, *J* = 9.0 Hz, 2H, C***H₂***), 3.89 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.2, 160.6, 144.7, 143.4, 131.6, 126.0, 121.3, 114.7, 81.0, 70.9,

55.6.; FTIR: 3331 (br), 2945 (w), 2876 (w), 2840 (w), 1680 (m), 1608 (w), 1535 (m), 1517 (s), 1463(w), 1304 (m), 1254 (m), 1185 (m), 1030 (m), 983 (m), 838 (m), 813 (m), 787 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{14}N_2O_4$: 275.1023, found: 275.1032.

Synthesis of 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (83)



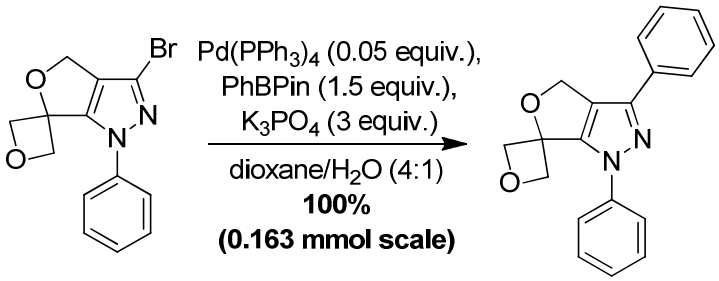
80 **83**

A solution of ceric ammonium nitrate (0.313 g, 0.57 mmol, 3 equiv.) in H_2O (1 mL) was added to a solution of (**80**) (50 mg, 0.19 mmol, 1 equiv.) in acetonitrile (5 mL) at 0 °C. The resulting mixture was then warmed to room temperature and stirred for 4 hrs. The reaction mixture was then concentrated, extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (eluting with 50% ethyl acetate in CH_2Cl_2) to afford 5-(3-hydroxyoxetan-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**83**) as a pale yellow solid (32 mg, 61%). Compound shows identical spectroscopic data to that described earlier.

<u>General procedure 7:</u> Suzuki-Miyaura coupling

A mixture of (1 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), K_3PO_4 (3 equiv.) and boronic acid derivatives (1.5 equiv.) in dioxane/H_2O (4:1) (1.25 mL) was stirred at 90 °C under nitrogen for the stated time. The reaction mixture was then cooled, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired product.

Synthesis of 1,3-diphenyl-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (86)

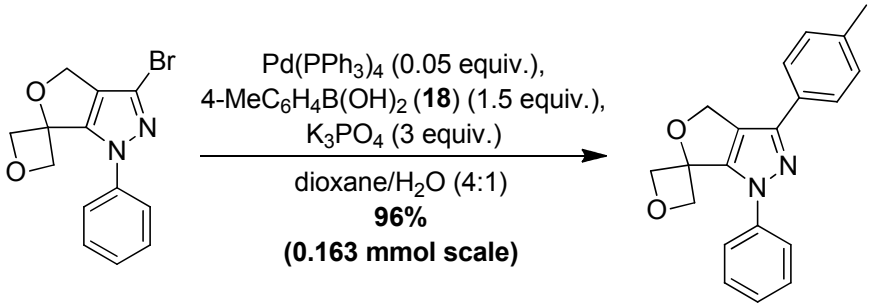


79 **86**

Using general procedure 7 with (**79**) (0.050 g, 0.163 mmol) and phenyl boronic acid pinacol ester (0.050 g, 0.244 mmol), the mixture was stirred for 30 min and purified by flash chromatography on silica gel (eluting with a gradient from 10 to 20% ethyl acetate in petroleum ether), 1,3-diphenyl-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**86**) was isolated as a beige solid (49 mg, quant.).

M.p. = 174 - 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 10.0, 2.0 Hz, 2H, Ar***H***), 7.71 (dd, *J* = 5.0, 3.5 Hz, 2H, Ar***H***), 7.60 – 7.54 (m, 2H, Ar***H***), 7.48 – 7.34 (m, 4H, Ar***H***), 5.15 (s, 2H, C***H₂***), 5.11 (d, *J* = 8.0 Hz, 2H, C***H₂***), 5.02 (d, *J* = 8.0 Hz, 2H, C***H₂***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 143.9, 139.4, 132.0, 129.7, 128.9, 128.3, 127.2, 126.0, 125.9, 120.7, 82.7, 81.3, 66.5.; FTIR: 3064 (w), 2952 (w), 2915 (w), 2878 (w), 1596 (w), 1550 (w), 1501 (m), 1462 (m), 1322 (w), 1154 (w), 1075 (w), 1005 (w), 974 (s), 862 (w), 752 (s), 694 (s); HRMS: m/z $[M+H]^+$ calcd. for $C_{19}H_{16}N_2O_2$: 305.1304, found: 305.1290.

Synthesis of 1-phenyl-3-(*p*-tolyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (87)

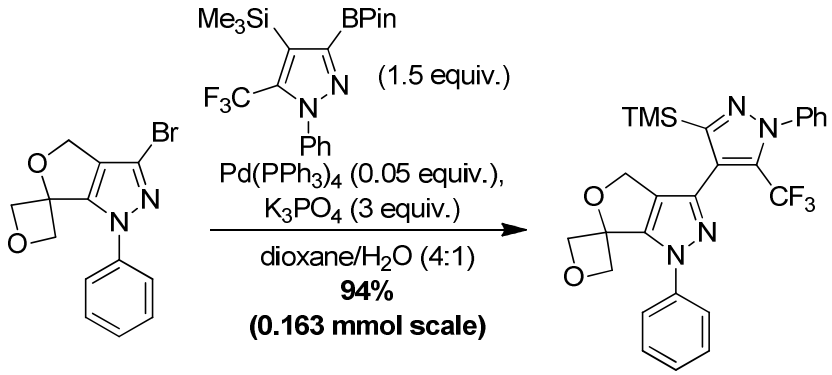


79 **87**

Using general procedure 7 with (**79**) (0.050 g, 0.163 mmol) and 4-tolylboronic acid (0.033 g, 0.244 mmol), the reaction was stirred for 1 day and purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in petroleum ether), 1-phenyl-3-(*p*-tolyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**87**) was isolated as a beige solid (50 mg, 96%).

M.p. = 156 - 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H, Ar***H***), 7.63 – 7.53 (m, 4H, Ar***H***), 7.39 (t, *J* = 7.5 Hz, 1H, Ar***H***), 7.26 (d, *J* = 8.0 Hz, 2H, Ar***H***), 5.13 (s, 2H, C***H₂***), 5.11 (d, *J* = 8.0 Hz, 2H, C***H₂***), 5.01 (d, *J* = 8.0 Hz, 2H, C***H₂***), 2.41 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 144.0, 139.5, 138.2 (2 signals), 129.6, 129.5, 129.2, 127.0, 125.8, 120.7, 82.7, 81.3, 66.5, 21.3.; FTIR: 3031 (w), 2949 (m), 2921 (m), 2872 (m), 1596 (m), 1550 (w), 1507 (s), 1489 (s), 1465 (s), 1373 (w), 1328 (w), 1185 (w), 1151 (m), 1099 (w), 974 (s), 938 (w), 819 (m), 761 (s), 691 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{20}H_{18}N_2O_2$: 319.1454, found: 319.1447.

Synthesis of 1-phenyl-3-(1-phenyl-5-(trifluoromethyl)-3-(trimethylsilyl)-1*H*-pyrazol-4-yl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (88)

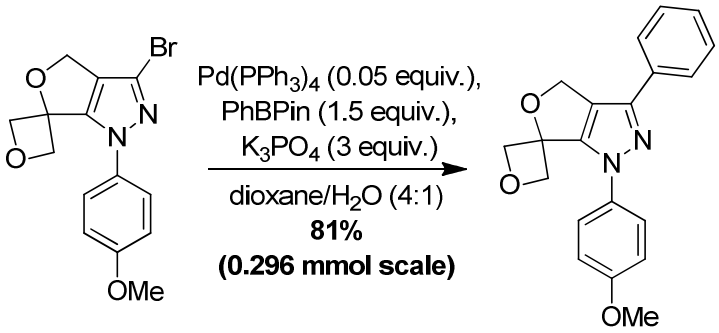


79 **88**

Using general procedure 7 with (**79**) (0.050 g, 0.163 mmol) and pyrazole boronic ester (0.050 g, 0.244 mmol), the mixture was stirred for 20 hrs and purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in petroleum ether), 1-phenyl-3-(1-phenyl-5-(trifluoromethyl)-3-(trimethylsilyl)-1*H*-pyrazol-4-yl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**88**) was isolated as a beige solid (78 mg, 94%).

M.p. = 138 - 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H, Ar***H***), 7.57 (d, *J* = 11.0 Hz, 2H, Ar***H***), 7.52 (s, 5H, Ar***H***), 7.41 (t, *J* = 7.5 Hz, 1H, Ar***H***), 5.14 (d, *J* = 8.0 Hz, 2H, C***H₂***), 5.06 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.91 (s, 2H, C***H₂***), 0.30 – 0.23 (s, 9H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 146.1, 139.6 (q, *J* = 35.3 Hz), 139.3, 136.2, 129.7, 129.3, 129.0, 127.2, 126.0, 122.0, 121.7, 120.3 (q, *J* = 265.6 Hz), 119.0, 82.7, 81.6, 65.8, 29.7, -0.8; FTIR: 3424 (br), 3070 (w), 2955 (m), 2878 (m), 1599 (m), 1501 (s), 1447 (w), 1386 (w), 1325(m), 1245 (m), 1200 (s), 1160 (s), 1127 (s), 1093 (m), 983 (s), 846 (s), 755 (m), 694 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{26}H_{25}F_3N_4O_2Si$: 511.1797, found: 511.1777.

Synthesis of 1-(4-methoxyphenyl)-3-phenyl-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (89)



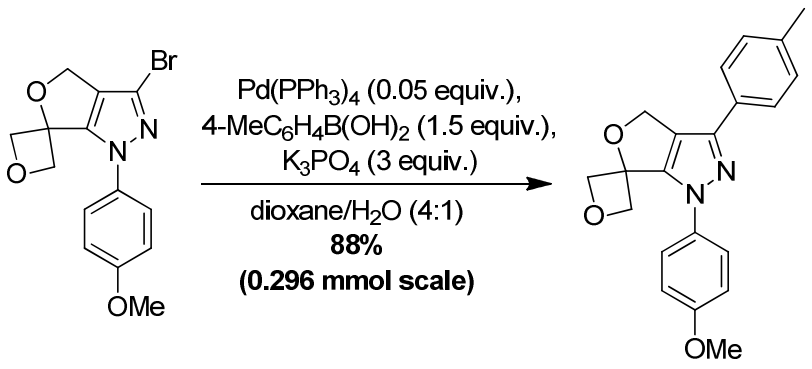
81 **89**

Using general procedure 7 with (**81**) (0.100 g, 0.296 mmol) and phenyl boronic acid pinacol ester (0.091 g, 0.444 mmol), the mixture was stirred for 22 hrs and purified by flash chromatography on silica gel (eluting with a gradient from 10 to 100% ethyl acetate in petroleum ether), 1-(4-methoxyphenyl)-3-phenyl-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**89**) was isolated as a grey solid (81 mg, 81%).

M.p. = 219 - 221 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.68 (d, *J* = 7.0 Hz, 2H, Ar***H***), 7.44 (t, *J* = 7.5 Hz, 2H, Ar***H***), 7.35 (t, *J* = 7.0 Hz, 1H, Ar***H***), 7.07 (d, *J* = 9.0 Hz, 2H, Ar***H***), 5.15 (s, 2H, C***H₂***), 5.07 (d, *J* = 8.0 Hz, 2H, C***H₂***), 4.95 (d, *J* = 8.0 Hz, 2H, C***H₂***), 3.89 (s, 3H, C***H₃***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 147.0, 143.5, 132.7, 132.1, 128.8, 128.2, 125.8, 125.2, 123.1, 114.7, 82.7, 81.0, 66.6, 55.6.; FTIR: 2955 (w), 2909 (w), 2839 (w), 1517 (m), 1444 (m), 1303 (w), 1258 (m), 1175 (w), 1099 (w), 1072 (w), 1032 (m), 974 (s), 938 (w), 858 (w),

825 (s), 801 (m), 691 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{20}H_{18}N_2O_3$: 335.1407, found: 335.1396.

Synthesis of 1-(4-methoxyphenyl)-3-(*p*-tolyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (90)

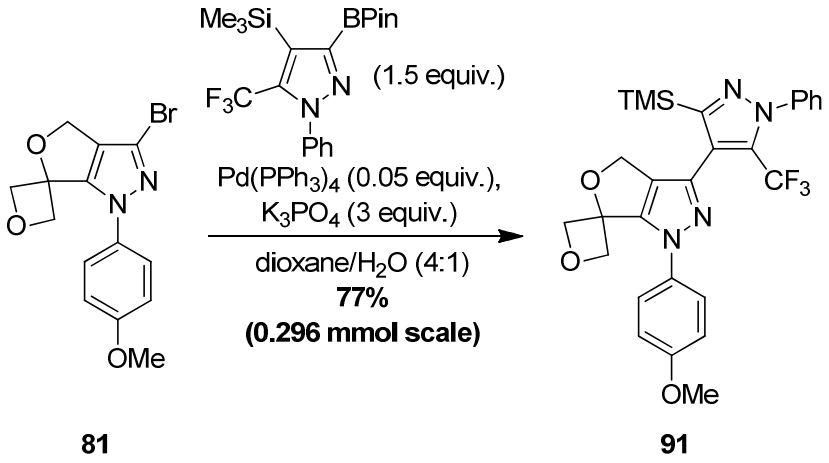


81 **90**

Using general procedure 7 with (**81**) (0.100 g, 0.296 mmol) and 4-tolylboronic acid (0.060 g, 0.444 mmol), mixture stirred for 22 hrs and purified by flash chromatography on silica gel (eluting with a gradient from 30 to 50% ethyl acetate in petroleum ether), 1-(4-methoxyphenyl)-3-(*p*-tolyl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**90**) was isolated as a beige solid (91 mg, 88%).

M.p. = 190 - 191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.57 (d, *J* = 8.0 Hz, 2H, Ar***H***), 7.24 (d, *J* = 8.0 Hz, 2H, Ar***H***), 7.06 (d, *J* = 9.0 Hz, 2H, Ar***H***), 5.13 (s, 2H, C***H*****$_2$**), 5.07 (d, *J* = 8.0 Hz, 2H, C***H*****$_2$**), 4.95 (d, *J* = 8.0 Hz, 2H, C***H*****$_2$**), 3.89 (s, 3H, C***H*****$_3$**), 2.40 (s, 3H, C***H*****$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 146.9, 143.6, 138.1, 132.8, 129.5, 129.3, 125.8, 125.0, 123.0, 114.7, 82.8, 81.0, 66.6, 55.6, 21.3; FTIR: 3029 (w), 2953 (w), 2901 (w), 2837 (w), 1519 (s), 1491 (m), 1443 (m), 1309 (w), 1254 (m), 1193 (w), 1099 (m), 1029 (m), 974 (s), 937 (m), 858 (m), 828 (s), 721 (m);); HRMS: m/z $[M+H]^+$ calcd. for $C_{21}H_{20}N_2O_3$: 349.1561, found: 349.1552.

Synthesis of 1-(4-methoxyphenyl)-3-(1-phenyl-5-(trifluoromethyl)-3-(trimethylsilyl)-1*H*-pyrazol-4-yl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (91)



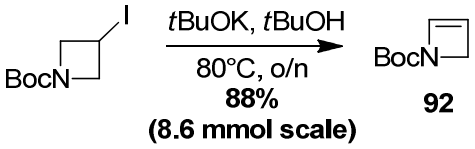
81 **91**

Using general procedure 7 with (**81**) (0.100 g, 0.296 mmol) and pyrazole boronic ester (0.182 g, 0.444 mmol), the mixture was stirred for 1 day and purified by flash chromatography on silica gel (eluting with 10% ethyl acetate in petroleum ether), 1-(4-methoxyphenyl)-3-(1-phenyl-5-(trifluoromethyl)-3-(trimethylsilyl)-1*H*-pyrazol-4-yl)-1,4-dihydrospiro[furo[3,4-c]pyrazole-6,3'-oxetane] (**91**) was isolated as a beige solid (124 mg, 77%).

M.p. = 128 - 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2H, Ar***H***), 7.51 (s, 5H, Ar***H***), 7.07 (d, *J* = 9.0 Hz, 2H, Ar***H***), 5.11 (d, *J* = 8.0 Hz, 2H, C***H*****$_2$**), 4.99 (d, *J* = 8.0 Hz, 2H, C***H*****$_2$**), 4.90 (s, 2H, C***H*****$_2$**), 3.90 (s, *J* = 7.0 Hz, 3H, C***H*****$_3$**), 0.27 (s, 9H, C***H*****$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 154.4, 146.2, 139.6, 135.6, 132.6, 130.1 (q, *J* = 36.4 Hz), 129.3, 129.0, 128.2, 126.0, 122.6, 122.2, 119.0 (q, *J* = 249.5), 114.7, 82.7, 81.2, 66.0, 55.6, -0.8.; FTIR: 3055 (w), 2952 (m), 2875 (m), 2839 (w), 1596 (m), 1520 (s), 1498 (s), 1456 (m), 1440 (m), 1386 (m), 1316 (m), 1249 (s), 1203 (s), 1160 (s), 1133 (s), 1093 (m), 1029 (s), 980 (s), 938 (m), 843 (s), 767 (m), 694 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{27}H_{27}F_3N_4O_3Si$: 541.1881, found: 541.1883.

6. Synthesis of boronic acid derivatives of azetidine and oxetane

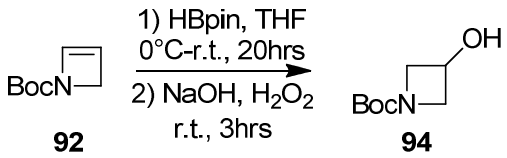
Synthesis of *tert*-butyl azete-1(2*H*)-carboxylate (92) [182]



A solution of potassium *tert*-butoxide (1.448 g, 12.9 mmol, 1.5 equiv.) in *tert*-butanol (20 mL) was added dropwise to 1-boc-3-iodoazetidine (1.5 mL, 8.6 mmol, 1 equiv.) under argon. The resulting mixture was heated at 80 °C o/n and was then allowed to cool at r.t.. Water (30 mL) was then added and the solution was extracted with petroleum ether (3x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford *tert*-butyl azete-1(2*H*)-carboxylate (**92**) as a clear oil (1.186 g, 88%). The compound was characterised by ^{1}H, ^{13}C NMR and FTIR only.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 – 6.52 (s, 1H, C***H***), 5.53 – 5.47 (m, 1H, C***H***), 4.40 – 4.34 (m, 2H, C$\boldsymbol{H}_2$), 1.46 (s, 9H, C$\boldsymbol{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 138.7, 111.8, 80.2, 58.4, 28.4; FTIR: 2976 (s), 1703 (s), 1403 (s), 1153 (s), 956 (m), 860 (m). Analysis are in accordance with those reported in the literature.

Synthesis of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (94) [183]

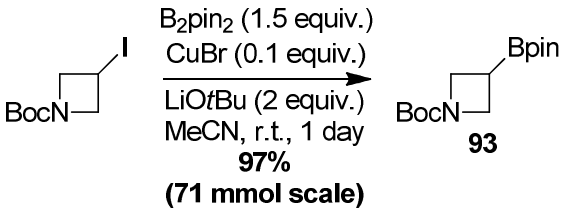


Borane tetrahydrofuran complex solution (1 M in THF, 1.8 mL, 1.8 mmol, 2 equiv.) was added dropwise to a solution of *tert*-butyl azete-1(2*H*)-carboxylate (**92**) (0.140 g, 0.9 mmol, 1 equiv.) in THF (2 mL) at 0 °C under argon. The reaction was then allowed to warm to r.t. and was left to stir o/n before being cooled at 0 °C. An aqueous solution of NaOH (1 M, 0.9 mL, 0.9 mmol, 1 equiv.) and hydrogen peroxide

(1 M, 0.9 mL, 0.9 mmol, 1 equiv.) were then added sequentially. The resulting mixture was then warmed to r.t. and stirred for 3 hrs. A saturated solution of NH_4Cl (5 mL) was then added and the solution was extracted with ethyl acetate (3x 5 mL). The combined organic layer were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford an orange residue which contained *tert*-butyl 3-hydroxyazetidine-1-carboxylate (**94**) and *N*-Boc-azetidine. This compound was tentatively assigned by ^{1}H NMR spectroscopy only.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 – 4.58 (m, 1H, C***H***), 4.19 (dd, *J* = 9.5, 7.0 Hz, 2H, C***H***$_2$), 3.88 – 3.80 (m, 3H, C***H***$_2$ and O***H***), 1.46 (s, 9H, C***H***$_3$). Analysis are in accordance with those reported in the literature.

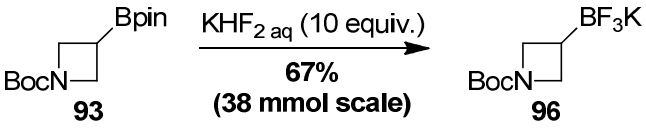
Synthesis of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (93)



CuBr (1.02 g, 7.1 mmol) and LiO^tBu (11.37 g, 142 mmol) were added to a solution of 1-boc-3-iodoazetidine (12.3 mL, 71 mmol) in MeCN (300 mL). The resulting solution was then cooled to 0 °C using an ice bath and B_2pin_2 (27.05 g, 106.5 mmol) was then added portion wise to the mixture at 0 °C. The resulting mixture was allowed to warm to r.t. and stirred for 48 hrs. The reaction was monitored via TLC analysis over the 48 hrs period, whereupon two additional portions of CuBr (1.02 g, 7.1 mmol) were added at time intervals of 4 and 22 hrs. In order to drive the reaction to completion CuBr (1.02 g, 7.1 mmol) was added along with B_2Pin_2 (1.80 g, 7.1 mmol) after 24 hrs. The solvent was then removed *in vacuo* and the crude mixture was extracted with petroleum ether (3x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (**93**) as a clear yellow oil (19.5 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (dd, *J* = 10.0, 8.0 Hz, 2H, C***H***$_2$), 3.91 (dd, *J* = 7.5, 7.5 Hz, 2H, C***H***$_2$), 2.16 – 2.05 (m, 1H, C***H***), 1.43 (s, 9H, C***H***$_3$), 1.26 (s, 12H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 83.9, 79.2, 50.6 (br), 28.5, 24.9; ^{11}B NMR (160.5 MHz, $CDCl_3$) δ 33.2 (s, br); FTIR: ν_{max}/ cm^{-1} (thin film, NaCl plates) 3373 (br), 2980 (s), 2937 (s), 2890 (m), 1679 (s), 1525 (m), 1478 (s), 1451 (m), 1371 (s), 1331 (s), 1253 (w), 1217 (m), 1150 (s), 978 (s) 851 (s), 774 (w), 677 (m); HRMS: m/z $[M+H]^+$ calcd. for $C_{14}H_{27}NO_4{}^{11}B$: 284.2033, found: 284.2037.

