The University Of Sheffield.

Ynone Trifluoroborates: Valuable Intermediates for the Synthesis of Heteroaromatic Compounds

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“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Curie (1867 – 1934)

Abstract

Heteroaromatic scaffolds are at the core of Organic Chemistry, not only are they the base of a high number of biologically active molecules, but they are also invaluable in the daily practice of chemistry. Considering those high value targets, there are numerous synthetic routes for their synthesis.

Since their discovery, boronates have demonstrated a very broad range of applications. On heteroaromatic substrates, the boron handle is usually installed after the ring is formed, through a multiple-step sequence. We became interested in the trifluoroborate class for they possess an advantageous balance of stability *versus* reactivity. Indeed, it has been shown that they are as, or more, reactive than boronic acid and ester derivatives. Furthermore, it has been demonstrated that under certain conditions, reactions could be carried out on other functionalities on the molecule while leaving the trifluoroborate handle intact.

Herein, we first report the successful scope extension of a newly discovered class of compounds: ynone trifluoroborates. Next, we will show that such compounds are highly versatile, as we could carry out condensation reactions with various reagents in order to achieve the synthesis of novel heteroaromatic substrates bearing a readily installed trifluoroborate handle. We have investigated three types of heteroaromatics: pyrazoles, thiophenes and pyrimidines which are reported here. As part of this thesis, a prolong stay in our industrial partner, Sanofi Deutschland in Frankfurt, was carried out. Having access to the entire facility, we decided to synthesise entire libraries of pyrazole- and thiophene-based compounds with via automated processes. Finally, the substrates isolated were submitted for early ADME measurement to assess their potential as drug candidates.

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My first thanks go of course to you Joe. I'm very grateful for this amazing opportunity that you have entrusted me with. Thank you for your guidance with those trifluoroborates and for giving me this project. I hope all and all it has been a productive 3 years.

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Abbreviations

ADME Absorption, Distribution, Metabolism and Excretion

Alk Alkyl

app Apparent

Ar Aryl

$B(OMe)_3$ / $B(O^iPr)_3$ Trimethoxyborane / Triisopropoxyborane

$B(O^iPr)$Pin 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Bdan Naphthalene boronamide

BF_3 ($.OEt_2$) Boron trifluoride (etherate salt) / BCl_3 Boron trichloride

Bn Benzyl

Bu Butyl

^{n}BuLi ^{n}Butyl lithium

$^n Bu_4NOH$ / $^n Bu_4NI$ Tetrabutylammonium hydroxide / Tetrabutylammonium iodide

^{t}BuOH, ^{t}BuOK / *tert*-butanol, *tert*-butoxide

°C Degrees Celsius

Caco-2 Human colon adenocarcinoma cells

cat. Catalyst

CCl_4 Carbon tetrachloride

CF_3 Trifluoromethyl

$CFCl_3$ Trichlorofluoromethane

$CHCl_3$ / $CDCl_3$ (Deuterated) Chloroform

CH_2Cl_2 Dichloromethane

Cs_2CO_3 Cesium carbonate

CYP(450) cytochromes (P450)

1,2-DCB 1,2-Dichlorobenzene

DCE 1,2-Dichloroethane

DIAD Diisopropyl azodicarboxylate

DMAP Dimethylaminopyridine

DMDO Dimethyldioxirane

DME 1,2-Dimethoxyethane

N-*N*-DMF *N,N*-Dimethylformamide

DMSO($-d_6$) (Deuterated) Dimethyl sulfoxide

EDC 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt

EI Electron ionisation

eq. Equivalent or Equation

Et Ethyl

et al. et alius, and others

Et_3N Triethylamine

Et_4NOH Tetraethylammonium hydroxide

EtOAc Ethyl acetate

EtOH Ethanol

FTIR Fourier transform infrared

GIT Gastrointestinal track

HATU *N,*N-dimethylaniminium hexafluorophosphate

H_2O Water

H_2O_2 Hydrogen peroxide

HF / HCl Hydrofluoric acid / Hydrochloric acid

HOBt 1-Hydroxybenzotriazole hydrate

Hr(s) Hour(s)