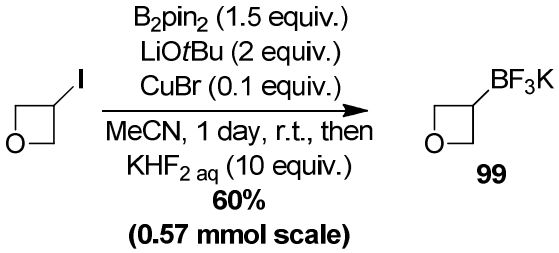
Synthesis of potassium (1-(*tert*-butoxycarbonyl)azetidin-3-yl)trifluoroborate (96) [148]



An aqueous saturated solution of KHF_2 (2.13 g, 27. 3 mmol) was added slowly to a solution of **93** (11 g, 38 mmol) in H_2O (50 mL) under stirring. The resulting mixture was then stirred at r.t. for 24 hrs before the solvent was removed *in vacuo* and the residue was dried under high vacuum for an additional 3 hrs. The resulting crude solid was extracted three times by stirring for 15 min in acetone (50 mL) followed by filtration to remove any undissolved solids. The filtrate was concentrated *in vacuo* and the product was purified by trituration with minimal amounts of CH_2Cl_2 (x 2) and Et_2O (x 1). The resulting solid was then collected via filtration, washed with Et_2O (50 mL), and dried under vacuum to afford potassium (1-(*tert*-butoxycarbonyl)azetidin-3-yl)trifluoroborate (**96**) as a white crystalline solid (6.81 g, 67%).

M.p. = 60 - 61 °C ; ^{1}H NMR (400 MHz, DMSO) δ 3.69 – 3.46 (m, 4H, C***H***$_2$), 3.35 (s, 1H, C***H***), 1.39 – 1.30 (m, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, DMSO) δ 155.6, 77.2, 51.9, 50.7, 28.3; ^{19}F NMR (235.1 MHz, DMSO) δ 145.1; ^{11}B NMR (160.5 MHz, DMSO) δ 4.04 (s, br); FTIR: ν_{max}/ cm^{-1} (thin film, NaCl plates) 3594 (br), 2977 (s), 2883 (s), 1673 (s), 1478 (m), 1428 (s), 1367 (m), 1304 (m), 1253 (w), 1146 (s), 1056 (m), 958 (s), 767 (w); HRMS: m/z $[M-K]^-$ calcd. for $C_8H_{14}NO_2{}^{11}BF_3$: 224.1070, found: 224.1069. Analysis are in accordance with those reported in the literature.

Synthesis of potassium trifluoro(oxetan-3-yl)borate (99)[148]

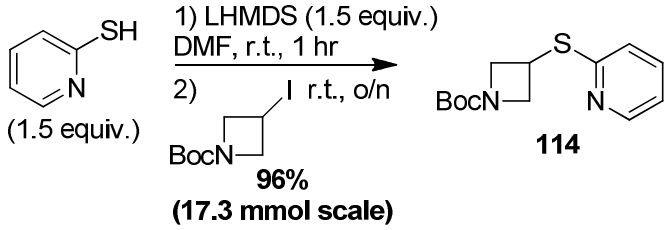


CuBr (0.01 g, 0.06 mmol) and LiO^tBu (0.09 g, 1.136 mmol) were added to a solution of 3-iodo-oxetane (0.05 mL, 0.57 mmol) in MeCN (1 mL) under stirring. The resulting solution was then cooled to 0 °C using an ice bath and B_2pin_2 (0.22 g, 0.85 mmol) was added portion wise. The reaction mixture was allowed to warm to room temperature and stirred for 24 hrs. A second additional portion of CuBr (0.01 g, 0.06 mmol) was added after a time interval of 4 hrs. The solvent was then removed *in vacuo*. The residue was diluted with H_2O (1 mL) and an aqueous saturated solution of KHF_2 (0.44 g, 5.7 mmol) was added. The resulting mixture was stirred at r.t. for 24 hrs and the solvent was then removed *in vacuo* and the residue was dried under high vacuum for an additional 3 hrs. The resulting solid was extracted three times with MeCN (10mL) followed by filtration to remove any undissolved solids. The filtrate was concentrated *in vacuo* and the product was purified by trituration with a minimal amount of CH_2Cl_2. The resulting solid was then dried under vacuum to afford potassium trifluoro(oxetan-3-yl)borate (**99**) as a white crystalline solid (0.06 g, 60%).

M.p. = 212 -213 °C (lit. 211 – 213 ºC); ^{1}H NMR (250 MHz, DMSO) δ 4.53 – 4.32 (m, 4H, C***H***$_2$), 1.92 (s, 1H, C***H***); ^{13}C NMR (101 MHz, DMSO) δ 75.1; ^{19}F NMR (235.1 MHz, DMSO) δ 143.9; ^{11}B NMR (160.5 MHz, DMSO) δ 3.94 (q, *J* = 116.0, 57.5 Hz).; FTIR: ν_{max}/ cm^{-1} (thin film, NaCl plates) 3433 (br), 2889 (w), 1642 (s), 1309 (w), 1101 (w); m/z [M-K]$^-$ 125.0 (85%).

7. Synthesis of sodium sulfinate salt

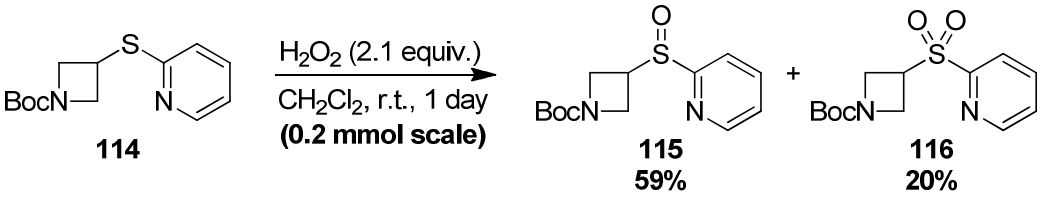
Synthesis of *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (114)



LHMDS (1 M in THF, 25.9 mL, 25.9 mmol) was added to pyridine-2-thiol (1.2 g, 17.27 mmol) in DMF (45 mL) at room temperature and the resulting solution was stirred at r.t. for 1 hr. *tert*-Butyl 3-iodoazetidine-1-carboxylate (3.0 mL, 17.27 mmol) was then added and the mixture was stirred at r.t. overnight. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the solution was extracted with CH_2Cl_2 (3x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (**114**) as a white solid (4.42 g, 96%).

Mp = 48 – 49°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H, Ar***H***), 7.51 – 7.42 (m, 1H, Ar***H***), 7.11 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 6.97 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Ar***H***), 4.46 – 4.36 (m, 3H, C***H***$_2$ andC***H***), 3.92 – 3.82 (m, 2H, C***H***$_2$), 1.42 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 156.1, 149.8, 136.2, 122.0, 119.8, 79.7, 56.3 (br), 31.4, 28.5; FTIR: 3512 (br), 3391 (w), 3047 (m), 2975 (s), 2882 (s), 1707 (s), 1578 (s), 1556 (s), 1477 (s), 1452 (s), 1391 (s), 1302 (m), 1280 (m), 1248 (s), 1130 (s), 1044 (m), 986 (s), 900 (m), 857 (s), 761 (s), 725 (s), 621 (m); HRMS: m/z [M+H]+ calcd. for $C_{13}H_{19}N_2O_2S$: 267.1177, found: 267.1167.

Synthesis of *tert*-butyl 3-(pyridin-2-ylsulfinyl)azetidine-1-carboxylate (115) [152c]

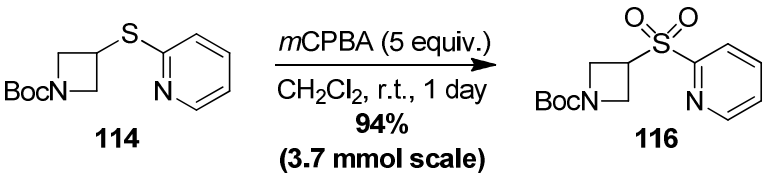


Hydrogen peroxide (30% w/v in H_2O, 0.5 mL, 2.1 equiv.) was added to a solution of 114 (53.3 mg, 0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL). The resulting mixture was then stirred at room temperature for 1 day before being concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in dichloromethane to afford *tert*-butyl 3-(pyridin-2-ylsulfinyl)azetidine-1-carboxylate (**115**) a white solid (33.2 mg, 59%) and *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (**116**) as a beige solid (11.7 mg, 20%).

115: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.68 (m, 1H, Ar***H***), 8.10 (d, J = 8.0 Hz, 1H, Ar***H***), 7.99 (td, J = 8.0, 1.5 Hz, 1H, Ar***H***), 7.58 (ddd, J = 7.5, 4.5, 1.1 Hz, 1H, Ar***H***), 4.50 – 4.42 (m, J = 8.5, 5.5 Hz, 1H, C***H***), 4.37 (s, 2H, C***H***$_2$), 4.17 (t, J = 9.0 Hz, 2H, C***H***$_2$), 1.43 (s, 10H); HRMS: m/z $[M+H]^+$ calcd. for $C_{13}H_{19}N_2O_3S$: 283.1116, found: 283.1125.

116: Mp = 68 – 69 °C (lit. 74-78 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H, Ar***H***), 8.07 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 7.97 (ddd, *J* = 8.0, 6.0, 1.5 Hz, 1H, Ar***H***), 7.56 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H, Ar***H***), 4.48 – 4.26 (m, 3H, C***H***$_2$ and C***H***), 4.15 (t, *J* = 9.0 Hz, 2H, C***H***$_2$), 1.40 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.8, 150.4, 138.5, 127.9, 122.4, 80.5, 49.5 (br), 48.2, 28.3; FTIR: 2982 (m), 2889 (w), 1703 (s), 1581 (m), 1456 (m), 1431 (m), 1395 (s), 1320 (s), 1259 (m), 1166 (s), 1116 (m), 1087 (m), 990 (m), 897 (m), 779 (m), 746 (m); HRMS: m/z [M+H]+ calcd. for $C_{13}H_{19}N_2O_4S$: 299.1076, found: 299.1066.

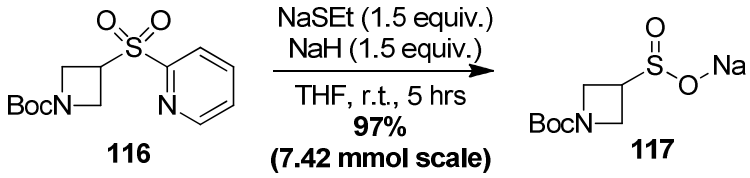
Synthesis of *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (116)



*m*CPBA (3.223 g, 18.7 mmol) was added to *tert*-butyl 3-(pyridin-2-ylthio)azetidine-1-carboxylate (**114**) (0.995 g, 3.7 mmol) in CH_2Cl_2 (20 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. A saturated aqueous solution of sodium bisulfite (20 mL) was then added and the solution was extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford the crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in dichloromethane affording *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (**116**) as a beige solid (1.05 g, 94%).

Analysis described above.

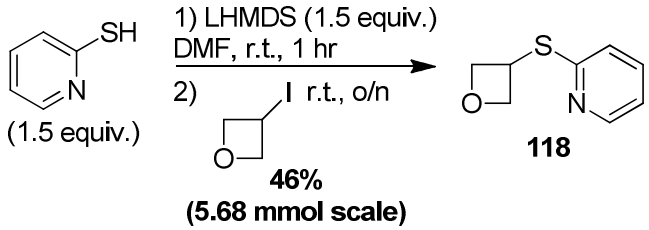
Synthesis of sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (117) [152c]



Sodium hydride (0.445 g, 11.13 mmol) was added to *tert*-butyl 3-(pyridin-2-ylsulfonyl)azetidine-1-carboxylate (**116**) (2.214 g, 7.42 mmol) and sodium ethanethiolate (0.936 g, 11.13 mmol) in THF (45 mL) at room temperature. The resulting solution was stirred at r.t. for 5 hrs. Water (100 mL) were then added. Volatiles were then removed *in vacuo* and the solution was washed with CH_2Cl_2 (3x 40 mL). The aqueous layer was concentrated to afford the crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 20% to 50% methanol in dichloromethane affording sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**117**) as a beige solid (1.75 g, 97%).

Mp = 48 – 50 °C ; ^{1}H NMR (400 MHz, D_2O) δ 4.13 – 3.89 (m, 4H, C***H***$_2$), 3.19 – 3.06 (m, 1H, C***H***), 1.39 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, D_2O) δ 157.9, 81.9, 52.3, 48.0 (br), 27.6; FTIR: 3394 (s), 2979 (w), 2875 (w), 1714 (s), 1674 (s), 1477 (w), 1424 (s), 1391 (s), 1370 (m), 1248 (w), 1151 (m), 1055 (m), 1019 (s), 976 (s), 771 (w); HRMS: m/z [M-Na]- calcd. for $C_8H_{14}NO_4S$: 220.0644, found: 220.0637. Analysis are in accordance with those reported in the literature.

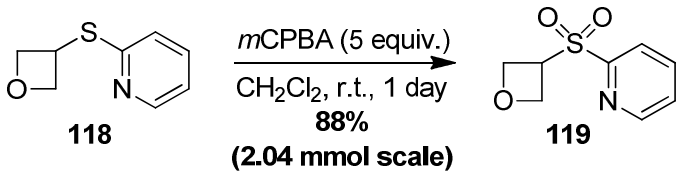
Synthesis of 2-(oxetan-3-ylthio)pyridine (118)



LHMDS (1 M in THF, 8.52 mL, 8.52 mmol) was added to pyridine-2-thiol (0.947 g, 8.52 mmol) in DMF (10 mL) at room temperature and the resulting solution was stirred at r.t. for 1 hr. 3-iodooxetane (0.5 mL, 5.68 mmol) was then added and the mixture was stirred at r.t. overnight. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the solution was extracted with CH_2Cl_2 (3x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylthio)pyridine (**118**) as a yellow oil (0.44 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Ar***H***), 7.48 – 7.41 (m, 1H, Ar***H***), 7.09 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 6.94 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Ar***H***), 5.10 (dd, *J* = 7.5, 6.5 Hz, 2H, C***H***$_2$), 4.92 – 4.83 (m, 1H, C***H***), 4.63 (t, *J* = 6.5 Hz, 2H, C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 149.6, 136.1, 121.9, 119.7, 78.2, 36.8; FTIR: 3487 (br), 3047 (m), 2950 (s), 2871 (s), 1664 (w), 1578 (s), 1556 (s), 1456 (s), 1416 (s), 1280 (m), 1255 (m), 1126 (s), 1087 (w), 1044 (m), 976 (s), 904 (s), 822 (s), 761 (s), 725 (s), 621 (w); HRMS: m/z [M+H]+ calcd. for $C_8H_{10}NOS$: 168.0491, found: 168.0483.

Synthesis of 2-(oxetan-3-ylsulfonyl)pyridine (119)

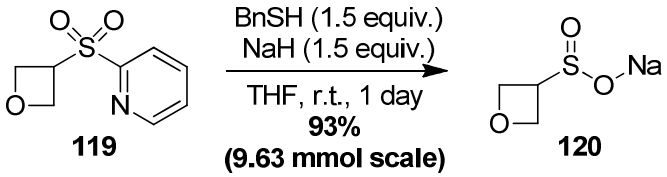


118 119

*m*CPBA (1.74 g, 10.2 mmol) was added to 2-(oxetan-3-ylthio)pyridine (**118**) (0.341 g, 2.04 mmol) in CH_2Cl_2 (12 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. A saturated aqueous solution of sodium bisulfite (10 mL) was then added and the solution was extracted with CH_2Cl_2 (3x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 30% ethyl acetate in dichloromethane affording 2-(oxetan-3-ylsulfonyl)pyridine (**119**) as a colorless oil (0.356 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H, Ar***H***), 8.09 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 7.99 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.60 – 7.54 (m, 1H, Ar***H***), 5.13 – 5.07 (m, 2H, C***H***$_2$), 4.93 – 4.88 (m, 3H, C***H***$_2$ and C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 150.3, 138.5, 127.9, 122.2, 70.3, 54.3; FTIR: 3616 (br), 3061 (w), 2961 (m), 2889 (m), 1721 (w), 1578 (m), 1456 (m), 1424 (m), 1313 (s), 1266 (m), 1162 (s), 1108 (s), 1083 (m), 994 (s), 904 (s), 779 (m), 746 (s), 664 (m); HRMS: m/z [M+H]+ calcd. for $C_8H_{10}NO_3S$: 200.0385, found: 200.0381.

Synthesis of sodium oxetane-3-sulfinate (120)



119 120

Sodium hydride (0.578 g, 14.44 mmol) was added to 2-(oxetan-3-ylsulfonyl)pyridine (**119**) (1.918 g, 9.63 mmol) and benzyl mercaptan (1.7 mL, 14.44 mmol) in THF (80 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. Water (100 mL) was then added. Volatiles were removed *in vacuo* and the solution was washed with CH_2Cl_2 (3x 40 mL). The aqueous layer was concentrated *in vacuo* to

afford the crude product. The residue was purified via flash chromatography on silica gel eluting with a gradient from 20% to 50% methanol in dichloromethane affording sodium oxetane-3-sulfinate (**120**) as a beige solid (1.292 g, 93%).

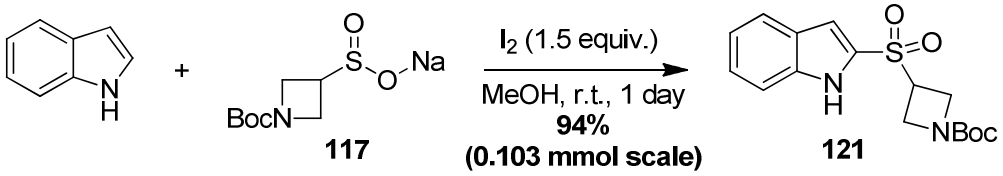
Mp = 223 - 224 ^{o}C ; ^{1}H NMR (400 MHz, MeOD) δ 4.82 – 4.77 (m, 4H, C***H***$_2$), 3.49 – 3.37 (m, 1H, C***H***); ^{13}C NMR (101 MHz, MeOD) δ 72.1, 61.1; FTIR: 2962 (w), 2889 (w), 1650 (s), 1028 (s), 964 (s), 904 (m), 775 (w); HRMS: m/z [M+Na]+ calcd. for $C_3H_5O_3SNa_2$: 166.9755, found: 166.9751.

8. Coupling of sodium sulfinate salt to the position 2 of indole

General procedure 8: sodium sulfinate of azetidine coupling to position 2 of indole

Iodine (39 mg, 0.154 mmol, 1.5 equiv.) was added to the desired indole (0.103 mmol, 1 equiv.)) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**117**) (75 mg, 0.309 mmol, 3 equiv.) in MeOH (0.5 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. All volatiles were removed *in vacuo* and the residue was purified via flash chromatography on silica gel to provide the title product.

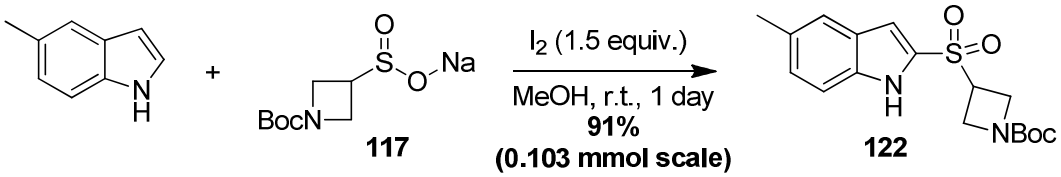
Synthesis of *tert*-butyl 3-((1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (121)



Using general procedure 8 with indole (12 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**121**) as a grey-brown solid (33 mg, 94%).

Mp = 138 - 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H, N***H***), 7.73 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.50 (d, *J* = 8.5 Hz, 1H, Ar***H***), 7.44 – 7.38 (m, 1H, Ar***H***), 7.25 – 7.20 (m, 2H, Ar***H***), 4.33 (dd, *J* = 9.5, 4.5 Hz, 2H, C***H***$_2$), 4.17 – 4.04 (m, 3H, C***H***$_2$ and C***H***), 1.40 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 137.5, 129.6, 127.2, 126.8, 123.0, 122.1, 112.6, 110.8, 80.9, 52.3, 49.9, 28.4; FTIR: 3318 (br), 2975 (w), 2928 (w), 1680 (s), 1414 (m), 1328 (m), 1136 (s), 900 (w), 741 (m), 702 (m), 630 (m); HRMS: m/z [M+Na]- calcd. for $C_{16}H_{20}N_2O_4SNa$: 359.1041, found: 359.1046.

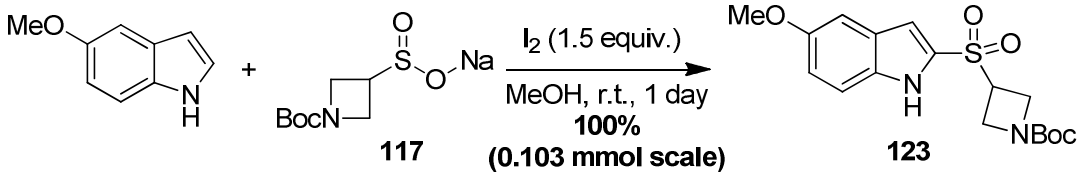
Synthesis of *tert*-butyl 3-((5-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (122)



Using general procedure 8 with 5-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**122**) as a beige solid (33 mg, 91%).

Mp = 143 - 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H, N***H***), 7.47 (s, 1H, Ar***H***), 7.38 (d, *J* = 8.5 Hz, 1H, Ar***H***), 7.22 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar***H***), 7.15 (d, *J* = 1.5 Hz, 1H, Ar***H***), 4.37 – 4.28 (m, 2H, C***H***$_2$), 4.16 – 4.02 (m, 3H, C***H***$_2$ and C***H***), 2.44 (s, 3H, C***H***$_3$), 1.39 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 136.2, 131.4, 129.2, 128.7, 127.3, 122.0, 112.4, 110.3, 80.8, 52.2, 49.9, 28.3, 21.5; FTIR: 3323 (br), 2976 (s), 2925 (s), 2891 (m), 1683 (s), 1516 (s), 1405 (s), 1315 (s), 1255 (m), 1135 (s), 1092 (s), 951 (m), 904 (s), 818 (m), 724 (s), 634 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1183.

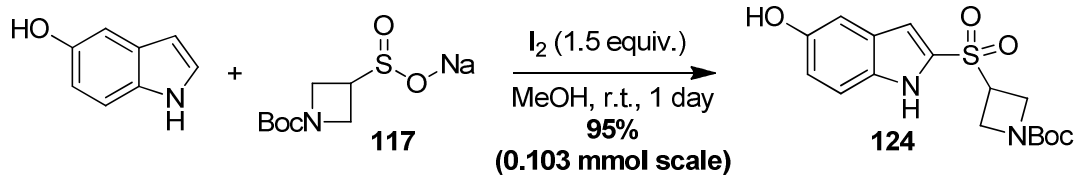
Synthesis of *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (123)



Using general procedure 8 with 5-methoxyindole (15 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**123**) as a grey solid (38 mg, 100%).

Mp = 116 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H, N***H***), 7.38 (d, *J* = 9.5 Hz, 1H, Ar***H***), 7.14 (d, *J* = 1.5 Hz, 1H, Ar***H***), 7.07 – 7.02 (m, 2H, Ar***H***), 4.32 (dd, *J* = 9.0, 4.0 Hz, 2H, C***H***$_2$), 4.16 – 4.05 (m, 3H, C***H***$_2$ and C***H***), 3.83 (s, 3H, C***H***$_3$), 1.38 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 155.4, 133.2, 129.4, 127.4, 118.6, 113.7, 110.2, 102.4, 80.9, 55.8, 52.2, 49.9, 28.3; FTIR: 2979 (w), 2889 (w), 2829 (w), 1676 (s), 1521 (m), 1401 (m), 1324 (m), 1161 (m), 1136 (m), 1028 (w), 955 (m), 835 (m), 694 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1130.

Synthesis of *tert*-butyl 3-((5-hydroxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (124)

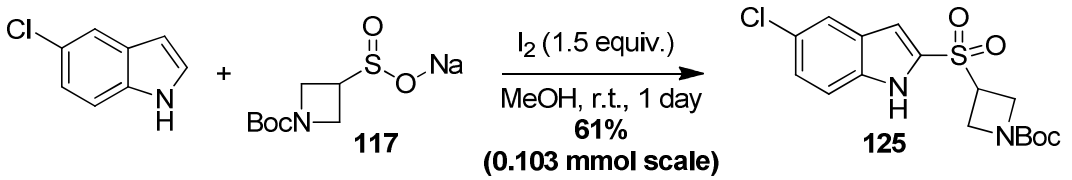


Using general procedure 8 with 5-hydroxyindole (13.7 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-hydroxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**124**) as a brown solid (34.5 mg, 95%).

M.p. = 158 - 160 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.34 (d, *J* = 9.0 Hz, 1H, Ar***H***), 7.06 – 7.01 (m, 2H, Ar***H***), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar***H***), 4.28 – 4.07 (m, 6H,

C***H***$_2$, C***H*** and O***H***), 1.36 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, MeOD) δ 157.6, 153.2, 134.7, 130.9, 128.8, 118.5, 114.3, 110.2, 106.0, 81.8, 53.1, 50.9 (d, *J* = 82.5 Hz), 28.4; FTIR: 3412 (br), 2982 (w), 1651 (s), 1517 (m), 1414 (m), 1318 (m), 1173 (m), 1132 (m), 1091 (w), 953 (w), 854 (w); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{20}N_2O_5SNa$: 375.0991, found: 375.0988.

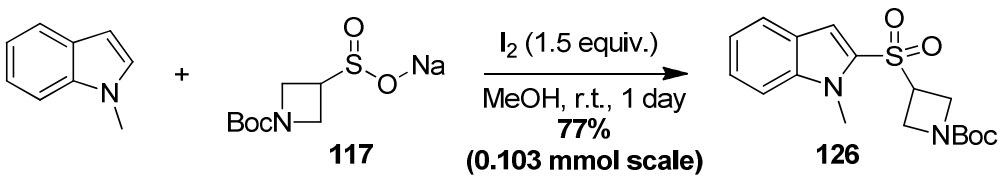
Synthesis of *tert*-butyl 3-((5-chloro-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (125)



Using general procedure 8 with 5-chloroindole (15.6 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-chloro-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**125**) as a brown gum (23.1 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H, N***H***), 7.70 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.43 (d, J = 9.0 Hz, 1H, Ar***H***), 7.36 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar***H***), 7.17 (dd, *J* = 2.0, 0.5 Hz, 1H, Ar***H***), 4.32 (dd, *J* = 9.5, 5.0 Hz, 2H, C***H***$_2$), 4.18 – 4.09 (m, 3H, C***H***$_2$ and C***H***), 1.40 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 135.8, 131.0, 128.0, 127.9, 127.5, 122.2, 113.8, 109.9, 81.0, 52.4, 49.9, 28.4; FTIR: 2975 (w), 2930 (w), 1679 (s), 1407 (s), 1325 (s), 1139 (s), 916 (w), 809 (m), 699 (m); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{19}N_2O_4S^{35}ClNa$: 393.0652, found: 393.0638.

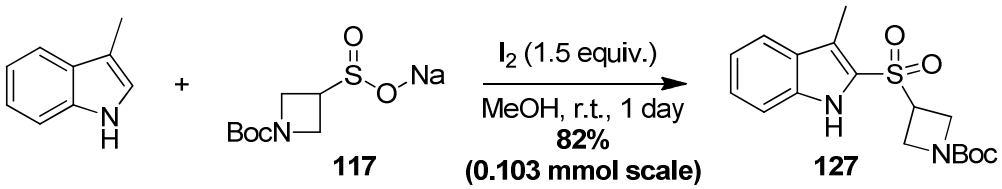
Synthesis of *tert*-butyl 3-((1-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (126)



Using general procedure 8 with 1-methylindole (13 µL), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**126**) as a pale brown solid (28 mg, 77%).

Mp = 104 - 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.48 – 7.39 (m, 2H, Ar***H***), 7.32 (s, 1H, Ar***H***), 7.24 (ddd, *J* = 8.0, 6.5, 1.0 Hz, 1H, Ar***H***), 4.31 (dd, *J* = 9.0, 5.0 Hz, 2H, C***H***$_2$), 4.13 – 3.99 (m, 6H, C***H***$_3$, C***H***$_2$ and C***H***), 1.42 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 140.1, 130.6, 126.6, 125.3, 123.2, 121.7, 112.9, 110.7, 80.7, 52.1, 49.8, 31.5, 28.4; FTIR: 2972 (w), 2925 (w), 1704 (s), 1469 (m), 1396 (s), 1323 (s), 1148 (s), 1071 (w), 899 (w), 805 (w), 737 (m), 685 (w); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1186.

Synthesis of *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (127)

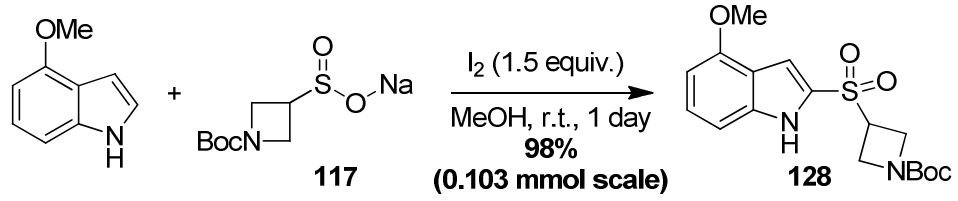


117 127

Using general procedure 8 with 3-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**127**) as an orange oil (29.5 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, N***H***), 7.66 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.45 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.41 – 7.35 (m, 1H, Ar***H***), 7.21 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar***H***), 4.39 – 4.26 (m, 2H, C***H***$_2$), 4.18 – 4.02 (m, 3H, C***H***$_2$ and C***H***), 2.61 (s, 3H, C***H***$_3$), 1.39 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 136.6, 128.2, 126.8, 125.2, 121.1, 121.0, 120.8, 112.6, 80.8, 52.4, 49.7, 28.3, 9.3; FTIR: 3335 (br), 2983 (w), 2921 (w), 1689 (s), 1406 (s), 1320 (s), 1208 (w), 1144 (s), 904 (w), 801 (w), 750 (m), 694 (m); HRMS: m/z [M+Na]- calcd. for $C_{17}H_{22}N_2O_4SNa$: 373.1198, found: 373.1184.

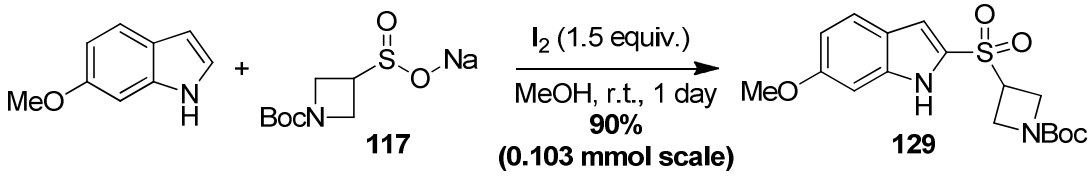
Synthesis of *tert*-butyl 3-((4-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (128)



Using general procedure 8 with 4-methoxyindole (15 mg), the product was purified eluting with a gradient from 30% to 40% ethyl acetate in petroleum ether affording *tert*-butyl 3-((4-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**128**) as a brown foam (37.0 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H, N***H***), 7.36 – 7.32 (m, 1H, Ar***H***), 7.31 – 7.29 (m, 1H, Ar***H***), 7.06 (d, *J* = 8.5 Hz, 1H, Ar***H***), 6.56 (d, *J* = 8.0 Hz, 1H, Ar***H***), 4.35 – 4.26 (m, 2H, C***H***$_2$), 4.15 – 4.05 (m, 3H, C***H***$_2$ and C***H***), 3.95 (s, 3H, C***H***$_3$), 1.38 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 154.7, 138.9, 128.0 (2 carbons), 118.9, 108.6, 105.3, 100.7, 80.8, 55.6, 52.3, 49.9, 28.4; FTIR: 3241 (br), 2978 (m), 2934 (m), 2844 (w), 1688 (s), 1622 (m), 1588 (m), 1518 (m), 1411 (s), 1368 (s), 1331 (s), 1261 (s), 1137 (s), 1117 (s), 977 (w), 950 (w), 777 (m), 736 (s); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1147.

Synthesis of *tert*-butyl 3-((6-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (129)

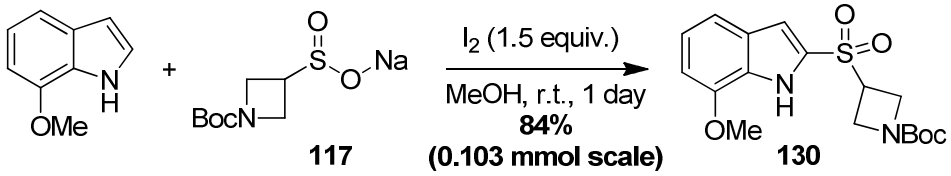


Using general procedure 8 with 6-methoxyindole (15 mg), the product was purified eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *tert*-butyl 3-((6-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**129**) as a grey solid (34 mg, 90%).

Mp = 178 - 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H, N***H***), 7.55 (d, *J* = 9.0 Hz, 1H, Ar***H***), 7.17 (d, *J* = 1.5 Hz, 1H, Ar***H***), 6.91 – 6.84 (m, 2H, Ar***H***), 4.33 (dd, *J*

= 9.5, 4.5 Hz, 2H, C***H***$_2$), 4.16 – 4.03 (m, 3H, C***H***$_2$ and C***H***), 3.84 (s, 3H, C***H***$_3$), 1.39 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.0, 139.2, 127.5, 123.6, 121.2, 113.9, 111.4, 94.0, 80.8, 55.6, 52.3, 49.9, 28.3; FTIR: 2985 (w), 2933 (w), 1674 (s), 1632 (s), 1507 (m), 1409 (m), 1310 (m), 1233 (m), 1139 (s), 959 (w), 899 (w), 826 (m), 702 (m); HRMS: m/z [M+H]- calcd. for $C_{17}H_{23}N_2O_5S$: 367.1328, found: 367.1330.

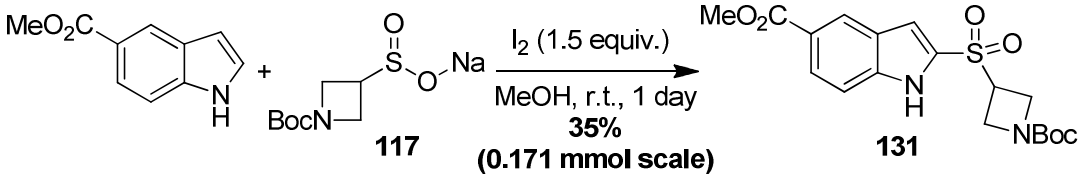
Synthesis of *tert*-butyl 3-((7-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (130)



Using general procedure 8 with 7-methoxyindole (13.5 µL), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((7-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**130**) as a beige solid (31.7 mg, 84%).

M.p. = 128 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H, N***H***), 7.29 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.20 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.14 (t, *J* = 8.0 Hz, 1H, Ar***H***), 6.79 (d, *J* = 8.0 Hz, 1H, Ar***H***), 4.32 (dd, *J* = 9.0, 4.5 Hz, 2H, C***H***$_2$), 4.15 – 4.08 (m, 3H, C***H***$_2$ and C***H***), 3.98 (s, 3H, C***H***$_3$), 1.40 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 146.8, 129.3, 128.9, 128.3, 122.6, 114.9, 110.9, 105.1, 80.8, 55.7, 52.2, 49.8, 28.3; FTIR: 3309 (br), 2978 (m), 2934 (m), 2889 (w), 1696 (s), 1583 (m), 1524 (m), 1411 (s), 1321 (s), 1256 (s), 1139 (s), 1108 (s), 974 (m), 905 (m), 771 (m), 726 (s), 695 (m), 606 (m); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_5SNa$: 389.1147, found: 389.1130.

Synthesis of methyl 2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)sulfonyl)-1*H*-indole-5-carboxylate (131)



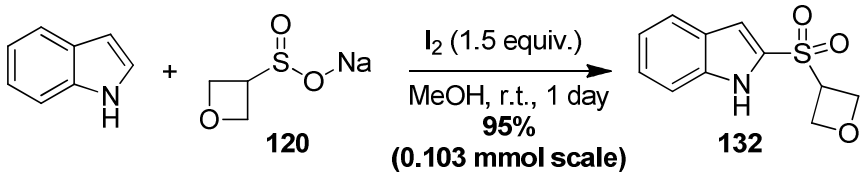
Using general procedure 8 with methyl 1*H*-indole-5-carboxylate (30 mg, 0.171 mmol) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (125 mg, 0.514 mmol), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording methyl 2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)sulfonyl)-1*H*-indole-5-carboxylate (**131**) as a yellow solid (23.6 mg, 35%).

M.p. = 108 - 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, N***H***), 8.50 (s, 1H, Ar***H***), 8.08 (dd, *J* = 9.0, 1.5 Hz, 1H, Ar***H***), 7.52 (d, *J* = 9.0 Hz, 1H, Ar***H***), 7.32 (dd, *J* = 2.0, 0.5 Hz, 1H, Ar***H***), 4.34 (dd, *J* = 9.5, 4.5 Hz, 2H, C***H***$_2$), 4.18 – 4.10 (m, 3H, C***H***$_2$ and C***H***), 3.95 (s, 3H, C***H***$_3$), 1.40 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 156.0, 139.8, 131.3, 127.5, 126.6, 126.1, 124.3, 112.6, 111.8, 81.0, 52.3, 49.8, 28.5, 28.4.; FTIR: 3257 (br), 2975 (w), 2930 (w), 1706 (s), 1617 (m), 1404 (m), 1311 (s), 1256 (m), 1139 (s), 905 (w), 768 (w); HRMS: m/z [M+Na]+ calcd. for $C_{18}H_{22}N_2O_6SNa$: 417.1096, found: 417.1090.

<u>General procedure 9:</u> sodium sulfinate of oxetane coupling to position 2 of indole

Iodine (39 mg, 0.154 mmol, 1.5 equiv.) was added to the desired indole (0.103 mmol, 1 equiv.)) and sodium oxetane-3-sulfinate (**120**) (75 mg, 0.309 mmol, 3 equiv.) in MeOH (0.5 mL) at room temperature. The resulting solution was stirred at r.t. for 1 day. Volatiles were removed *in vacuo* and the residue was purified via flash chromatography on florisil to provide the title product.

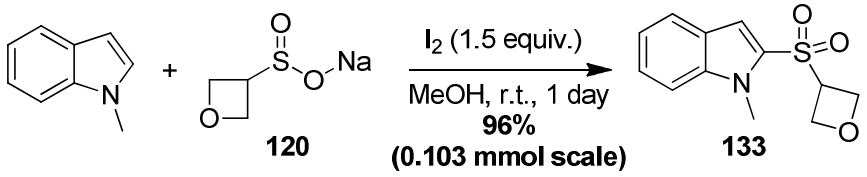
Synthesis of 2-(oxetan-3-ylsulfonyl)-1*H*-indole (132)



Using general procedure 9 with indole (12 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylsulfonyl)-1*H*-indole (**132**) as a brown solid (23.1 mg, 95%).

M.p. = 136 - 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H, N***H***), 7.73 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.49 (d, *J* = 8.5 Hz, 1H, Ar***H***), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar***H***), 7.24 (dd, *J* = 5.0, 5.0 Hz, 2H, Ar***H***), 5.04 – 4.98 (m, 2H, C***H***$_2$), 4.85 (t, *J* = 8.0 Hz, 2H, C***H***$_2$), 4.58 (tt, *J* = 8.0, 6.0 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 129.7, 127.2, 126.8, 123.0, 122.1, 112.6, 110.7, 70.4, 58.2; FTIR: 3435 (br), 2953 (w), 2933 (w), 2853 (w), 1623 (w), 1320 (m), 1136 (s), 980 (w), 906 (w), 746 (m), 693 (m); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{12}NO_3S$: 238.0538, found: 238.0529.

Synthesis of 1-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (133)

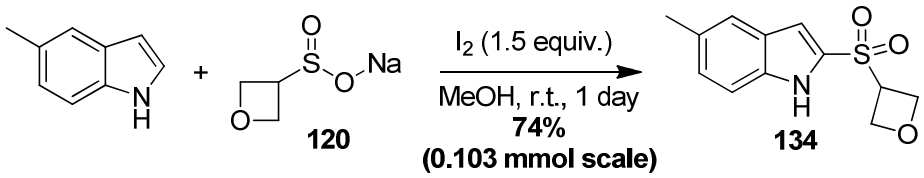


Using general procedure 9 with *N*-methyl indole (13 µL), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 1-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**133**) as a brown solid (24.8 mg, 96%).

M.p. = 100 - 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.49 – 7.40 (m, 2H, Ar***H***), 7.31 (s, 1H, Ar***H***), 7.26 – 7.20 (m, 1H, Ar***H***), 5.04 – 4.97 (m, 2H, C***H***$_2$), 4.82 (t, *J* = 8.0 Hz, 2H, C***H***$_2$), 4.55 (tt, *J* = 8.0, 6.0 Hz, 1H, C***H***), 4.01 (s, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 130.8, 126.5, 125.3, 123.1, 121.7, 112.7, 110.7, 70.3, 57.9, 31.5; FTIR:2953 (m), 2923 (m), 2890 (m), 2850 (w), 1613 (w), 1506 (m), 1466 (s), 1323 (s), 1146 (s), 986 (m), 910 (s), 806 (s), 750 (s),

676 (s), 626 (s); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_3S$: 252.0694, found: 252.0682.

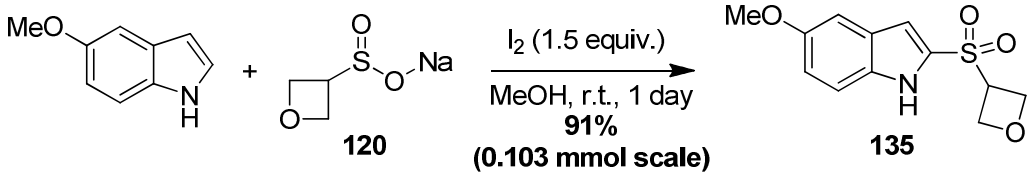
Synthesis of 5-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (134)



Using general procedure 9 with 5-methyl indole (13.5 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 5-methyl-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**134**) as a brown solid (19.1 mg, 74%).

M.p. = 132 - 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H, N***H***), 7.48 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.37 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.26 – 7.22 (m, 1H, Ar***H***), 7.15 (d, *J* = 1.5 Hz, 1H, Ar***H***), 4.99 (dd, *J* = 7.5, 6.5 Hz, 2H, C***H***$_2$), 4.90 – 4.79 (m, 2H, C***H***$_2$), 4.62 - 4.52 (m, 1H, C***H***), 2.45 (s, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 131.7, 129.6, 128.9, 127.5, 122.2, 112.2, 110.2, 70.5, 58.2, 21.5; FTIR: 3410 (br), 2960 (w), 2926 (w), 1636 (m), 1513 (w), 1316 (m), 1133 (m), 906 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_3S$: 252.0694, found: 252.0682.

Synthesis of 5-methoxy-2-(oxetan-3-ylsulfonyl)-1*H*-indole (135)

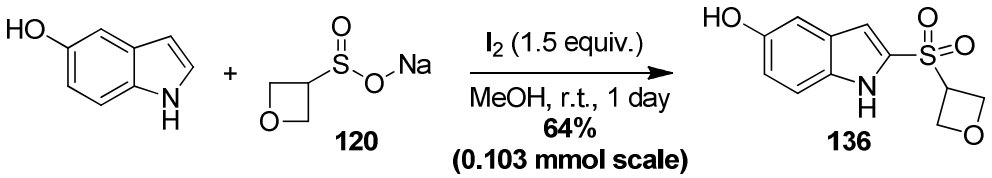


Using general procedure 9 with 5-methoxyindole (15 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 5-methoxy-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**135**) as a brown gum (25.1 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H, N***H***), 7.39 – 7.34 (m, 1H, Ar***H***), 7.15 (d, *J* = 1.5 Hz, 1H, Ar***H***), 7.09 – 7.04 (m, 2H, Ar***H***), 5.00 (dd, *J* = 7.5, 6.0 Hz, 2H, C***H***$_2$), 4.85 (t, *J* = 7.5 Hz, 2H, C***H***$_2$), 4.57 (tt, *J* = 7.5, 6.0 Hz, 1H, C***H***), 3.84 (s, 3H, C***H***$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 133.0, 129.6, 127.6, 118.7, 113.6, 110.2, 102.5, 70.5, 58.2, 55.8; FTIR: 3423 (br), 2953 (w), 2920 (w), 1633 (m), 1513 (m), 1316 (m), 1200 (m), 1166 (m), 1136 (m), 906 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{14}NO_4S$: 268.0644, found: 268.0632.