HRMS High resolution mass spectrometry

HSQC Heteronuclear single quantum coherence spectroscopy

IBX 2-Iodoxybenzoic acid

ID Identification number

IR Infrared

K_2CO_3 Potassium carbonate

K_3PO_4 Tripotassium phosphate

KF Potassium fluoride

KHF_2 Potassium hydrogen difluoride

LA Lewis acid

LC-MS Liquid chromatography coupled with mass spectrometry

LDA.Et_2O Lithium diisopropylamide etherate

Log(D) Distribution coefficient

(μ)M (micro)molar

Me Methyl

MeCN Acetonitrile

MeOH Methanol

$MgSO_4$ Magnesium sulfate

MHz Megahertz

min Minute(s)

MnO_2 Manganese(IV) oxide

mw Under microwave irradiation

N_2 Under nitrogen atmosphere

na not applicable

Na_2CO_3 Sodium carbonate

NaH Sodium hydride

NaN_3 Sodium azide

NaOH Sodium hydroxide

NXS *N*-Xsuccinimide (X= B, bromo; C, chloro; I, iodo)

NMR Nuclear magnetic resonance spectroscopy

nOe Nuclear Overhauser Effect

NoVal no value measured

o/n overnight (between 18 and 20 hours)

OTs Tosylate (*p*-Toluenesulfonate)

OTf Triflate (Trifluoromethanesulfonate)

$Pd(OAc)_2$ Palladium(II) acetate

$Pd(PPh_3)_4$ Tetrakis(triphenylphosphine)palladium(0)

PDB Protodeboration

Ph Phenyl

pH $-\log_{10}[H_+]$

pKa $-\log_{10}([A_-][H_+]/[HA])$

PPh_3 Triphenylphosphine

ppm Parts per million

$^iPr_2NEt$ Diisopropylethylamine

RSM Recovered starting material

rt Room temperature

S_NAr Aromatic nulcleophilic substitution

TBDMS *tert*-butyldimethylsilyl

TBHP *tert*-Butyl hydroperoxide

TFA Trifluoroacetic acid

THF Tetrahydrofuran

TLC Thin layer chromatography

TMS(-Cl) Trimethylsilyl(chloride)

Tol Tolyl

Ts(Cl) Tosy,l, *p*-Toluenesulfonyl (chloride)

TSTU (O)-(*N*-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate

X Halogen (Br, Bromide / Cl, Chloride / I, Iodide)

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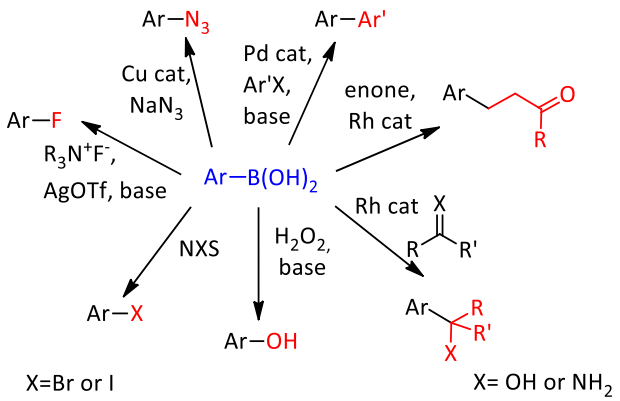
Chapter 1 – Organoboranes in literature

1. *Introduction*

Since the discovery and publication of the Suzuki-Miyaura reaction,[1] organoboranes have rapidly become the most popular and important organometallic reagents for the formation of carbon-carbon bonds. This reaction has been optimised and thoroughly investigated and now represents one of the most frequently used processes in academia and industry. One reason for the popularity of this method is the employment of organoborane precursors. Organoboranes possess features that make them invaluable: they are compatible with a wide range of functional groups, they are also accessible through relatively simple reactions (hydroboration and transmetalation) which means that a diverse range of organoboron compounds can be accessed. They are less toxic than other organometallic coupling partners, which makes the handling and disposal of the boron-containing by-products easier than, for example, organostannanes.

Furthermore, over the years, it was discovered that organoboranes could also undergo a wide range of alternative reactions, either in the presence or absence of metal catalysts (scheme 1).