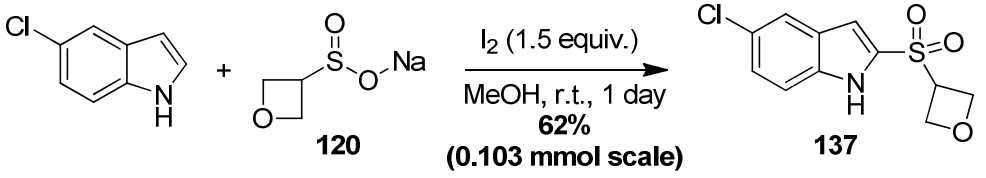
Synthesis of 2-(oxetan-3-ylsulfonyl)-1*H*-indol-5-ol (136)



Using general procedure 9 with 5-hydroxyindole (13.7 mg), the product was purified eluting with a gradient from 30% to 60% ethyl acetate in petroleum ether affording 2-(oxetan-3-ylsulfonyl)-1*H*-indol-5-ol (**136**) as a brown solid (16.8 mg, 64%).

M.p. = 120 - 122 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.33 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar***H***), 7.04 - 7.00 (m, 2H, Ar***H***), 6.93 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H, Ar***H***), 5.02 - 4.81 (m, 5H, C***H***$_2$ and O***H***), 4.73 – 4.66 (m, 1H, C***H***); ^{13}C NMR (101 MHz, MeOD) δ 153.2, 134.6, 131.5, 128.8, 118.4, 114.3, 109.8, 106.0, 71.5, 58.9; FTIR: 3425 (br), 2961 (w), 2538 (s), 1644 (s), 1442 (s), 1314 (m), 1173 (m), 1129 (m), 967 (w), 902 (w); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{11}NO_4S$: 254.0487, found: 254.0495.

Synthesis of 5-chloro-2-(oxetan-3-ylsulfonyl)-1*H*-indole (137)



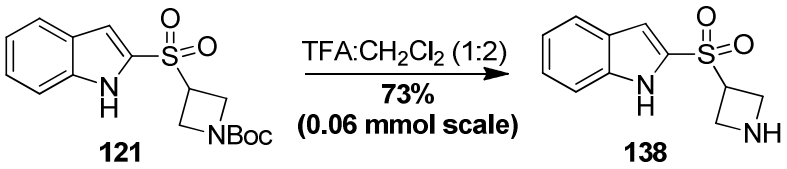
Using general procedure 9 with 5-chloroindole (15.6 mg), the product was purified eluting with a gradient from 10% to 40% ethyl acetate in petroleum ether affording 5-chloro-2-(oxetan-3-ylsulfonyl)-1*H*-indole (**137**) as a brown solid (17.3 mg, 62%).

M.p. = 108 – 110°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H, N***H***), 7.69 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.43 - 7.40 (m, 1H, Ar***H***), 7.37 – 7.32 (m, 1H, Ar***H***), 7.17 (d, *J* =

1.5 Hz, 1H, Ar***H***), 5.00 (dd, *J* = 8.0, 6.0 Hz, 2H, C***H***$_2$), 4.88 (t, *J* = 8.0 Hz, 2H, C***H***$_2$), 4.65 – 4.55 (m, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 131.0, 127.9, 127.8, 127.4, 122.1, 113.8, 109.9, 70.3, 58.2; FTIR: 3376 (br), 2956 (m), 2924 (m), 2885 (m), 1641 (w), 1507 (m), 1319 (s), 1268 (w), 1138 (s), 1097 (m), 979 (m), 950 (m), 905 (m), 807 (m); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{11}NO_3S^{35}Cl$: 272.0148, found: 272.0155.

9. Synthesis of Atevirdine analogue

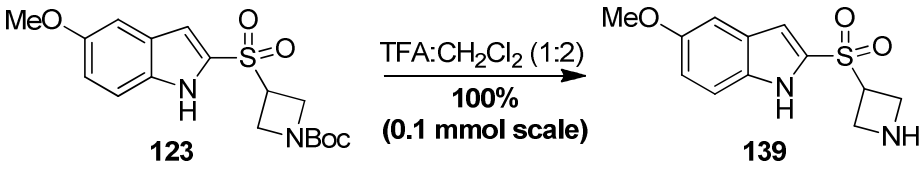
Synthesis 2-(azetidin-3-ylsulfonyl)-1*H*-indole (138)



TFA (0.15 mL) was added to *tert*-butyl 3-((1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**121**) (20 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) at room temperature. The resulting solution was stirred at 40 °C for 1 day. Volatiles were removed under vacuo and the residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 15% methanol in dichloromethane affording 2-(azetidin-3-ylsulfonyl)-1*H*-indole (**138**) as a brown solid (10.2 mg, 73%).

M.p. = 138 - 140 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.51 (d, *J* = 8.5 Hz, 1H, Ar***H***), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar***H***), 7.28 (s, 1H, Ar***H***), 7.19 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar***H***), 4.57 – 4.45 (m, 1H, C***H***), 4.40 – 4.16 (m, 4H, C***H***$_2$); ^{13}C NMR (101 MHz, MeOD) δ 139.9, 130.5, 128.0, 127.3, 123.6, 122.5, 113.7, 111.6, 55.7, 47.3; FTIR: 3400 (br), 2917 (w), 2851 (w), 1659 (s), 1425 (m), 1319 (s), 1189 (s), 1136 (s), 946 (w), 836 (m), 793 (s), 763 (m), 716 (s); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{13}N_2O_2S$: 237.0698, found: 237.0703.

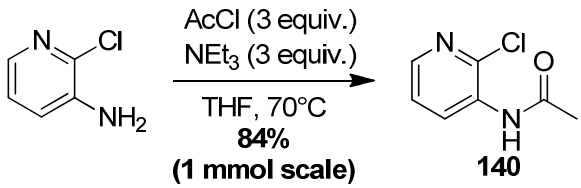
Synthesis 2-(azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (139)



TFA (0.25 mL) was added to *tert*-butyl 3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidine-1-carboxylate (**123**) (36.6 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The resulting solution was stirred at 40 °C for 1 day. Volatiles were removed under vacuo and the residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 15% methanol in dichloromethane affording 2-(azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (**139**) as a beige solid (26.5 mg, 100%).

M.p. = 102 - 104 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.40 (d, *J* = 9.0 Hz, 1H, Ar***H***), 7.21 (d, *J* = 1.0 Hz, 1H, Ar***H***), 7.15 (d, *J* = 2.5 Hz, 1H, Ar***H***), 7.04 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar***H***), 4.57 – 4.47 (m, 1H, C***H***), 4.43 – 4.39 (m, 4H, C$\boldsymbol{H}_2$), 3.82 (s, 3H, C$\boldsymbol{H}_3$); ^{13}C NMR (101 MHz, MeOD) δ 156.7, 135.3, 130.1, 128.4, 119.5, 114.7, 111.4, 103.1, 56.0, 55.1, 47.4; FTIR: 3296 (br), 2916 (w), 2846 (w), 1670 (s), 1513 (m),1436 (m), 1316 (m), 1203 (s), 1136 (s), 1033 (w), 790 (w); HRMS: m/z [M+H]+ calcd. for $C_{12}H_{15}N_2O_3S$: 267.0803, found: 267.0796.

Synthesis of *N*-(2-chloropyridin-3-yl)acetamide (140)[184]

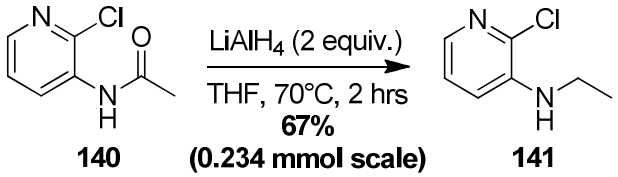


Acetyl chloride (0.21 mL, 3 mmol) was added to 2-chloropyridin-3-amine (128.6 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in THF (3 mL) at room temperature. The resulting solution was stirred at 70 °C for 8 hrs and cooled to r.t.. Volatiles were then removed under vacuo and the residue was diluted with CH_2Cl_2 (10 mL). Water (10 mL) was then added and the mixture was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layer were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography on

silica gel eluting with a gradient from 40% to 50% ethyl acetate in petroleum ether affording *N*-(2-chloropyridin-3-yl)acetamide (**140**) as a beige solid (144.3 mg, 84%)

M.p. = 78 - 80 °C (lit. 81 – 83°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (td, *J* = 8.0, 1.5 Hz, 1H, N***H***), 8.13 – 8.06 (m, 1H, Ar***H***), 7.65 (s, 1H, Ar***H***), 7.28 – 7.19 (m, 1H, Ar***H***), 2.26 (s, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 143.9, 132.0, 129.1, 123.5, 26.5, 25.0; FTIR: 3350 (s), 3021 (w), 2927 (w), 2874 (w), 1695 (s), 1582 (s), 1519 (s), 1452 (s), 1362 (s), 1299 (s), 1236 (s), 1082 (m), 1039 (s), 1013 (s) 952 (m), 803 (s), 729 (s), 643 (s); HRMS: m/z [M+H]+ calcd. for $C_7H_8N_2OCl$: 171.0324, found: 171.0325.

Synthesis of 2-chloro-*N*-ethylpyridin-3-amine (141)[163]

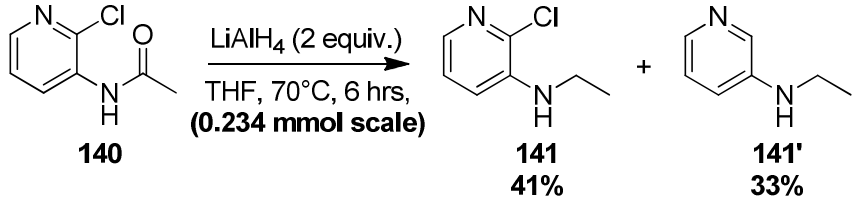


140 **141**

$LiAlH_4$ (17.8 mg, 0.469 mmol) was added to *N*-(2-chloropyridin-3-yl)acetamide (**140**) (40 mg, 0.234 mmol) in THF (1 mL) at room temperature. The resulting solution was stirred at 70 °C for 2 hrs and cooled to r.t.. Water (10 mL) was then added and the mixture was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with 30% ethyl acetate in petroleum ether affording 2-chloro-*N*-ethylpyridin-3-amine (**141**) as an orange oil (24.5 mg, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar***H***), 7.08 (dd, *J* = 8.0, 4.5 Hz, 1H, Ar***H***), 6.86 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 4.26 (s, 1H, N***H***), 3.22 – 3.11 (m, 2H, C***H***$_2$), 1.31 (t, *J* = 7.0 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 137.0, 136.2, 123.5, 117.3, 38.0, 14.6; FTIR: 3420 (s), 3063 (w), 2973 (s), 2876 (m), 1586 (s), 1493 (s), 1383 (s), 1323 (s), 1273 (m), 1213 (s), 1150 (s), 1120 (m), 1076 (m), 1053(s), 790 (s), 730 (m), 710 (m); HRMS: m/z [M+H]+ calcd. for $C_7H_{10}N_2Cl$: 157.0533, found: 157.0535. Analysis are in accordance with those reported in the literature.

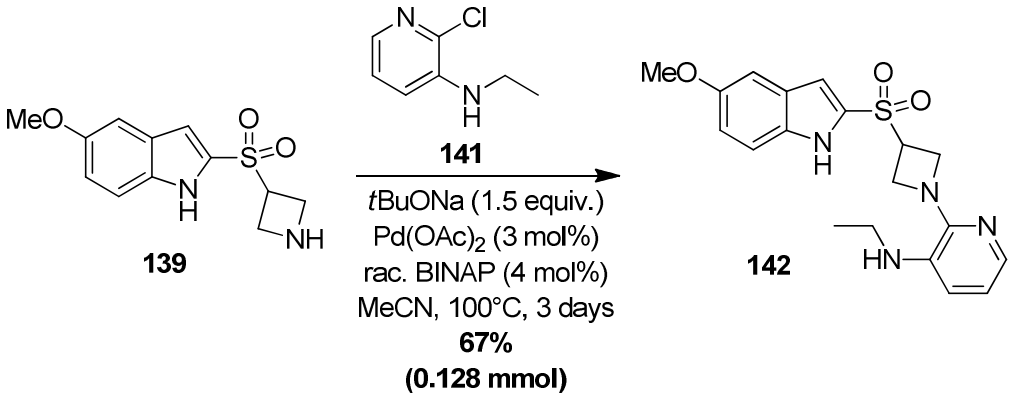
Synthesis of 2-chloro-*N*-ethylpyridin-3-amine (141) and *N*-ethylpyridin-3-amine (141')



$LiAlH_4$ (44.5 mg, 1.117 mmol) was added to *N*-(2-chloropyridin-3-yl)acetamide (**140**) (40 mg, 0.234 mmol) in THF (1 mL) at room temperature. The resulting solution was stirred at 70°C for 6 hrs and cooled to r.t.. Water (10 mL) was then added and the mixture was extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with a gradient from 30% to 100% ethyl acetate in petroleum ether affording 2-chloro-*N*-ethylpyridin-3-amine (**141**) as an orange oil (15.2 mg, 41%) and *N*-ethylpyridin-3-amine (9.4 mg, 33%) (**141'**) as a yellow oil.

141' ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.5 Hz, 1H, Ar***H***), 7.93 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar***H***), 7.08 (ddd, *J* = 8.5, 4.5, 0.5 Hz, 1H, Ar***H***), 6.86 (ddd, *J* = 8.5, 3.0, 1.5 Hz, 1H, Ar***H***), 3.16 (q, *J* = 7.0 Hz, 2H, C***H***$_2$), 2.11 (s, *J* = 13.0 Hz, 1H, N***H***), 1.27 (t, *J* = 7.0 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 138.5, 135.9, 123.9, 118.6, 38.2, 14.8; FTIR: 3276 (br), 3096 (w), 3042 (w), 2973 (m), 2930 (w), 1590 (s), 1520 (m), 1483 (s), 1420 (m), 1323 (m), 1250 (m), 1150 (m), 1106 (w), 1010 (w), 793 (m), 713 (s); HRMS: m/z [M+H]+ calcd. for $C_7H_{11}N_2$: 123.0922, found: 123.0919.

Synthesis of *N*-ethyl-2-(3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidin-1-yl)pyridin-3-amine (142)

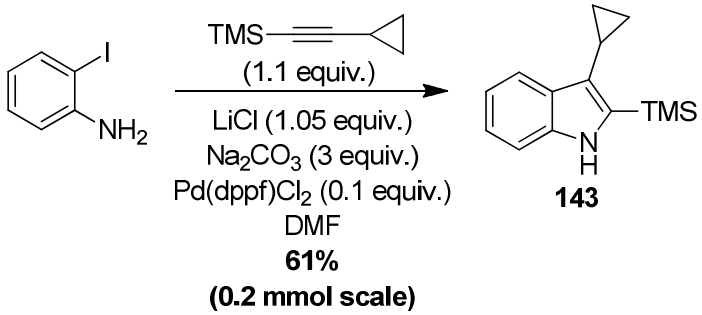


Into a flame-dried Schlenk tube were introduced 2-chloro-*N*-ethylpyridin-3-amine (**141**) (10 mg, 0.064 mmol), *t*BuONa (9.2 mg, 0.096 mmol), $Pd(OAc)_2$ (0.5 mg, 0.002 mmol) and rac. BINAP (1.6 mg, 0.0026 mmol) under argon. The Schlenk tube was sealed, and the atmosphere was evacuated and purged 3 times with argon. 2-(Azetidin-3-ylsulfonyl)-5-methoxy-1*H*-indole (**139**) (34 mg, 0.128 mmol) and acetonitrile were then added. The Schlenk tube was sealed, and the atmosphere was evacuated and purged 3 times with argon. The resulting solution was stirred at 100 °C for 3 days, cooled to r.t. and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with a gradient from 30% to 50% ethyl acetate in petroleum ether affording *N*-ethyl-2-(3-((5-methoxy-1*H*-indol-2-yl)sulfonyl)azetidin-1-yl)pyridin-3-amine (**142**) as a beige solid (16.6 mg, 67%).

M.p. = 110 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H, N***H***), 7.63 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar***H***), 7.34 (d, *J* = 9.0 Hz, 1H, Ar***H***), 7.19 – 7.16 (m, 1H, Ar***H***), 7.09 – 7.03 (m, 2H, Ar***H***), 6.79 – 6.71 (m, 2H, Ar***H***), 4.44 – 4.38 (m, 2H, C***H*** and N***H***), 4.30 – 4.17 (m, 4H, C***H***$_2$), 3.85 (s, 3H, C***H***$_3$), 3.01 (q, *J* = 7.0 Hz, 2H, C***H***$_2$), 1.21 (t, *J* = 7.0 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 149.5, 135.6, 132.8, 130.4, 129.4, 127.7, 118.4, 118.2, 116.6, 113.5, 110.0, 102.6, 55.8, 54.4, 51.5, 38.4, 14.8; FTIR: 3367 (w), 2954 (w), 2861 (w), 1575 (m), 1479 (m), 1445 (m), 1422 (s), 1282 (s), 1136 (m), 1096 (m), 1029 (m), 956 (m), 896 (m), 789 (m), 716 (s); HRMS: m/z [M+H]+ calcd. for $C_{19}H_{23}N_4O_3S$: 387.1491, found: 387.1492.

10. Mechanistic investigation

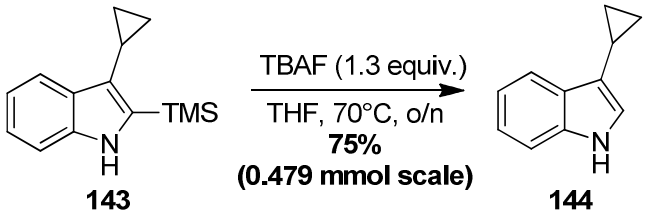
Synthesis of 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole (143)[185]



4 Reactions were set-up in quadruplicate: $Pd(dppf)Cl_2$ (16.3 mg, 0.02 mmol) was added to a mixture of 2-iodoaniline (43.8 mg, 0.2 mmol), trimethylsilyl acetylene (30.4 mg, 0.22 mmol), lithium chloride (8.9 mg, 0.21 mmol) and sodium carbonate (63.6 mg, 0.6 mmol) in DMF (0.9 mL) in 4 different flame-dried flasks under argon. The resulting mixture was then stirred at 100 °C for 6 hrs and at r.t. overnight. Water (10 mL) and ethyl acetate (10 mL) were added and the mixtures were filtered on a pad of celite and extracted with ethyl acetate (3x 30 mL). The combined organic layers were dried, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with a gradient from 3% to 5% ethyl acetate in petroleum ether affording 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole (**143**) as a brown solid (111.8 mg, 61%).

M.p. = 58 - 60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H, N***H***), 7.81 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.39 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.26 – 7.20 (m, 1H, Ar***H***), 7.17 – 7.11 (m, 1H, Ar***H***), 2.02 (tt, *J* = 8.5, 5.5 Hz, 1H, C***H***), 1.05 – 0.98 (m, 2H, C$\boldsymbol{H}_2$), 0.91 – 0.85 (m, 2H, C$\boldsymbol{H}_2$), 0.48 (s, 9H, C$\boldsymbol{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 135.3, 129.1, 126.5, 122.3, 119.8, 119.2, 111.0, 7.8, 6.4, -0.5; FTIR: 3436 (s), 3080 (m), 3006 (m), 2953 (m), 1640 (w), 1516 (m), 1456 (m), 1333 (m), 1246 (s), 1153 (m), 1036 (m), 926 (m), 836 (s), 743 (s), 636 (m); HRMS: m/z [M+H]+ calcd. for $C_{14}H_{20}NSi$: 230.1365, found: 230.1369. Analysis are in accordance with those reported in the literature.

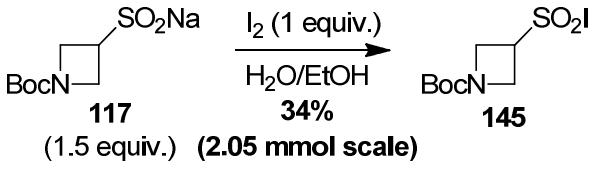
Synthesis 3-cyclopropyl-1*H*-indole (144) [185]



TBAF (1M in THF, 0.62 mL, 0.62 mmol) was added to a solution of 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole (**143**) (110 mg, 0.479 mmol) in THF (2.5 mL). The resulting mixture was stirred at 70 °C overnight and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel eluting with a gradient from 10% to 20% ethyl acetate in petroleum ether affording 3-cyclopropyl-1*H*-indole (**144**) as a brown solid (56.8 mg, 75%).

M.p. = 30 - 31 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.70 (m, 2H, Ar***H*** and N***H***), 7.34 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.27 – 7.21 (m, 1H, Ar***H***), 7.21 – 7.15 (m, 1H, Ar***H***), 6.88 (d, *J* = 1.5 Hz, 1H, Ar***H***), 2.05 – 1.95 (m, 1H, C***H***), 0.97 – 0.89 (m, 2H, C***H***$_2$), 0.71 – 0.65 (m, 2H, C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 128.2, 122.2, 120.5, 119.3, 119.3 (2 signals), 111.2, 6.2, 6.1; FTIR: 3416 (s), 3080 (m), 3003 (m), 2926 (m), 2853 (m), 1620 (w), 1456 (s), 1426 (m), 1336 (m), 1230 (m), 1093 (m), 1030 (m), 743 (s); HRMS: m/z [M+H]+ calcd. for $C_{11}H_{12}N$: 158.0970, found: 158.0972. Analysis are in accordance with those reported in the literature.

Synthesis *tert*-butyl 3-(iodosulfonyl)azetidine-1-carboxylate (145)

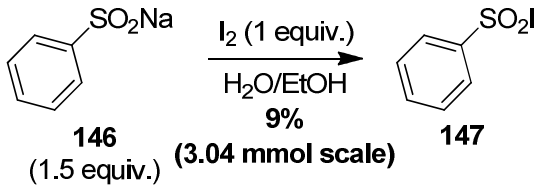


Iodine (347.7 mg, 1.37 mmol) in ethanol (4 mL) was added to sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**117**) (500 mg, 2.05 mmol) in water (0.5 mL). The mixture was stirred at r.t. for 1 hr and was then extracted with CH_2Cl_2 (3x 10 mL). Hexane (10 mL) was then added and the mixture was stored in a freezer overnight, filtered and washed with hexane (3x 5 mL). *tert*-Butyl 3-(iodosulfonyl)azetidine-1-carboxylate (**145**) was isolated as a tan solid (161 mg,

34%). The compound was found to be unstable and was characterized by ^{1}H NMR spectroscopy only

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 – 4.35 (m, 1H, C***H***), 4.10 – 4.00 (m, 4H, C***H***$_2$), 1.45 (s, 9H, C***H***$_3$).

Synthesis benzenesulfonyl iodide (147) [186]



Iodine (515 mg, 2.03 mmol) in ethanol (4 mL) was added to sodium benzenesulfinate (**146**) (500 mg, 3.04 mmol) in water (1 mL). The mixture was stirred at r.t. for 1 hr and was then extracted with CH_2Cl_2 (3x 10 mL). Hexane (10 mL) was then added and the mixture was stored in a freezer overnight, filtered and washed with hexane (3x 5 mL). Benzenesulfonyl iodide (**147**) was isolated as a tan solid (76.2 mg, 9%). The compound was found to be unstable and was characterized by ^{1}H NMR spectroscopy only

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dt, *J* = 8.5, 1.5 Hz, 2H, Ar***H***), 7.73 – 7.61 (m, 1H, Ar***H***), 7.60 – 7.52 (m, 2H, Ar***H***). Analysis are in accordance with those reported in the literature.

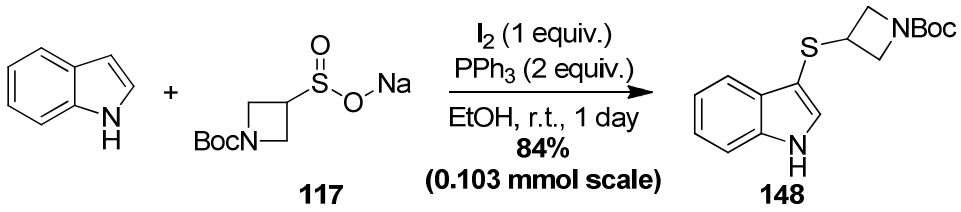
11. Coupling of sodium sulfinate salt to the position 3 of indole

General procedure 10:

Iodine (26.1 mg, 0.206 mmol) was added to indole (12 mg, 0.103 mmol), triphenylphosphine (54 mg, 0.206 mmol) and sodium 1-(*tert*-butoxycarbonyl)azetidine-3-sulfinate (**117**) (50.1 mg, 0.206 mmol) in EtOH (0.5 mL) at room temperature. The resulting solution was stirred at 70 °C for 1.5 days. All

volatiles were removed *in vacuo* and the residue was directly purified via flash chromatography on silica gel to provide the title product.

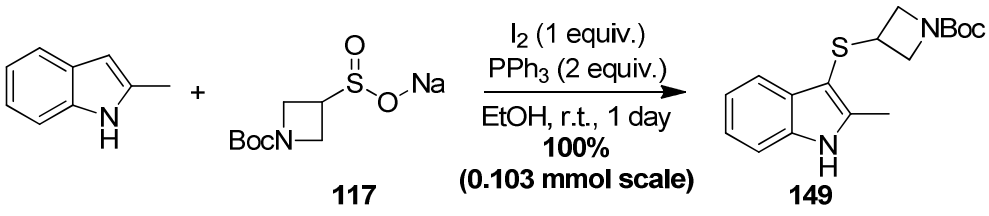
Synthesis of *tert*-butyl 3-((1*H*-indol-3-yl)thio)azetidine-1-carboxylate (148)



Using general procedure 10 with indole (12 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**148**) as a brown gum (26.3 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H, N***H***), 7.77 – 7.71 (m, 1H, Ar***H***), 7.42 – 7.37 (m, 2H, Ar***H***), 7.28 – 7.19 (m, 2H, Ar***H***), 4.15 – 4.10 (m, 2H, C***H***$_2$), 3.85 (dd, *J* = 9.0, 5.5 Hz, 2H, C***H***$_2$), 3.78 – 3.70 (m, 1H, C***H***), 1.35 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.4, 130.6, 129.9, 123.0, 120.9, 119.3, 111.8, 102.7, 79.7, 56.2 (br), 35.7, 28.4; FTIR: 3278 (s), 2975 (s), 2882 (s), 1675 (s), 1407 (s), 1249 (m), 1156 (s), 1008 (m), 977 (w), 898 (w), 857 (m), 744 (s); HRMS: m/z [M+H]+ calcd. for $C_{16}H_{21}N_2O_2S$: 305.1324, found: 305.1319.

Synthesis of *tert*-butyl 3-((2-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (149)

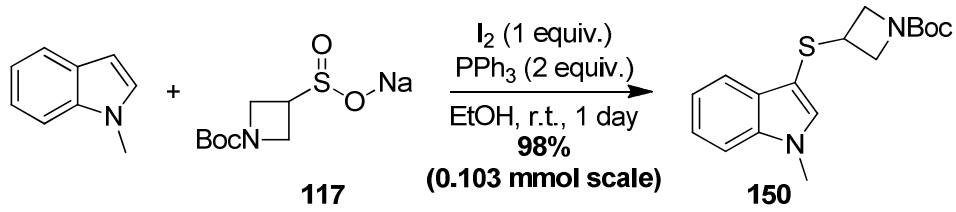


Using general procedure 10 with 2-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording

tert-butyl 3-((2-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**149**) as a brown solid (33.1 mg, 100%).

M.p. = 130 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H, N***H***), 7.68 – 7.62 (m, 1H, Ar***H***), 7.32 – 7.28 (m, 1H, Ar***H***), 7.19 – 7.15 (m, 2H, Ar***H***), 4.12 (t, *J* = 9.0 Hz, 2H, C***H***$_2$), 3.84 (dd, *J* = 9.0, 5.5 Hz, 2H, C***H***$_2$), 3.77 – 3.69 (m, 1H, C***H***), 2.54 (s, 3H, C***H***$_3$), 1.37 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 141.2, 135.4, 131.1, 122.1, 120.6, 118.6, 110.9, 99.5, 79.8, 56.4 (br), 36.2, 28.4, 12.4; FTIR: 3283 (m), 2976 (m), 2880 (w), 1676 (s), 1473 (m), 1453 (m), 1413 (s), 1363 (m), 1230 (w), 1153 (m), 743 (m); HRMS: m/z [M+H]+ calcd. for $C_{17}H_{23}N_2O_2S$: 319.1480, found: 319.1485.

Synthesis of *tert*-butyl 3-((1-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (150)

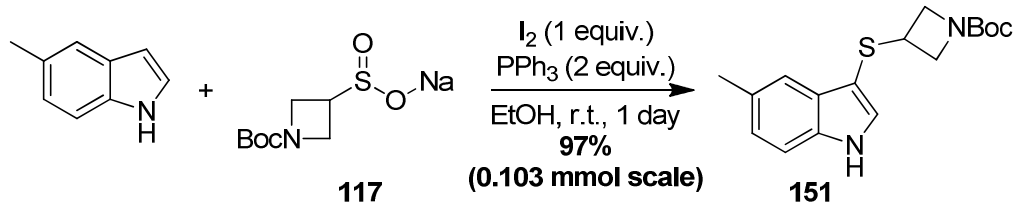


117 **150**

Using general procedure 10 with *N*-methylindole (13 µL), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((1-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**150**) as a beige solid (32.3 mg, 98%).

M.p. = 86 – 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 1H, Ar***H***), 7.37 – 7.33 (m, 1H, Ar***H***), 7.32 – 7.26 (m, 1H, Ar***H***), 7.25 (s, 1H, Ar***H***), 7.22 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar***H***), 4.15 – 4.09 (m, 2H, C***H***$_2$), 3.88 – 3.82 (m, 2H, C***H***$_2$), 3.81 (s, 3H, C***H***$_3$), 3.77 – 3.67 (m, 1H, C***H***), 1.35 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 137.4, 135.0, 130.6, 122.6, 120.6, 119.4, 109.8, 100.7, 79.6, 56.2 (br), 35.9, 33.2, 28.4; FTIR: 3103 (w), 2973 (m), 2930 (m), 2880 (m), 1700 (s), 1510 (m), 1460 (m), 1393 (s), 1366 (s), 1240 (m), 1156 (s), 1126 (s), 743 (m); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_2SNa$: 341.1300, found: 341.1287.

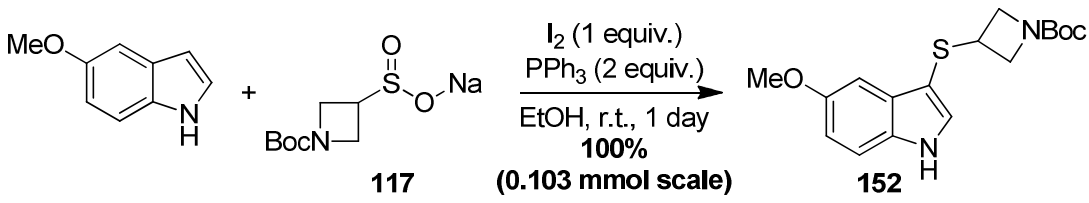
Synthesis of *tert*-butyl 3-((5-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (151)



Using general procedure 10 with 5-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methyl-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**151**) as a pale red solid (31.8 mg, 97%).

M.p. = 118 - 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H, N***H***), 7.52 (s, 1H, Ar***H***), 7.35 (d, *J* = 1.5 Hz, 1H, Ar***H***), 7.29 (d, *J* = 8.5 Hz, 1H, Ar***H***), 7.08 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar***H***), 4.16 – 4.08 (m, 2H, C***H***$_2$), 3.85 (dd, *J* = 9.0, 5.5 Hz, 2H, C***H***$_2$), 3.80 – 3.69 (m, 1H, C***H***), 2.48 (s, 3H, C***H***$_3$), 1.36 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 134.7, 130.6, 130.4, 130.0, 124.7, 118.8, 111.4, 102.1, 79.7, 56.1 (br), 35.7, 28.4, 21.7; FTIR: 3282 (br), 2974 (m), 2877 (w), 1675 (s), 1478 (m), 1411 (s), 1368 (m), 1241 (w), 1161 (s), 797 (w); HRMS: m/z [M+H]+ calcd. for $C_{17}H_{23}N_2O_2S$: 319.1480, found: 319.1473.

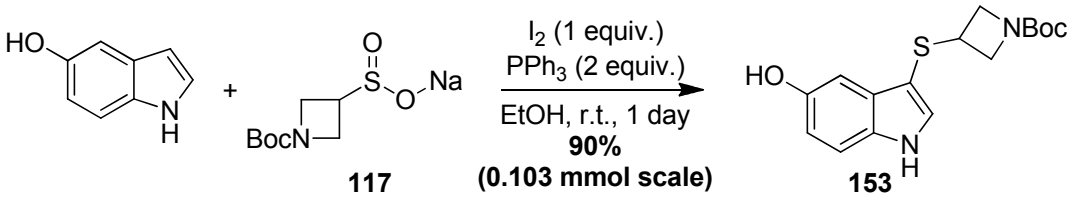
Synthesis of *tert*-butyl 3-((5-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (152)



Using general procedure 10 with 5-methoxylindole (15.1 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**152**) as a pale red solid (34.2 mg, 100%).

M.p. = 84 - 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H, N***H***), 7.33 (d, *J* = 2.5 Hz, 1H, Ar***H***), 7.30 - 7.28 (m, 1H, Ar***H***), 7.17 (d, *J* = 2.5 Hz, 1H, Ar***H***), 6.93 – 6.89 (m, 1H, Ar***H***), 4.16 – 4.10 (m, 2H, C***H***$_2$), 3.88 (s, 3H, C***H***$_3$), 3.87 – 3.83 (m, 2H, C***H***$_2$), 3.77 – 3.67 (m, 1H, C***H***), 1.36 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 155.2, 131.4, 131.3, 130.6, 113.4, 112.6, 101.9, 100.5, 79.8, 56.2 (br), 56.0, 35.7, 28.4; FTIR: 3283 (br), 2973 (m), 2930 (m), 2880 (w), 1676 (s), 1580 (w), 1486 (m), 1416 (s), 1370 (m), 1280 (m), 1206 (m), 1166 (s), 1036 (m), 923 (w), 803 (w), 733 (w); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_3SNa$: 357.1249, found: 357.1263.

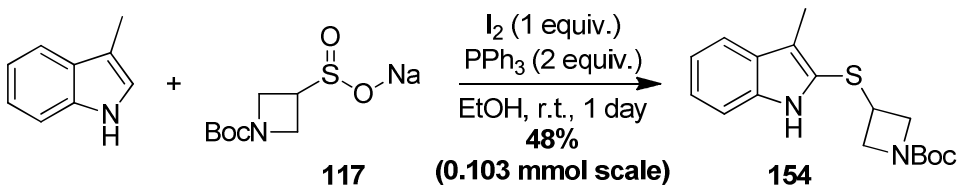
Synthesis of *tert*-butyl 3-((5-hydroxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (153)



Using general procedure 10 with 5-hydroxylindole (13.7 mg), the product was putified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((5-hydroxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**153**) as a brown gum (29.6 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, N***H***), 7.27 (d, *J* = 2.5 Hz, 1H, Ar***H***), 7.22 – 7.19 (m, 1H, Ar***H***), 7.14 (d, *J* = 2.0 Hz, 1H, Ar***H***), 6.85 – 6.81 (m, 1H, Ar***H***), 4.14 – 4.06 (m, 3H, C***H***$_2$ and O***H***), 3.88 – 3.79 (m, 2H, C***H***$_2$), 3.69 – 3.60 (m, 1H, C***H***), 1.37 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 151.1, 131.7, 131.4, 130.9, 113.0, 112.6, 103.5, 101.3, 80.1, 56.2 (br), 35.6, 28.4; FTIR: 3422 (br), 2978 (w), 1648 (s), 1414 (m), 1366 (m), 1153 (m), 1015 (w); HRMS: m/z [M+Na]+ calcd. for $C_{16}H_{20}N_2O_3SNa$: 343.1092, found: 343.1106.

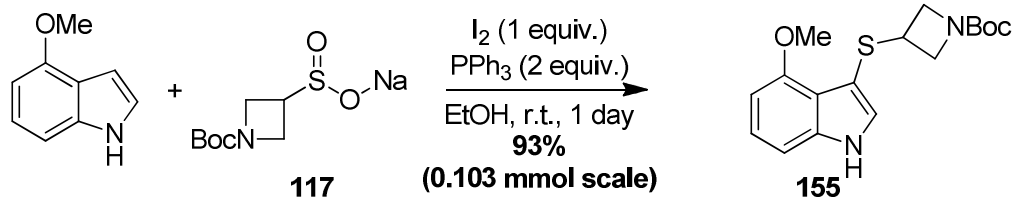
Synthesis of *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)thio)azetidine-1-carboxylate (154)



Using general procedure 10 with 3-methylindole (13.5 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((3-methyl-1*H*-indol-2-yl)thio)azetidine-1-carboxylate (**154**) as a white solid (15.7 mg, 48%).

M.p. = 132 - 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, N***H***), 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 7.33 – 7.29 (m, 1H, Ar***H***), 7.26 – 7.21 (m, 1H, Ar***H***), 7.15 – 7.10 (m, 1H, Ar***H***), 4.22 – 4.15 (m, 2H, C***H***$_2$), 3.87 (dd, *J* = 9.0, 5.5 Hz, 2H, C***H***$_2$), 3.82 – 3.73 (m, 1H, C***H***), 2.41 (s, 3H, C***H***$_3$), 1.38 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 136.8, 128.6, 123.6, 122.0, 119.8, 119.6, 119.5, 110.9, 80.0, 56.5 (br), 36.5, 28.4, 9.8; FTIR: 3408 (br), 2978 (w), 2930 (w), 2886 (w), 1682 (s), 1452 (w), 1414 (m), 1366 (m), 1156 (m), 744 (m); HRMS: m/z [M+H]+ calcd. for $C_{17}H_{23}N_2O_2S$: 319.1480, found: 319.1485.

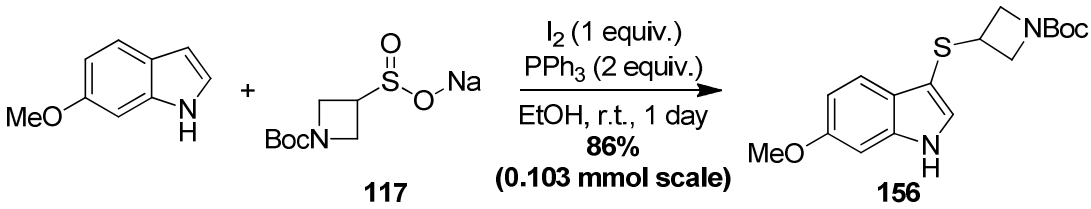
Synthesis of *tert*-butyl 3-((4-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (155)



Using general procedure 10 with 4-methoxyindole (15.1 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((4-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**155**) as a brown gum (32 mg, 93%).

M.p. = 120 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H, N***H***), 7.18 - 7.13 (m, 2H, Ar***H***), 7.00 (dd, *J* = 8.0, 0.5 Hz, 1H, Ar***H***), 6.57 (d, *J* = 7.5 Hz, 1H, Ar***H***), 4.17 – 4.12 (m, 2H, C***H***$_2$), 3.96 (s, 3H, C***H***$_3$), 3.94 – 3.87 (m, 3H, C***H***$_2$ and C***H***), 1.39 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 154.5, 138.5, 128.7, 123.9, 118.5, 105.1, 102.8, 101.0, 79.6, 55.7 (br), 55.6, 36.0, 28.5; FTIR: 3270 (br), 2970 (m), 2883 (m), 2836 (w), 1676 (s), 1586 (m), 1510 (m), 1413 (s), 1366 (m), 1316 (m), 1250 (s), 1163 (s), 1086 (m), 776 (m), 733 (m); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_3SNa$: 357.1249, found: 357.1255.

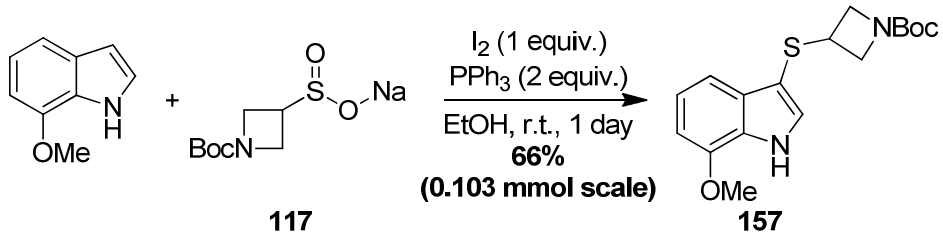
Synthesis of *tert*-butyl 3-((6-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (156)



Using general procedure 10 with 6-methoxylindole (15.1 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((6-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**156**) as a brown gum (29.7 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H, N***H***), 7.61 – 7.55 (m, 1H, Ar***H***), 7.24 (d, *J* = 2.5 Hz, 1H, Ar***H***), 6.90 – 6.85 (m, 2H, Ar***H***), 4.12 (dd, *J* = 11.0, 6.5 Hz, 2H, C***H***$_2$), 3.88 – 3.81 (m, 5H, C***H***$_3$ and C***H***$_2$), 3.76 – 3.69 (m, 1H, C***H***), 1.36 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 156.4, 137.2, 129.5, 124.1, 119.8, 110.9, 102.4, 95.2, 79.8, 56.2 (br), 55.8, 35.7, 28.4; FTIR: 3290 (br), 2960 (m), 2923 (m), 2856 (m), 1680 (s), 1630 (m), 1513 (w), 1456 (m), 1403 (s), 1370 (m), 1296 (w), 1243 (w), 1160 (s), 1033 (w), 806 (w); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_3SNa$: 357.1249, found: 357.1241.

Synthesis of *tert*-butyl 3-((7-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (157)



Using general procedure 10 with 7-methoxylindole (15.1 mg), the product was purified eluting with a gradient from 20% to 30% ethyl acetate in petroleum ether affording *tert*-butyl 3-((7-methoxy-1*H*-indol-3-yl)thio)azetidine-1-carboxylate (**157**) as a brown solid (22.8 mg, 66%).

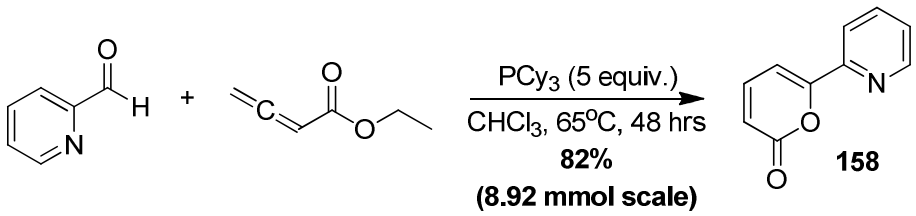
M.p. = 144 – 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H, N***H***), 7.38 – 7.29 (m, 2H, Ar***H***), 7.13 (t, *J* = 8.0 Hz, 1H, Ar***H***), 6.70 (d, *J* = 8.0 Hz, 1H, Ar***H***), 4.16 – 4.08 (m, 2H, C$\boldsymbol{H}_2$), 3.96 (s, 3H, C$\boldsymbol{H}_3$), 3.85 (dd, *J* = 9.0, 5.5 Hz, 2H, C$\boldsymbol{H}_2$), 3.78 – 3.69 (m, 1H, C***H***), 1.35 (s, 9H, C$\boldsymbol{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 146.4, 131.2, 130.0, 126.9, 121.4, 111.8, 103.1, 102.8, 79.6, 56.3 (br), 55.5, 35.8, 28.4; FTIR: 3309 (br), 2975 (m), 2882 (w), 1679 (s), 1579 (m), 1411 (s), 1311 (w), 1256 (), 1146 (s), 1091 (m), 1015 (m), 781 (m), 733 (m); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{22}N_2O_3SNa$: 357.1249, found: 357.1255.