Scheme 1. Examples of published reactions involving organoboranes



It was shown that rhodium could also efficiently catalyse the addition of boronic acid derivatives to 1,4-enones,[2] ketones[3] and imines.[4] Organoboranes could also be transformed in various functional groups. For example, via oxidation using hydrogen peroxide,[5] the borane

moiety could be transformed into a hydroxyl. Interestingly, other groups have shown that they could transform the boron handle into a halide[6] thereby changing the electronic properties of the carbon atom bearing that group. As a final example, with the help of a copper catalyst, Tao *et al.* were the first to describe the transformation of a boronic acid to an azide.[7] Most of the new groups that can be installed offer a platform for further functionalisation which makes organoboranes very valuable compounds. For the aforementioned reasons, having a quick and reliable way to make such compounds is invaluable for all organic chemists.

The most widely used class of organoboranes are boronic acids ($R\text{-}B(OH)_2$) and boronate esters ($R\text{-}B(OR')_2$), however, these reagents have some associated problems. For example, the purification of these compounds can present challenges. Indeed, boronic acids usually contain significant quantities of inseparable impurities such as anhydrides or boroxines. In addition, some boronic esters are not stable to silica gel therefore must be purified by recrystallisation or distillation, which can narrow the scope of compounds that can be easily purified. Finally, boronic acids and esters are trivalent and are therefore Lewis acidic by nature. They are then susceptible to being attacked by oxygen (air) and water and other nucleophiles which can lead to protodeboration (degradation) of the reagent. For the abovementioned reasons, generally boronic acids and esters are reacted as soon as they are installed.

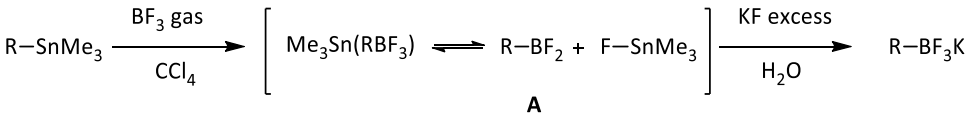
An alternative class of organoboron reagents that solve several of the aforementioned problems is the organotrifluoroborates. They are generally solids and can be purified by precipitation and/or recrystallisation. Furthermore, the tetravalent nature of the boron atom gives those compounds a remarkable stability towards nucleophilic reagents (including air and moisture) and also towards Lewis and Brønsted bases. It has been demonstrated that in some isolated cases however, these compounds are sensitive to Lewis acids, especially to silica gel. Indeed, attempts to purify those compounds by silica column chromatography resulted in the formation of the corresponding boronic acids.[8]

2. Preparation and properties of organotrifluoroborate salts

2.1. Preparation of potassium organotrifluoroborates

The first reported synthesis of potassium organotrifluoroborates[9] used trimethyltin derivatives as starting materials. The target compounds were synthesised by successive treatment of the reagents with trifluoroborane and an excess of potassium fluoride (scheme 2).

Scheme 2. First published synthesis of potassium organotrifluoroborates

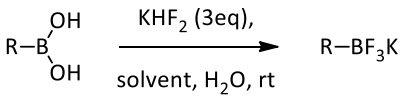


The formation of the 1:1 adduct **A** was believed to go through the transfer of the R group which was the first example of such reaction reported in the literature. Due to the strong acceptor properties of the boron atom in the trivalent intermediate **A**, this compound could not be isolated. However, as a tetravalent ion, the compound was more stable and could be isolated as an ionic pair: a potassium organotrifluoroborate salt.

Several counterions were introduced to stabilise the trifluoroborate product. It turned out that the potassium trifluoroborate derivative was the most stable. It was synthesised by treating the solution of trimethyltin and trifluoroborane etherate with potassium fluoride. Such salt was found to be soluble in water but not hygroscopic, contrary to the other salts synthesised and also was stable at high temperature.

However, the conditions used to access those stable compounds required the use of highly toxic organostannanes and KF as a source of fluoride. Also, organodihaloboranes are highly reactive and unstable compounds. In the 1990's, a new reagent emerged as a viable solution to the toxicity issues: potassium hydrogen fluoride (KHF_2).[10] The potassium organoborates could be obtained directly by the transformation of boronic acids and their derivatives (which are less toxic than organostannanes) into the target molecules by treatment with an aqueous mixture of KHF_2 (scheme 3). Therefore, manipulation of organodihaloboranes was no longer an issue.