12. Synthesis of 2-pyrones

General procedure 11: Synthesis of 6-aryl-pyran-2-ones

Aryl carboxaldehyde (5 equiv.) and tricyclohexyl phosphine (1.5 equiv.) were dissolved in $CHCl_3$ (1 M). To this mixture ethyl buta-2,3-dienoate (1 equiv.) was added dropwise, resulting in a deep red solution which was stirred at 65 °C for 48 hrs. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The dark brown residue was purified via flash column chromatography on silica gel eluting with a gradient from 20 to 50% ethyl acetate in heptane.

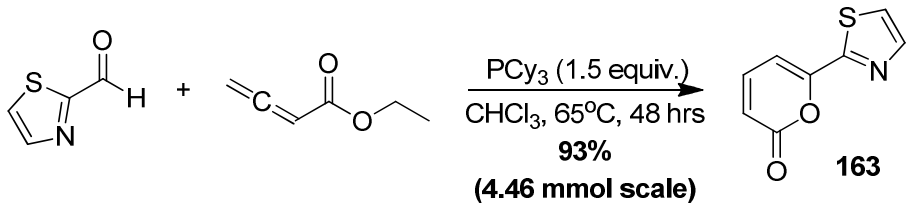
Synthesis of 6-(pyridin-2-yl)-2*H*-pyran-2-one (158) [176b]



Using general procedure 11, with picolinaldehyde (4.24 mL, 44.59 mmol), tricyclohexylphosphine (3.75 g, 13.38 mmol) and ethyl buta-2,3-dienoate (1.04 mL, 8.92 mmol) in $CHCl_3$ (90 mL), 6-(pyridin-2-yl)-2*H*-pyran-2-one (**158**) was isolated as a pale yellow solid (1.27 g, 82%).

M.p. 106.8 - 108.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H, C***H***), 8.01 (dt, *J* = 8.0, 1.0 Hz, 1H, C***H***), 7.82 (td, *J* = 8.0, 2.0 Hz, 1H, C***H***), 7.48 (dd, *J* = 9.5, 7.0 Hz, 1H, C***H***), 7.33 - 7.35 (m, 2H, C***H***), 6.37 (dd, *J* = 9.5, 1.0 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 159.5, 150.0, 149.1, 144.0, 137.3, 125.1, 120.6, 116.1, 102.9; FTIR: 1739 (s), 1630 (w), 1572 (w), 1542 (m), 1469 (w), 1435 (m), 1337 (w), 1073 (s), 991 (m), 845 (m), 776 (s), 737 (m); HRMS: m/z [M+H]+ calcd. for $C_{10}H_7NO_2$: 174.0550, found: 174.0548. Analysis are in accordance with those reported in the literature.

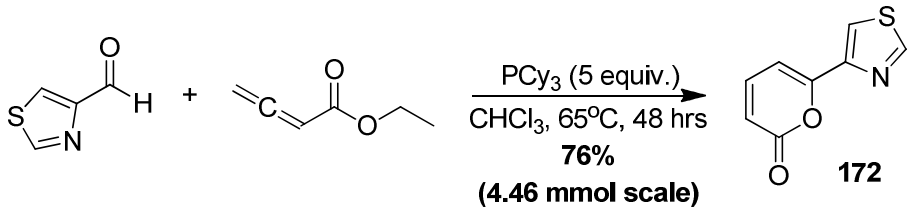
Synthesis of 6-(thiazol-2-yl)-2*H*-pyran-2-one (163) [187]



Using general procedure 11 with 1.02 equiv. of aldehyde and 1.5 equiv. of phosphine, with thiazole-2-carbaldehyde (0.40 mL, 4.55 mmol), tricyclohexylphosphine (1.88 g, 6.69 mmol) and ethyl buta-2,3-dienoate (0.52 mL, 4.46 mmol) in $CHCl_3$ (45 mL), 6-(thiazol-2-yl)-2*H*-pyran-2-one (**163**) was isolated as a beige solid (0.74 g, 93%).

M.p. 123.9 – 125.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 3.0 Hz, 1H, C***H***), 7.55 (d, *J* = 3.0 Hz, 1H, C***H***), 7.45 (dd, *J* = 9.5, 7.0 Hz, 1H, C***H***), 7.14 (dd, *J* = 7.0, 1.0 Hz, 1H, C***H***), 6.38 (dd, *J* = 9.5, 1.0 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 159.5, 154.9, 144.8, 143.4, 122.5, 116.5, 101.9; FTIR: 1744 (s), 1623 (s), 1539 (m), 1488 (w), 1324 (m), 1261 (m), 1096 (m), 1056 (w), 946 (m), 797 (s), 734 (w); HRMS: m/z [M+H]+ calcd. for $C_8H_6NO_2S$: 180.0114, found: 180.0113. Analysis are in accordance with those reported in the literature.

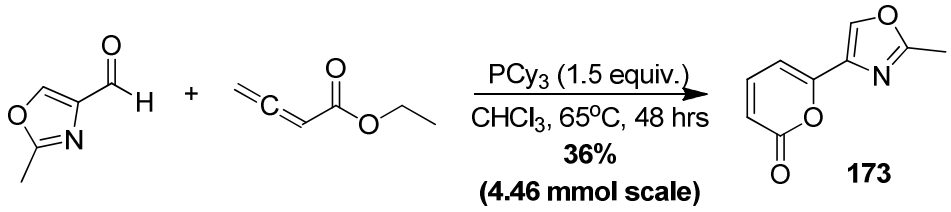
Synthesis of 6-(thiazol-4-yl)-2*H*-pyran-2-one (172) [176b]



Using general procedure 11, with thiazole-4-carbaldehyde (2.52 g, 22.30 mmol), tricyclohexylphosphine (1.88 g, 6.69 mmol) and ethyl buta-2,3-dienoate (0.52 mL, 4.46 mmol) in $CHCl_3$ (45 mL), 6-(thiazol-4-yl)-2*H*-pyran-2-one (**172**) was isolated as a beige solid (0.61 g, 76%).

M.p. 134.5 – 135.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.0 Hz, 1H, C***H***), 7.93 (d, *J* = 2.0 Hz, 1H, C***H***), 7.43 (dd, *J* = 9.5, 6.5 Hz, 1H, C***H***), 7.02 (dd, *J* = 6.5, 0.5 Hz, 1H, C***H***), 6.27 (dd, *J* = 9.5, 1.0 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 156.2, 154.0, 148.7, 144.0, 118.9, 115.0, 102.6; FTIR: 3060 (m), 1711 (s), 1631 (m), 1553 (m), 1490 (w), 1433 (w), 1364 (w), 1305 (m), 1267 (w), 1174 (w), 1119 (m), 1079 (s), 1027 (m), 907 (m), 867 (s), 844 (s), 786 (s); HRMS: m/z [M+H]+ calcd. for $C_8H_6NO_2S$: 180.0114, found: 180.0113. Analysis are in accordance with those reported in the literature.

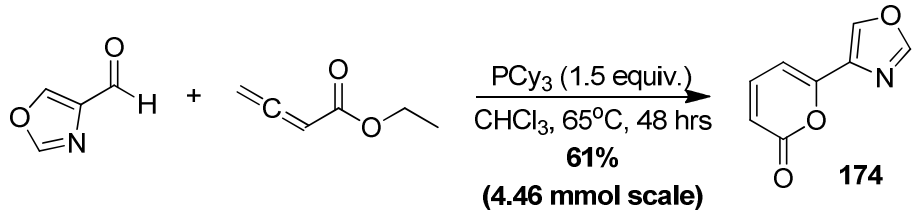
Synthesis of 6-(2-methyloxazol-4-yl)-2*H*-pyran-2-one (173) [176b]



Using general procedure 11 using 1.9 equiv of aldehyde and 1.5 equiv of phosphine, with 2-methyloxazole-4-carbaldehyde (0.940 g, 8.46 mmol), tricyclohexylphosphine (1.88 g, 6.69 mmol) and ethyl buta-2,3-dienoate (0.52 mL, 4.46 mmol) in $CHCl_3$ (45 mL), 6-(2-methyloxazol-4-yl)-2*H*-pyran-2-one (**173**) was isolated as a beige solid (0.29 g, 36%).

M.p. 120.0 – 120.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, C***H***), 7.39 (dd, *J* = 9.5, 6.5 Hz, 1H, C***H***), 6.72 - 6.74 (m, 1H, C***H***), 6.25 (dd, *J* = 9.5, 1.0 Hz, 1H, C***H***), 2.50 (s, 3H, C$\boldsymbol{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 161.3, 154.8, 143.9, 137.8, 134.4, 114.8, 101.5, 14.0; FTIR: 3119 (w), 1723 (s), 1643 (m), 1589 (m), 1535 (m), 1434 (w), 1389 (w), 1291 (m), 1085 (m), 933 (m), 913 (m), 800 (m); HRMS: m/z [M]+ calcd. for $C_9H_7NO_3$: 178.0499, found: 178.0498. Analysis are in accordance with those reported in the literature.

Synthesis of 6-(oxazol-4-yl)-2*H*-pyran-2-one (174)



Using general procedure 11 with 2.3 equiv of aldehyde and 1.5 equiv of phosphine, with oxazole-4-carbaldehyde (0.986 g, 10.16 mmol), tricyclohexylphosphine (1.876 g, 6.69 mmol) and ethyl buta-2,3-dienoate (0.52 mL, 4.46 mmol) in $CHCl_3$ (45 mL), 6-(oxazol-4-yl)-2*H*-pyran-2-one (**174**) was isolated as a white solid (0.45 g, 61%).

M.p. 158.6 - 160.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 1.0 Hz, 1H, C***H***), 7.92 (d, *J* = 1.0 Hz, 1H, C***H***), 7.42 (dd, *J* = 9.5, 7.0 Hz, 1H, C***H***), 6.81 - 6.82 (dd, *J*

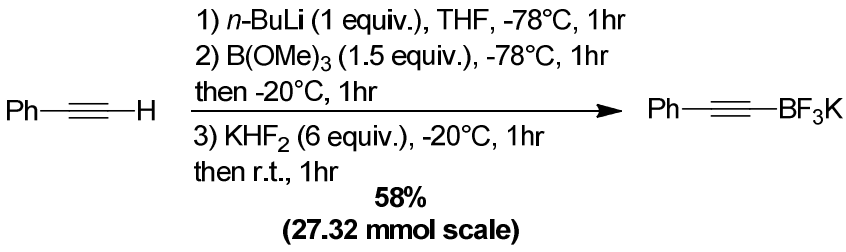
= 7.0, 0.5 Hz, 1H, C***H***), 6.29 (dd, *J* = 9.5, 1.0 Hz, 1H, C***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 154.4, 151.9, 143.7, 138.1, 134.3, 115.2, 101.9; FTIR: 3150 (w), 3096 (w), 1709 (s), 1643 (s), 1573 (m), 1519 (m), 1129 (m), 1090 (m), 1064 (m), 911 (m), 859 (s), 793 (s), 624 (s); HRMS: m/z [M]+ calcd. for $C_8H_5NO_3$: 164.0342, found: 164.0341.

13. Synthesis of potassium alkynyl trifluoroborate salt

General procedure 12: Synthesis of potassium ethynylborate

n-Butyllithium (1.6 M in hexane, 1 equiv.) was added to a solution of alkyne (1 equiv.) in THF (40 mL) under nitrogen at -78 °C. The resulting mixture was stirred for 1 hr at -78 °C before the addition of trimethyl borate (1.5 equiv.). The resulting mixture was then stirred at -78 °C for 1 hr and at -20 °C for another 1 hr. A saturated aqueous solution of potassium hydrogen fluoride (6 equiv.) was then added and the mixture was stirred for 1 hr at -20 °C before to be warmed up to room temperature and stirred another 1 hour. The crude mixture was then concentrated *in vacuo* and the resulting solid was dried under high vaccum, extracted with acetone (50 mL) twice and with warm acetone (50 mL) twice and filtered. The combined filtrate were concentrated and the resulting solid was dried to afford potassium ethynylborate as a white solid.

Synthesis of potassium trifluoro(phenylethynyl)borate [124b]

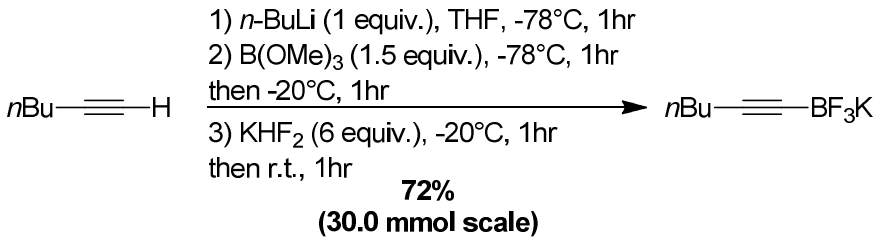


Using general procedure 12, with *n*-butyllithium (1.6 M in hexane, 10.9 mL, 27.32 mmol), ethynylbenzene (3 mL, 27.32 mmol), trimethyl borate (4.57 mL, 40.98 mmol) and potassium hydrogen fluoride (12.80 g, 163.90 mmol) in THF (40 mL),

potassium trifluoro(phenylethynyl)borate was isolated as a white solid (3.308 g, 58%).

M.p. > 230 °C (dec.); ^{1}H NMR (400 MHz, DMSO, 30°C) δ 7.27 – 7.28 (m, 5H, Ar***H***); ^{13}C NMR (101 MHz, DMSO, 30°C) δ 130.9, 128.2, 126.7, 125.5, 89.3; ^{19}F NMR (376 MHz, DMSO, 30 °C) δ -132.09, -131.47; FTIR: 3080 (w), 3019 (w), 2359 (w), 2190 (m), 1486 (m), 1443 (m), 1234 (m), 1072 (m), 977 (m), 756 (s), 690 (s); HRMS: m/z [M-K]$^{-}$ calcd. for $C_8H_5BF_3$: 169.04309, found: 169.04433. Analysis are in accordance with those reported in the literature.

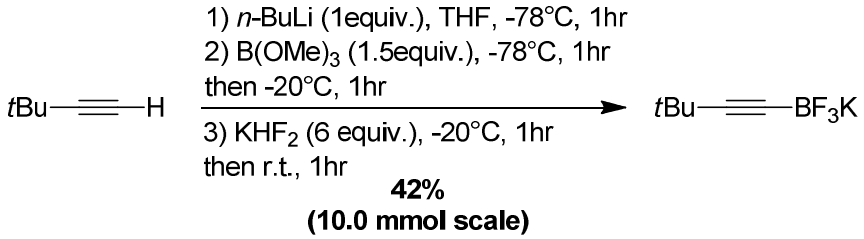
Synthesis of potassium trifluoro(hex-1-yn-1-yl)borate [124b]



Using general procedure 12, with *n*-butyllithium (2.5 M in hexane, 12.0 mL, 30.0 mmol), hex-1-yl (3.45 mL, 30.0 mmol), trimethyl borate (5.0 mL, 45.0 mmol) and potassium hydrogen fluoride (15.06 g, 180.0 mmol) in THF (60 mL), potassium trifluoro(hex-1-yn-1-yl)borate was isolated as a white solid (4.082 g, 72%).

M.p. > 240 °C (dec.); ^{1}H NMR (400 MHz, DMSO) δ 1.95 – 1.99 (m, 2H, C***H***$_2$), 1.34 – 1.31 (m, 4H, C***H***$_2$), 0.83 – 0.87 (m, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, DMSO) δ 31.1, 21.4, 18.5, 13.5; ^{19}F NMR (376 MHz, DMSO, 30 °C) δ -131.05, -130.88; FTIR: 2956 (m), 2931 (m), 2861 (w), 2186 (w), 1701 (s), 1645 (s), 1417 (w), 1363 (w), 1237 (w), 1121 (m), 967 (s); HRMS: m/z [M-K]$^{-}$ calcd. for $C_6H_9BF_3$: 149.0749, found: 149.0755. Analysis are in accordance with those reported in the literature.

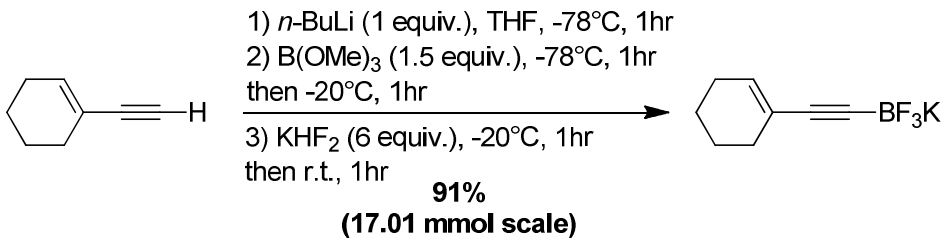
Synthesis of potassium (3,3-dimethylbut-1-yn-1-yl)trifluoroborate [188]



Using general procedure 12, with *n*-butyllithium (2.5 M in hexane, 4.00 mL, 10.0 mmol), 3,3-dimethyl-1-butyne (1.23 mL, 10.0 mmol), trimethyl borate (1.68 mL, 15.0 mmol) and potassium hydrogen fluoride (4.69 g, 60.0 mmol) in THF (20 mL), potassium (3,3-dimethylbut-1-yn-1-yl)trifluoroborate was isolated as a white solid (0.785 g, 42%).

M.p. > 260 °C (dec.); ^{1}H NMR (400 MHz, DMSO) δ 1.09 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, DMSO) δ 31.6, 26.9; ^{19}F NMR (235 MHz, DMSO) δ -130.64; FTIR: 2970 (w), 2193 (w), 1643 (m), 1362 (w), 1255(w), 964 (m), 892 (w); HRMS: m/z [M-K]$^-$ calcd. for $C_6H_9BF_3$: 149.0749, found: 149.0751. Analysis are in accordance with those reported in the literature.

Synthesis of potassium (cyclohexenylethynyl)trifluoroborate

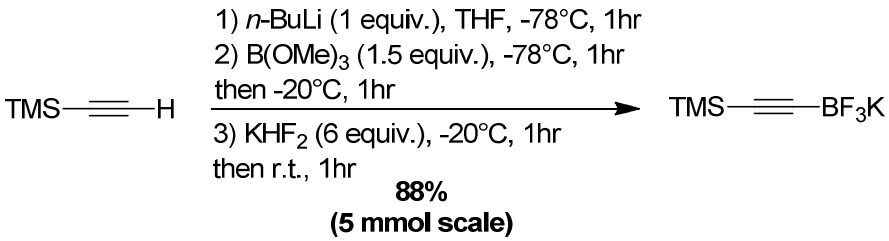


Using general procedure 12, with *n*-butyllithium (1.6 M in hexane, 6.80 mL, 17.01 mmol), 1-ethynylcyclohex-1-ene (2 mL, 17.01 mmol), trimethyl borate (2.84 mL, 25.52 mmol) and potassium hydrogen fluoride (7.97 g, 102.07 mmol) in THF (30 mL), potassium (cyclohexenylethynyl)trifluoroborate was isolated as a white solid (3.266 g, 91%).

M.p. > 165 °C (dec.); ^{1}H NMR (400 MHz, DMSO, 30 °C) δ 5.76 (dt, 1H, C***H***), 1.94 - 2.01 (m, 4H, C***H***$_2$), 1.45 - 1.56 (m, 4H, C***H***$_2$); ^{13}C NMR (101 MHz, DMSO, 30°C) δ 130.1, 129.6, 122.3, 91.3, 29.5, 24.9, 22.1, 21.3; ^{19}F NMR (376 MHz, DMSO,

30°C) δ -131.42; FTIR: 2928 (m), 2855 (w), 2830 (w), 2172 (m), 1635 (s), 1445 (w), 1186 (s), 1051 (s), 1024 (s), 957 (s), 841 (w); HRMS: m/z [M-K]- calcd. for $C_8H_9BF_3$: 173.07518, found: 173.07549.

Synthesis of potassium trifluoro((trimethylsilyl)ethynyl)borate [124b]

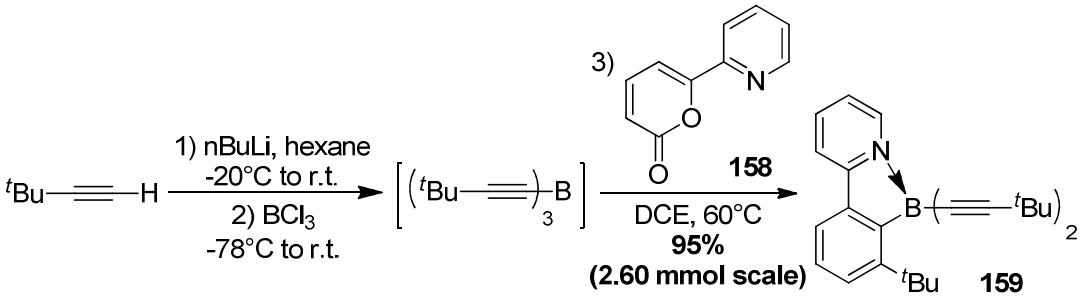


Using general procedure 12, with *n*-butyllithium (1.6 M in hexane, 3.13 mL, 5.00 mmol), ethynyltrimethylsilane (0.71 mL, 5 mmol), trimethyl borate (0.84 mL, 7.50 mmol) and potassium hydrogen fluoride (2.343 g, 30.00 mmol) in THF (20 mL), potassium trifluoro((trimethylsilyl)ethynyl)borate was isolated as a white solid (0.899 g, 88%).

M.p. > 210 °C (dec.); ^{1}H NMR (400 MHz, DMSO, 30 °C) δ 0.05 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, DMSO, 30°C) δ 93.3 (br), 78.6 (m), 0.5; ^{19}F NMR (376 MHz, DMSO, 30°C) δ -132.47 (*J* = 37.6Hz); FTIR: 2957 (m). 2900 (w), 2066 (s), 1644 (s), 1409 (w), 1253 (s), 1026 (s), 842 (m), 759 (w); HRMS: m/z [M-K]- calcd. for $C_5H_9BF_3Si$: 165.05242, found: 165.05264. Analysis are in accordance with those reported in the literature.