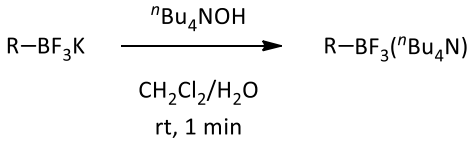
Scheme 3. Universal synthesis of potassium organotrifluoroborates using KHF_2



2.2. Properties of organotrifluoroborate salts

Potassium organotrifluoroborate salts are crystalline solids, which makes the handling and the purification of these compounds easier than for boronic acid derivatives. Due to their stability towards air and moisture, they can be stored almost indefinitely on the bench without taking further precautions. They are usually soluble in polar solvents such as methanol, acetonitrile, acetone, water and dimethylsulfoxide and generally not soluble in non-polar solvents such as dichloromethane and ether. In order to improve solubility in non-polar solvents, Batey *et al.*[11] found that changing the counterion of the trifluoroborate from potassium to $^{n}Bu_4N^+$ and $^{n}Bu_4P^+$ made the corresponding salts considerably more soluble in common organic solvents. This group had developed an efficient and rapid method to exchange counterions (scheme 4).

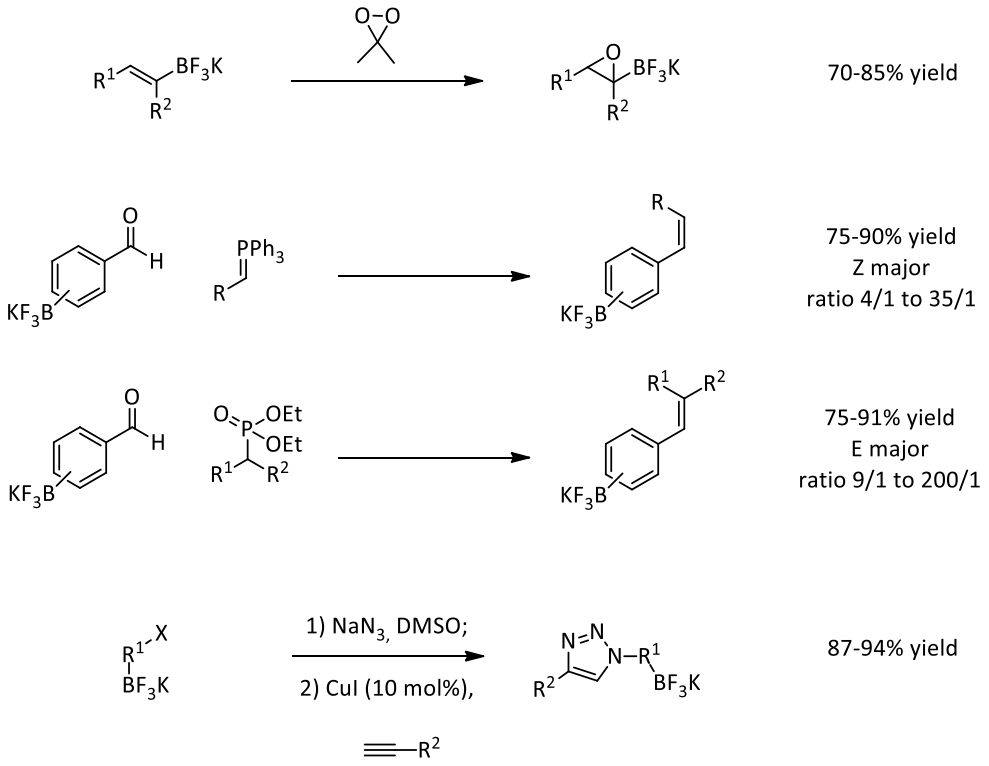
Scheme 4. Counterion exchange to yield more soluble tetrabutylammonium trifluoroborates