14. Mechanistic investigation

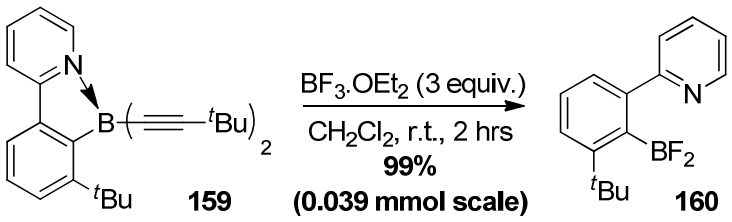
Synthesis of 2-(2-(bis(3,3-dimethylbut-1-yn-1-yl)boryl)-3-(*tert*-butyl)phenyl)pyridine (159)



A solution of *n*-BuLi in hexane (2.4 M, 1.08 mL, 2.60 mmol, 3 equiv.) was added to a solution of *tert*-butylacetylene (0.32 mL, 2.60 mmol, 3 equiv.) in hexane (3 mL) at -20 °C. The resulting mixture was then stirred at -20 °C for 20 min before warming to room temperature and stirring for 1 hour. The reaction mixture was then cooled to -78 °C and trichloroborane (1 M in CH_2Cl_2, 0.87 mL, 0.87 mmol, 1 equiv.) was added. The mixture was allowed to warm to 0 °C over 2 hours, and was then stirred at r.t. for 12 hours. A solution of **158** in DCE (1 mL) was added and the mixture was stirred at r.t. for 20 minutes. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 5% to 25% ethyl acetate in petroleum ether to afford 2-(2-(bis(3,3-dimethylbut-1-yn-1-yl)boryl)-3-(*tert*-butyl)phenyl)pyridine (**159**) (105 mg, 95%) as a white solid.

M.p. 222 – 223°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 6.0 Hz, 1H, Ar***H***), 7.84 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.75 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.55 – 7.58 (m, 2H, Ar***H***), 7.31 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1H, Ar***H***), 7.24 (t, *J* = 7.5 Hz, 1H, Ar***H***), 1.66 (s, 9H, C***H***$_3$), 1.14 (s, 18H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 155.2, 143.3, 140.5, 137.5, 129.6, 126.9, 121.9, 119.9, 117.4, 104.4, 38.0, 32.8, 31.6, 28.0; FTIR: 2962 (s), 2894 (m), 2864 (m), 2178 (w), 1620 (s), 1488 (s), 1455 (s),1360 (m), 1252 (s), 1360 (m), 1039 (m), 860 (s), 762 (s); HRMS: m/z [M+Na]+ calcd. for $C_{27}H_{34}{}^{11}BNNa$: 406.2682, found: 406.2682.

Synthesis of 2-(3-(*tert*-butyl)-2-(difluoroboryl)phenyl)pyridine (160)

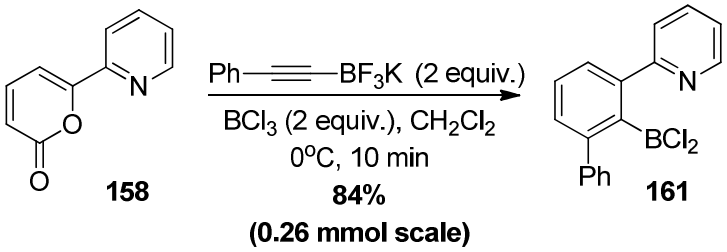


Boron trifluoride etherate in DCE (1 M, 0.12 mL, 0.12 mmol) was added to a mixture of **159** (0.015 g, 0.039 mmol) in dichloromethane (0.5 mL) at r.t. under argon to give a dark brown solution. The resulting mixture was stirred at r.t. for 2 hrs. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated and recrystallised from petroleum ether (3 mL) and CH_2Cl_2 (0.5 mL) to afford 2-(3-(*tert*-butyl)-2-(difluoroboryl)phenyl)pyridine (**160**) (10 mg, 99%) as a beige solid.

M.p. 172 - 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 5.5 Hz, 1H, Ar***H***), 8.09 (m, 1H, Ar***H***), 7.87 (t, *J* = 7.5 Hz, 1H, Ar***H***), 7.56 – 7.61 (m, 2H, Ar***H***), 7.46 (ddd, *J* = 7.5, 5.5, 1.0 Hz, 1H, Ar***H***), 7.38 – 7.32 (m, 1H, Ar***H***), 1.49 (s, 9H, C***H***$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 156.4, 143.4, 141.2, 137.4, 130.1, 128.9, 123.2, 119.6, 117.7, 36.9, 31.7; ^{19}F NMR (235 MHz, $CDCl_3$) δ -152.3 (d, *J* = 65.0 Hz); FTIR: 2947 (m), 2910 (m), 2867 (m), 1621 (m), 1467 (m), 1363 (w), 1160 (m), 1074 (s), 998 (m), 795 (m), 758 (s); HRMS: m/z [M]+ calcd. for $C_{15}H_{16}{}^{11}BF_2N$: 259.1344, found: 259.1333.

15. Lewis Base directed cycloaddition of 2-pyrones with alkynylboranes

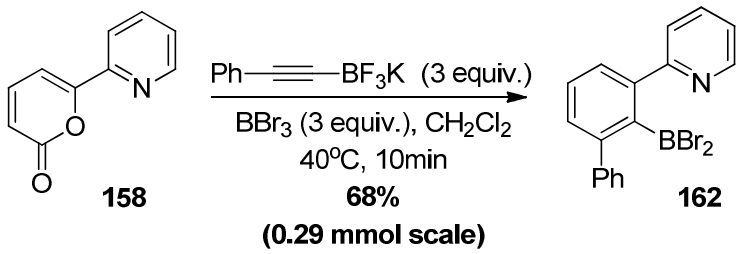
Synthesis of 2-(2-(dichloroboryl)-[1,1'-biphenyl]-3-yl)pyridine (161)



Trichloroborane (1 M in CH_2Cl_2) (0.52 mL, 0.52 mmol) was added to a mixture of **158** (0.045 g, 0.26 mmol) and potassium trifluoro(phenylethynyl)borate (0.108 g, 0.52 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C under nitrogen to give an orange solution. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(2-(dichloroboryl)-[1,1'-biphenyl]-3-yl)pyridine (**161**) (69 mg, 84%) as a beige solid.

M.p. 250 °C (dec.); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.80 (d, *J* = 6.0 Hz, 1H, Ar***H***), 8.17 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.97 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.84 – 7.76 (m, 3H, Ar***H***), 7.60 – 7.35 (m, 6H, Ar***H***); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 146.3, 143.7, 143.2, 141.5, 135.1, 134.3, 129.5, 129.3, 128.0, 127.5, 123.7, 121.0, 118.3; FTIR: 2918 (w), 1617 (w), 1492 (m), 1151 (m), 1073 (m), 857 (m), 822 (m), 746 (s), 689 (s); HRMS: m/z [M]+ calcd. for $C_{17}H_{12}{}^{11}B^{35}Cl_2N$: 311.0440, found: 311.0448.

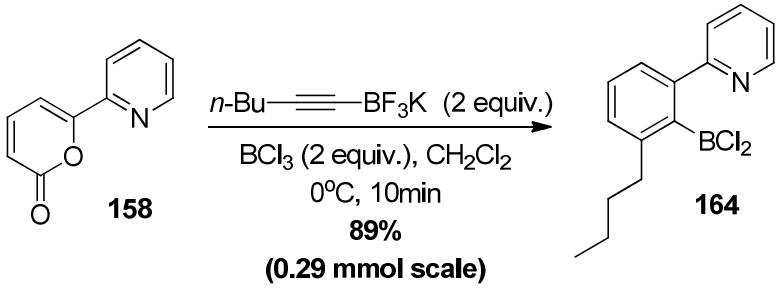
Synthesis of 2-(2-(dibromoboryl)-[1,1'-biphenyl]-3-yl)pyridine (162)



Boron tribromide (1 M in CH_2Cl_2) (0.86 mL, 0.86 mmol) was added to a mixture of **158** (0.050 g, 0.29 mmol) and potassium trifluoro(phenylethynyl)borate (0.163 g, 0.86 mmol) in dichloromethane (2.9 mL) at 40 °C under argon to give a dark brown solution. The resulting mixture was stirred at 40 °C for 10 min before addition of an aqueous saturated solution of $NaHCO_3$ (10 mL). The mixture was then extracted with CH_2Cl_2 (3x 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to afford a dark residue. The crude product was then recrystallized from CH_2Cl_2 (0.5 mL) and petroleum ether (3 mL) to afford 2-(2-(dibromoboryl)-[1,1'-biphenyl]-3-yl)pyridine (**162**) (79 mg, 68%) as a beige solid.

M.p. 256 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 6.0 Hz, 1H, Ar***H***), 8.16 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.96 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.84 – 7.78 (m, 3H, Ar***H***), 7.58 – 7.39 (m, 6H, Ar***H***); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 146.5, 144.3, 143.7, 141.3, 134.6, 134.2, 129.7, 129.3, 127.8, 127.5, 123.8, 121.2, 118.5; FTIR: 2923 (w), 2855 (w), 1623 (m), 1488 (s), 1454 (m), 1160 (m), 1079 (s), 755 (s), 697 (m), 650 (s); HRMS: m/z [M+Na]+ calcd. for $C_{17}H_{13}{}^{11}BN^{79}Br_2Na$: 422.9405, found: 422.9409.

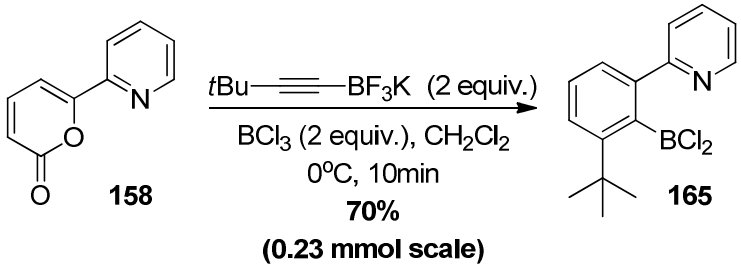
Synthesis of 2-(3-butyl-2-(dichloroboryl)phenyl)pyridine (164)



Trichloroborane (1 M in CH_2Cl_2) (0.58 mL, 0.58 mmol) was added to a mixture of **158** (0.050 g, 0.29 mmol) and potassium trifluoro(*n*-butylethynyl)borate (0.109 g, 0.58 mmol) in CH_2Cl_2 (2.9 mL) at 0 °C under nitrogen to give an orange solution. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) was then added. The product was extracted with CH_2Cl_2 (3x 10mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(3-butyl-2-(dichloroboryl)phenyl)pyridine (**164**) (75 mg, 89%) as a beige solid.

M.p. 175 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 6.0 Hz, 1H, Ar***H***), 8.09 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.86 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.57 (dd, *J* = 7.0, 1.5 Hz, 1H, Ar***H***), 7.50 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1H, Ar***H***), 7.38 - 7.33 (m, 2H, Ar***H***), 3.00 - 3.04 (m, 2H, C***H***$_2$), 1.74 - 1.79 (m, 2H, C***H***$_2$), 1.48 - 1.54 (m, 2H, C***H***$_2$), 1.00 (t, *J* = 7.5 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 146.9, 143.7, 143.0, 134.4, 133.1, 129.2, 123.4, 119.4, 118.3, 33.5, 33.3, 23.0, 14.2; FTIR: 2927 (m), 2859 (m), 2357 (w), 1625 (m), 1483 (m), 1468 (m), 1160 (m), 1081 (m), 880 (m), 861 (m), 811 (m), 780 (s), 757 (s), 729 (s), 681 (s), 647 (m); HRMS: m/z [M]+ calcd. for $C_{15}H_{16}{}^{11}B^{35}Cl_2N$: 291.0753, found: 291.0783.

Synthesis of 2-(3-(*tert*-butyl)-2-(dichloroboryl)phenyl)pyridine (165)

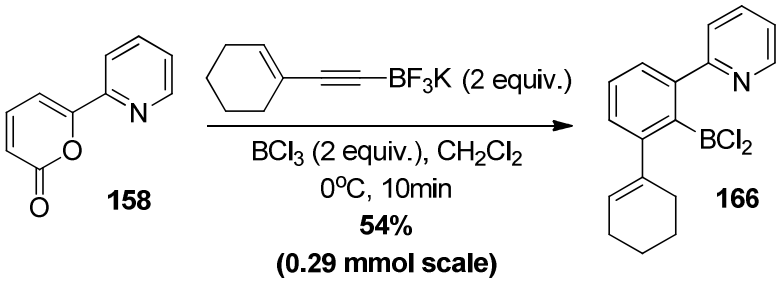


Trichloroborane (1 M in CH_2Cl_2) (0.46 mL, 0.46 mmol) was added to a mixture of **158** (0.040 g, 0.23 mmol) and potassium trifluoro(*tert*-butylethynyl)borate (0.087 g, 0.46 mmol) in dichloromethane (2.3 mL) at 0 °C under nitrogen to give an orange solution. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) was then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via

flash column chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in petroleum ether to afford 2-(3-(*tert*-butyl)-2-(dichloroboryl)phenyl)pyridine (**165**) (47 mg, 70%) as a white solid.

M.p. 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 6.0 Hz, 1H, Ar***H***), 8.12 (td, *J* = 8.0, 1.5 Hz, 1H, Ar***H***), 7.91 (d, *J* = 8.0 Hz, 1H, Ar***H***), 7.66 – 7.70 (m, 2H, Ar***H***), 7.56 – 7.51 (m, 1H, Ar***H***), 7.41 (t, *J* = 8.0 Hz, 1H, Ar***H***), 1.61 (s, 9H, C***H***$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 155.6, 143.4, 142.8, 135.9, 131.9, 129.2, 123.4, 120.3, 117.7, 38.0, 32.7; FTIR: 3378 (w), 2921 (w), 2857 (w), 1455 (m), 1069 (w), 846 (m), 809 (m), 758 (s), 681 (s); HRMS: m/z [M]+ calcd. for $C_{15}H_{16}{}^{11}B^{35}Cl_2N$: 291.0753, found: 291.0748.

Synthesis of 2-(3-cyclohexenyl-2-(dichloroboryl)phenyl)pyridine (166)

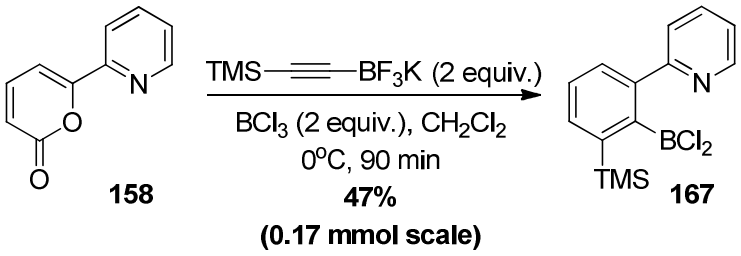


Trichloroborane (1 M in CH_2Cl_2) (0.58 mL, 0.58 mmol) was added to a mixture of **158** (0.05 g, 0.29 mmol) and potassium trifluoro(cyclohexenylethynyl)borate (0.122 g, 0.58 mmol) in dichloromethane (2.9 mL) at 0 °C under nitrogen to give an brown solution. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(3-cyclohexenyl-2-(dichloroboryl)phenyl)pyridine (**166**) (50 mg, 54%) as a beige solid.

M.p. 268 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 6.0 Hz, 1H, Ar***H***), 8.10 - 8.12 (m, 1H, Ar***H***), 7.89 - 7.91 (m, 1H, Ar***H***), 7.64 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.53 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1H, Ar***H***), 7.34 - 7.40 (m, 2H, Ar***H***), 6.02 (tt, *J* = 3.5, 1.5 Hz, 1H, C***H***), 2.46 (ddt, *J* = 6.0, 5.0, 2.0 Hz, 2H, C***H***$_2$), 2.24 (td, *J* = 6.0, 3.5 Hz, 2H, C***H***$_2$), 1.79 - 1.85 (m, 2H, C***H***$_2$), 1.73 (m, 2H, C***H***$_2$); ^{13}C NMR (101

MHz, $CDCl_3$) δ 143.5, 143.2, 132.7, 129.0, 127.7, 123.4, 120.2, 118,1; FTIR: 2923 (w), 1624 (m), 1490 (m), 1167 (m), 1141 (m), 1080 (m), 867 (m), 817 (m), 758 (s), 748 (m), 688 (s); HRMS: m/z [M]+ calcd. for $C_{17}H_{16}{}^{11}B^{35}Cl_2N$: 315.0753, found: 315.0758.

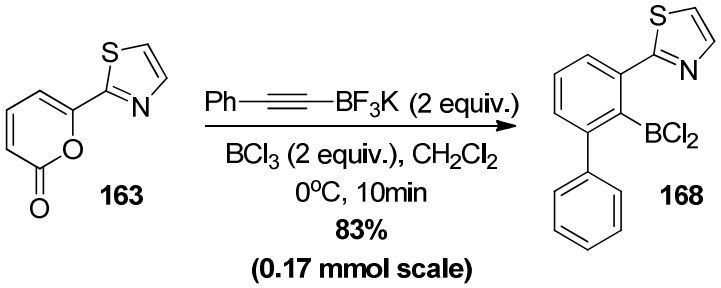
Synthesis of 2-(2-(dichloroboryl)-3-(trimethylsilyl)phenyl)pyridine (167)



Trichloroborane (1 M in CH_2Cl_2) (0.35 mL, 0.35 mmol) was added to a mixture of **158** (0.03 g, 0.17 mmol) and potassium trifluoro(trimethylsilylethynyl)borate (0.071 g, 0.35 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C under nitrogen to give a deep red solution. The resulting mixture was stirred at 0 °C for 90 minutes. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(2-(dichloroboryl)-3-(trimethylsilyl)phenyl)pyridine (**167**) (25 mg, 47%) as a white solid.

M.p. 250 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dt, 1H, Ar***H***), 8.13 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar***H***), 7.90 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar***H***), 7.79 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.75 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.52 – 7.55 (m, 1H, Ar***H***), 7.40 (t, *J* = 7.5 Hz, 1H, Ar***H***), 0.49 (s, 9H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 144.6, 143.4, 142.8, 139.3, 133.8, 127.8, 123.3, 122.3, 117.8, 1.0; FTIR: 2948 (w), 2896 (w), 2359 (w), 1489 (w), 1235 (w), 863 (m), 834 (s), 742 (s), 679 (s), 559 (m); HRMS: m/z [M-CH_3]+ calcd. for $C_{14}H_{16}{}^{11}B^{35}Cl_2NSi$: 292.0287, found: 292.0307.

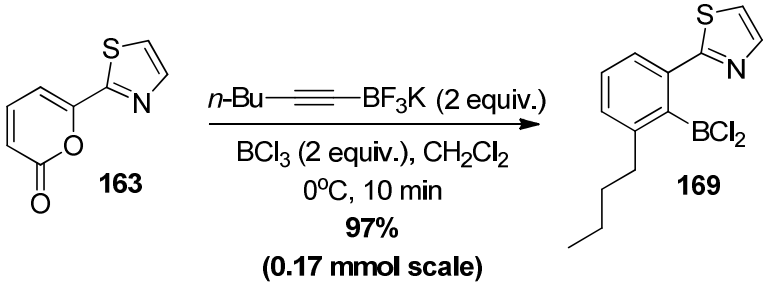
Synthesis of 2-(2-(dichloroboryl)biphenyl-3-yl)thiazole (168)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **163** (30 mg, 0.17 mmol) and potassium trifluoro(phenylethynyl)borate (69.7 mg, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(2-(dichloroboryl)biphenyl-3-yl)thiazole (**168**) (44 mg, 83%) as a beige solid.

M.p. 200 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.76 – 7.80 (m, 2H, Ar***H***), 7.64 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.55 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.44 - 7.50 (m, 4H, Ar***H***), 7.39 (s, 1H, Ar***H***); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.8, 146.3, 140.9, 134.7, 133.6, 131.8, 129.5, 129.3, 128.0, 127.6, 121.6, 121.2; FTIR: 3129 (w), 1631 (w), 1466 (w), 1331 (w), 1195 (w), 947 (w), 854 (m), 810 (s), 772 (m), 757 (s), 734 (m), 691 (s), 541 (w); HRMS: m/z [M]+ calcd. for $C_{15}H_{10}{}^{11}B^{35}Cl_2NS$: 317.0004, found: 316.9976.

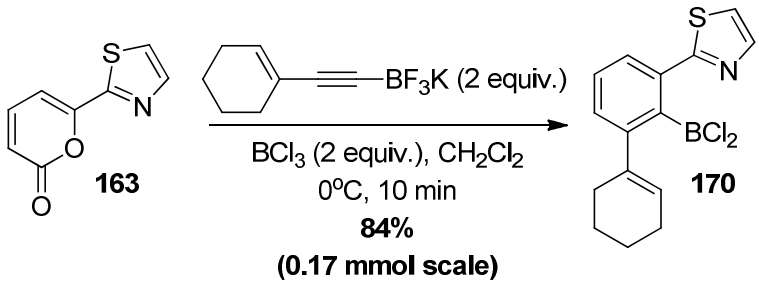
Synthesis of 2-(3-butyl-2-(dichloroboryl)phenyl)thiazole (169)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **163** (30 mg, 0.17 mmol) and potassium trifluoro(*n*-butylethynyl)borate (63.0 mg, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(3-butyl-2-(dichloroboryl)phenyl)thiazole (**169**) (48 mg, 97%) as a white solid.

M.p. 163.7 – 164.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.44 - 7.47 (m, 2H, Ar***H***), 7.39 (d, *J* = 7.0 Hz, 1H, Ar***H***), 7.33 (t, *J* = 7.5 Hz, 1H, Ar***H***), 2.97 - 3.01 (m, 2H, C***H***$_2$), 1.71 - 1.78 (m, 2H, C***H***$_2$), 1.47 - 1.50 (m, 2H, C***H***$_2$), 0.98 (t, *J* = 7.5 Hz, 3H, C***H***$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.7, 147.0, 133.7, 133.5, 131.2, 129.1, 120.8, 120.0, 33.2 (x2), 23.0, 14.2; FTIR: 2951 (m), 2928 (m), 2860 (m), 1643 (s), 1515 (m), 1469 (m), 1405 (m), 1338 (m), 1246 (w), 1186 (m), 1151 (m), 1096 (w), 957 (m), 855 (m), 800 (s), 773 (m), 704 (s); HRMS: m/z [M-Cl]+ calcd. for $C_{13}H_{14}{}^{11}B^{35}Cl_2NS$: 262.0629, found: 262.0623.

Synthesis of 2-(3-cyclohexenyl-2-(dichloroboryl)phenyl)thiazole (170)

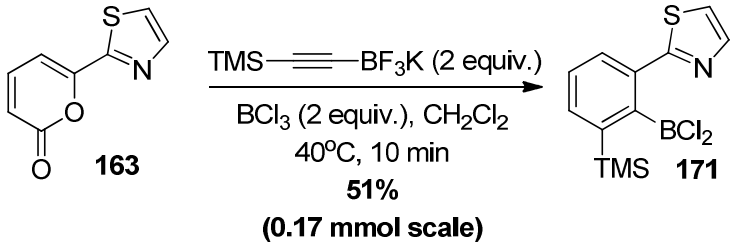


Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **163** (30 mg, 0.17 mmol) and potassium trifluoro(cyclohexenylethynyl)borate (71.0 mg, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford

2-(3-cyclohexenyl-2-(dichloroboryl)phenyl)thiazole (**170**) (45 mg, 84%) as a white solid.

M.p. 225 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.51 (dd, *J* = 5.0, 3.5 Hz, 1H, Ar***H***), 7.43 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.34 - 7.36 (m, 2H, Ar***H***), 6.00 – 6.03 (m, 1H, C***H***), 2.43 - 2.45 (m, 2H, C***H***$_2$), 2.23 (m, 2H, C***H***$_2$), 1.80 - 1.83 (m, 2H, C***H***$_2$), 1.70 - 1.73 (m, 2H, C***H***$_2$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.0, 149.2, 137.1, 133.6, 133.3, 131.7, 128.9, 128.1, 120.8, 30.2, 25.6, 23.3, 22.2; FTIR: 2922 (w), 1513 (w), 1330 (w), 1152 (w), 947 (w), 854 (w), 805 (s), 770 (m), 695 (s); HRMS: m/z [M]+ calcd. for $C_{15}H_{14}{}^{11}B^{35}Cl_2NS$: 321.0317, found: 321.0303.

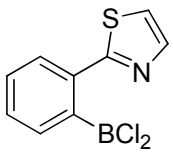
Synthesis of 2-(2-(dichloroboryl)-3-(trimethylsilyl)phenyl)thiazole (171)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **163** (30 mg, 0.17 mmol) and potassium trifluoro(trimethylsilylethynyl)borate (0.068 g, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 2-(2-(dichloroboryl)-3-(trimethylsilyl)phenyl)thiazole (**171**) (27 mg, 51%) as a white solid.

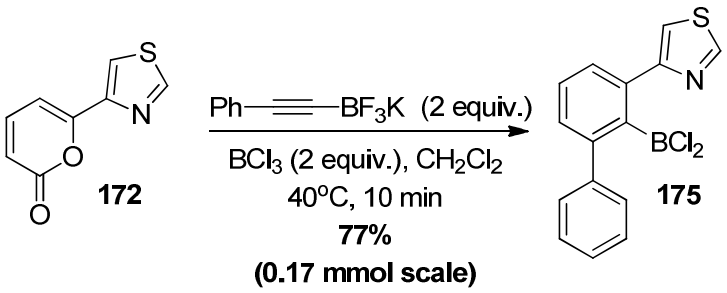
M.p. 278.4 – 279.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.80 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.61 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.43 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.37 (t, *J* = 7.5 Hz, 1H, Ar***H***), 0.48 (s, 9H, C***H***$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.3, 145.2, 139.7, 133.6, 131.0, 127.9, 123.0, 120.7, 1.0; FTIR: 3125 (w), 3102 (m), 2949 (m), 2896 (w), 2360 (w), 1510 (m), 1406 (m), 1329 (m),

1237 (m), 1145 (m), 1045 (m), 837 (s), 796 (s), 788 (s), 776 (s), 750 (s), 703 (s); HRMS: m/z [M-CH_3]+ calcd. for $C_{12}H_{14}{}^{11}B^{35}Cl_2NSSi$: 297.9852, found: 297.9855.



M.p. 220 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.81 (d, *J* = 7.5 Hz, 1H, Ar***H***), 7.63 (d, *J* = 7.5 Hz, 1H, Ar***H***), 7.57 (td, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.48 (d, *J* = 3.5 Hz, 1H, Ar***H***), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H, Ar***H***); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.6, 133.7, 133.6, 131.2, 130.5, 128.8, 122.4, 121.2; FTIR: 2094 (m), 1665 (s), 1332 (w), 1154 (w), 948 (w), 761 (w), 693 (w); HRMS: m/z [M]+ calcd. for $C_9H_6{}^{11}B^{35}Cl_2NS$: 240.9691, found: 240.9697.

Synthesis of 4-(2-(dichloroboryl)biphenyl-3-yl)thiazole (175)

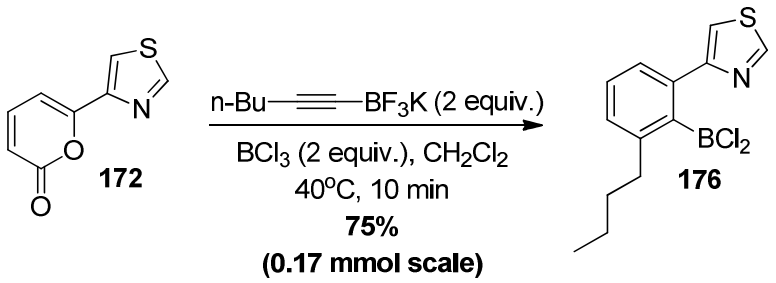


Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **172** (0.03 g, 0.17 mmol) and potassium trifluoro(phenylethynyl)borate (0.070 g, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(2-(dichloroboryl)biphenyl-3-yl)thiazole (**175**) (41 mg, 77%) as a white solid.

M.p. 266.5 – 268.8 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.74 - 7.76 (dd, *J* = 5.0, 3.0 Hz, 2H, Ar***H***), 7.59 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar***H***), 7.38 - 7.47 (m, 6H, Ar***H***); ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.7, 153.1, 146.9, 141.5, 132.8, 131.7, 129.6, 129.3, 127.9, 127.4, 120.4, 108.3; FTIR: 3101 (w), 3022

(w), 1643 (w), 1463 (w), 1067 (m), 906 (m), 886 (m), 856 (m), 803 (s), 763 (m), 742 (s), 710 (m), 665 (m); HRMS: m/z [M]+ calcd. for $C_{15}H_{10}{}^{11}B^{35}Cl_2NS$: 317.0004, found: 317.0023.

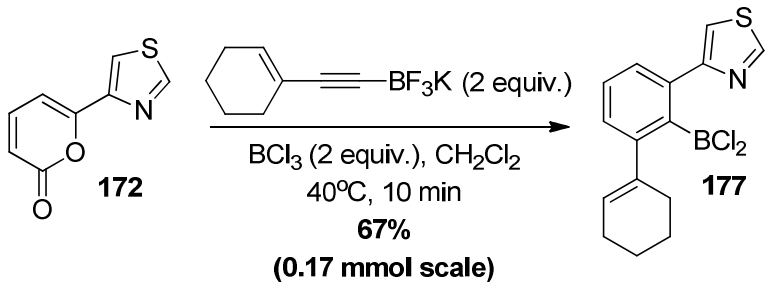
Synthesis of 4-(3-butyl-2-(dichloroboryl)phenyl)thiazole (176)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **172** (0.03 g, 0.17 mmol) and potassium trifluoro(n-butylethynyl)borate (0.063 g, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-butyl-2-(dichloroboryl)phenyl)thiazole (**176**) (37 mg, 75%) as a white solid.

M.p. 193 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.39 – 7.41 (m, 2H, Ar***H***), 7.29 - 7.34 (m, 2H, Ar***H***), 2.95 – 2.99 (m, 2H, C***H***$_2$), 1.71 – 1.78 (m, 2H, C***H***$_2$), 1.47 - 1.50 (m, 2H, C***H***$_2$), 0.98 (t, *J* = 7.5 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 153.0, 147.4, 131.4, 131.2, 129.2, 118.8, 108.0, 33.4, 33.3, 23.0, 14.2; FTIR: 3094 (w), 2952 (w), 2924 (w), 1475 (w), 1190 (w), 1150 (m), 1026 (m), 858 (m), 803 (s), 742 (s), 719 (s), 672 (s); HRMS: m/z [M-Cl]+ calcd. for $C_{13}H_{14}{}^{11}B^{35}Cl_2NS$: 262.0629, found: 262.0629.

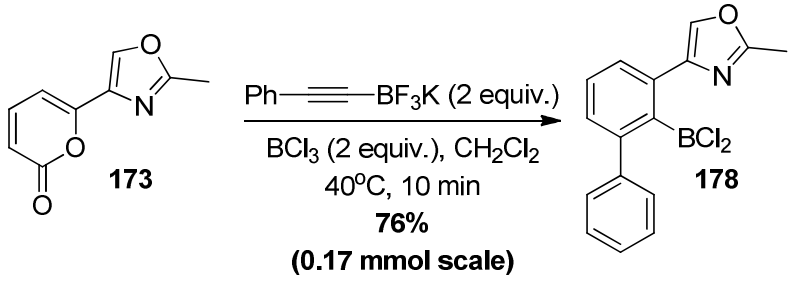
Synthesis of 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)thiazole (177)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.33 mmol) was added to a mixture of **172** (0.03 g, 0.17 mmol) and potassium trifluoro(cyclohexenylethynyl)borate (0.071 g, 0.33 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)thiazole (**177**) (36 mg, 67%) as a white solid.

M.p. 200 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.45 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.39 (d, *J* = 2.0 Hz, 1H, Ar***H***), 7.33 (t, *J* = 7.5 Hz, 1H, Ar***H***), 7.23 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 5.95 – 5.98 (m, 1H, C***H***), 2.40 – 2.44 (m, 2H, C***H***$_2$), 2.20 – 2.24 (m, 2H, C***H***$_2$), 1.80 - 1.82 (m, 2H, C***H***$_2$), 1.70 - 1.73 (m, 2H, C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 152.9, 149.8, 137.5, 131.6, 131.1, 129.0, 127.5, 119.5, 107.9, 30.5, 25.6, 23.4, 22.2; FTIR: 3108 (w), 2919 (w), 2831 (w), 1471 (w), 1151 (m), 1063 (w), 861 (m), 804 (s), 746 (s), 715 (s), 677 (m); HRMS: m/z [M]+ calcd. for $C_{15}H_{14}{}^{11}B^{35}Cl_2NS$: 321.0317, found: 321.0311.

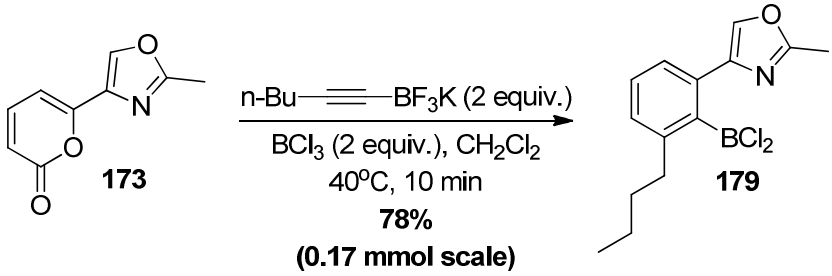
Synthesis of 4-(2-(dichloroboryl)biphenyl-3-yl)-2-methyloxazole (178)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.34 mmol) was added to a mixture of **173** (0.03 g, 0.17 mmol) and potassium trifluoro(phenylethynyl)borate (0.070 g, 0.34 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(2-(dichloroboryl)biphenyl-3-yl)-2-methyloxazole (**178**) (41 mg, 76%) as a white solid.

M.p. 260 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H, Ar***H***), 7.71 – 7.73 (m, 2H, Ar***H***), 7.42 - 7.45 (m, 4H, Ar***H***), 7.37 - 7.39 (m, 2H, Ar***H***), 2.89 (s, 3H, C***H***$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.5, 146.8, 141.6, 141.1, 132.5, 129.8, 129.7, 129.2, 128.1, 127.8, 127.3, 120.9, 12.8; FTIR: 2104 (w), 1643 (s), 1284 (w), 1146 (w), 1067 (w), 855 (w), 818 (w), 749 (w); HRMS: m/z [M]+ calcd. for $C_{16}H_{12}{}^{11}B^{35}Cl_2NO$: 315.0389, found: 315.0406.

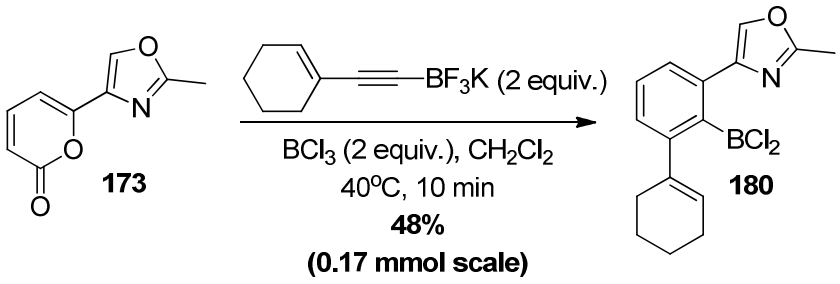
Synthesis of 4-(3-butyl-2-(dichloroboryl)phenyl)-2-methyloxazole (179)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.34 mmol) was added to a mixture of **173** (0.03 g, 0.17 mmol) and potassium trifluoro(*n*-butylethynyl)borate (0.064 g, 0.34 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-butyl-2-(dichloroboryl)phenyl)-2-methyloxazole (**179**) (39 mg, 78%) as a white solid.

M.p. 211.2 – 212.8 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar***H***), 7.27 (s, 3H, Ar***H***), 2.94 - 2.98 (m, 2H, C***H***$_2$), 2.93 (s, 3H, C***H***$_3$), 1.70 – 1.78 (m, 2H, C***H***$_2$), 1.46 - 1.5 (m, 2H, C***H***$_2$), 0.98 (t, *J* = 7.5 Hz, 3H, C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 147.2, 141.6, 131.1, 129.6, 129.1, 127.5, 119.3, 33.4, 33.2, 23.1, 14.2, 12.8; FTIR: 2930 (w), 2860 (w), 1611 (w), 1465 (w), 1389 (w), 1148 (m), 1064 (m), 856 (m), 808 (m), 753 (s), 722 (s); HRMS: m/z [M]+ calcd. for $C_{14}H_{16}{}^{11}B^{35}Cl_2NO$: 295.0702, found: 295.0692.

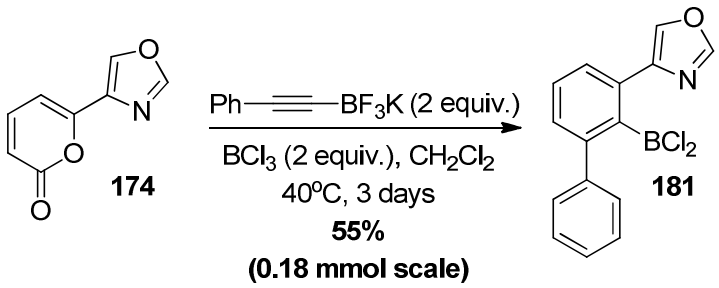
Synthesis of 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)-2-methyloxazole (180)



Trichloroborane (1 M in CH_2Cl_2) (0.34 mL, 0.34 mmol) was added to a mixture of **173** (0.03 g, 0.17 mmol) and potassium trifluoro(cyclohexenylethynyl)borate (0.072 g, 0.34 mmol) in CH_2Cl_2 (1.7 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 10 min. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)-2-methyloxazole (**180**) (26 mg, 48%) as a white solid.

M.p. 250 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ar***H***), 7.28 - 7.32 (m, 2H, Ar***H***), 7.18 – 7.21 (m, 1H, Ar***H***), 5.92 – 5.94 (m, 1H, C***H***), 2.91 (s, 3H, C***H***$_3$), 2.39 - 2.40 (m, 2H, C***H***$_2$), 2.19 – 2.24 (m, 2H, C***H***$_2$), 1.77 – 1.83 (m, 2H, C***H***$_2$), 1.68 – 1.74 (m, 2H, C***H***$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 149.7, 141.3, 137.4, 130.8, 129.5, 128.9, 128.0, 127.5, 120.1, 30.6, 25.5, 23.3, 22.2, 12.8; FTIR: 2925 (w), 2062 (w), 1633 (s), 1392 (w), 1148 (w), 1061 (w), 811 (w), 752 (w), 723 (w), 682 (w); HRMS: m/z [M]+ calcd. for $C_{16}H_{16}{}^{11}B^{35}Cl_2NO$: 319.0702, found: 319.0721.

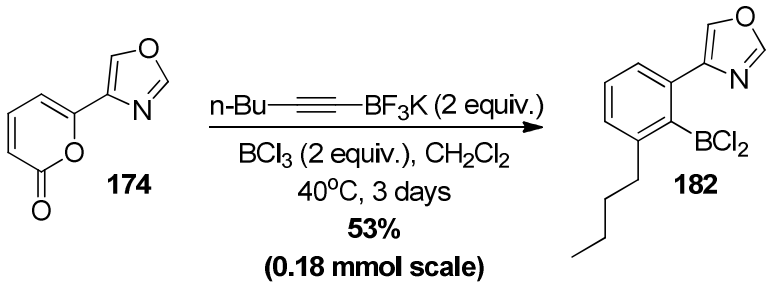
Synthesis of 4-(2-(dichloroboryl)-[1,1'-biphenyl]-3-yl)oxazole (181)



Trichloroborane (1 M in CH_2Cl_2) (0.37 mL, 0.37 mmol) was added to **174** (0.03 g, 0.18 mmol) and potassium trifluoro(phenylethynyl)borate (0.076 g, 0.37 mmol) in CH_2Cl_2 (1.8 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 3 days. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(2-(dichloroboryl)-[1,1'-biphenyl]-3-yl)oxazole (**181**) (31 mg, 55%) as a white solid.

M.p. 230 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, Ar***H***), 7.97 (s, 1H, Ar***H***), 7.70 – 7.72 (m, 2H, Ar***H***), 7.52 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar***H***), 7.37 – 7.48 (m, 5H, Ar***H***); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 146.8, 141.4, 141.1, 132.9, 131.4, 129.6, 129.4, 127.8, 127.6, 127.4, 121.2; FTIR: 3121 (w), 3060 (w), 1174 (m), 1147 (m), 850 (m), 816 (m), 755 (s), 721 (s), 681 (s); HRMS: m/z [M]+ calcd. for $C_{15}H_{10}{}^{11}B^{35}Cl_2NO$: 301.0233, found: 301.0226.

Synthesis of 4-(3-butyl-2-(dichloroboryl)phenyl)oxazole (182)

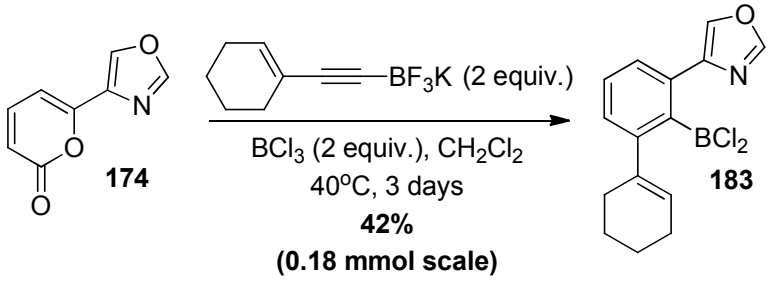


Trichloroborane (1 M in CH_2Cl_2) (0.37 mL, 0.37 mmol) was added to **174** (0.03 g, 0.18 mmol) and potassium trifluoro(*n*-butylethynyl)borate (0.069 g, 0.37 mmol) in

CH_2Cl_2 (1.8 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 3 days. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-butyl-2-(dichloroboryl)phenyl)oxazole (**182**) (27 mg, 53%) as a white solid.

M.p. 180 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 0.5 Hz, 1H, Ar***H***), 7.89 (d, *J* = 0.5 Hz, 1H, Ar***H***), 7.29 - 7.33 (m, 3H, Ar***H***), 2.94 – 2.98 (m, 2H, C***H***$_2$), 1.70 – 1.77 (m, 2H, C***H***$_2$), 1.44 – 1.53 (m, 2H, C***H***$_2$), 0.98 (t, *J* = 7.5 Hz, 3H, C***H***$_3$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 149.8, 147.3, 141.6, 131.5, 131.2, 129.3, 127.0, 119.5, 33.3, 33.2, 23.0, 14.2; FTIR: 3124 (w), 2959 (w), 2928 (w), 2858 (w), 2383 (w), 1465 (w), 1344 (w), 1224 (w), 1150 (m), 1059 (w), 863 (s), 842 (m), 803 (s), 761 (s), 717 (s); HRMS: m/z [M]+ calcd. for $C_{13}H_{14}{}^{11}B^{35}Cl_2NO$: 281.0545, found: 281.0526.

Synthesis of 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)oxazole (183)



Trichloroborane (1 M in CH_2Cl_2) (0.37 mL, 0.37 mmol) was added to **174** (0.03 g, 0.18 mmol) and potassium trifluoro(cyclohexenylethynyl)borate (0.078 g, 0.37 mmol) in CH_2Cl_2 (1.8 mL) at 40 °C under nitrogen. The resulting mixture was stirred at 40 °C for 3 days. CH_2Cl_2 (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) were then added. The product was extracted with CH_2Cl_2 (3x 10 mL), dried over $MgSO_4$, filtered, concentrated and purified via flash column chromatography on silica gel eluting with a gradient from 15% to 50% ethyl acetate in heptane to afford 4-(3-cyclohexenyl-2-(dichloroboryl)phenyl)oxazole (**183**) (24 mg, 42%) as a white solid.

M.p. 150 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 0.5 Hz, 1H, Ar***H***), 7.90 (d, *J* = 0.5 Hz, 1H, Ar***H***), 7.31 - 7.38 (m, 2H, Ar***H***), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar***H***), 5.91 – 5.94 (m, 1H, C***H***), 2.38 - 2.40 (m, 2H, C$\boldsymbol{H}_2$), 2.19 – 2.24 (m, 2H, C$\boldsymbol{H}_2$), 1.79 - 1.81 (m, 2H, C$\boldsymbol{H}_2$), 1.70 - 1.73 (m, 2H, C$\boldsymbol{H}_2$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 149.8, 141.3, 137.3, 131.3, 131.2, 130.2, 129.1, 127.6, 127.5, 120.3, 30.6, 25.5, 23.3, 22.2; FTIR: 3135 (m), 2923 (m), 2853 (w), 2348 (w), 1443 (w), 1346 (w), 1227 (w), 1149 (m), 1086 (w), 844 (m), 807 (m), 761 (s), 719 (s), 674 (s), 586 (w); HRMS: m/z [M]+ calcd. for $C_{15}H_{14}{}^{11}B^{35}Cl_2NO$: 305.0545, found: 305.0555.

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