The purity of the borate salts can be assessed by numerous analytical techniques. ^{11}B NMR spectroscopy shows a (sometimes poorly resolved) quartet (1:3:3:1) in the range of -2.5 to 7 ppm relative to $BF_3.Et_2O$, and ^{19}F NMR spectrum exhibits a quartet (1:1:1:1) in the range of -160 to -130 ppm relative to $CFCl_3$.[12]

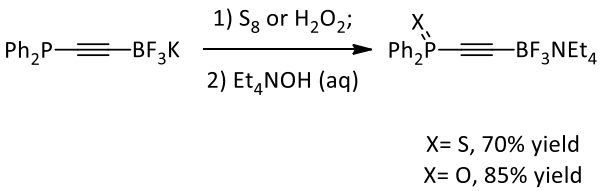
However, the main advantage of the trifluoroborate handle is that it can tolerate a wide range of conditions, so much so that they have been referred to as protecting groups for boronic acids or esters (scheme 5).

Scheme 5. Chemoselective reactions of functionalised organotrifluoroborates



Indeed, Molander has shown that he could epoxidise alkene groups using DMDO whilst leaving the trifluoroborate handle intact.[13] He has also shown that aldehydes could be oxidised using several reagents (IBX, Swern, Dess Martin).[14] He has also carried out a Wittig reaction and its variation (Wittig-Horner) on trifluoroborated compounds.[15] Finally, as another example, he found conditions to install an azide handle using a copper catalyst while conserving the trifluoroborate group.[16] We have shown in our group that one can oxidise a phosphine group on an alkyne trifluoroborate using sulfur or hydrogen peroxide (scheme 6).[17]

Scheme 6. Oxidation of phosphine group on alkynyltrifluoroborates



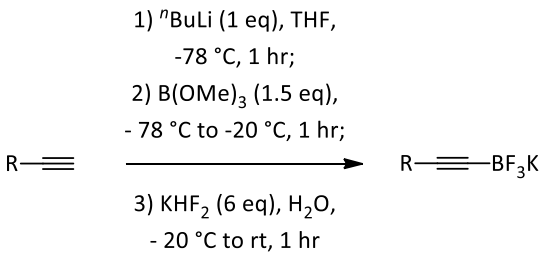
For the aforementioned reasons, trifluoroborates have been extensively studied and used. In this chapter, we will focus on a specific class of compounds which are alkynyltrifluoroborates, where the trifluoroborate handle is directly attached to the triple bond.

3. *Alkynyltrifluoroborates – Preparation and functionalisation*

3.1. Preparation of alkynyltrifluoroborates

With regard to alkynyltrifluoroborates, the most popular way to carry out their synthesis is through borylation of the corresponding lithium acetylide followed by treatment with aqueous KHF_2.[18] Following this one-pot sequence, the desired alkynyltrifluoroborates are generated in good to excellent yields for both alkyl and aryl substituted substrates (table 1).

Table 1. Synthesis of potassium alkynyltrifluoroborates from terminal alkynes



ENTRY	R	YIELD
1	^{n}Bu	78%
2	^{n}Oct	74%
3	Ph	78%
4	TMS	77%
5	$Ph(CH_2)_2$	70%
6	$Cl(CH_2)_3$	80%
7	$TBDMSO(CH_2)_2$	66%

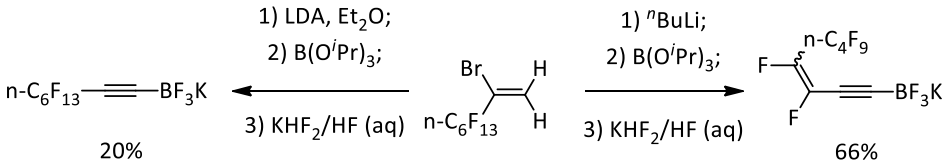
Also, this procedure shows interesting functional group tolerance, notably towards trialkylsilyl compounds (entries 4 and 7) which survive the large excess of KHF_2 (6 eq) used.

However, some functionalities are not tolerated such as those containing basic heteroatoms, cyano and ester groups.

Despite the need to screen for a suitable boron source to achieve high yields, this procedure is quite universal and therefore allows access to a wide range of alkynyltrifluoroborates. However, it had to be amended in the case of perfluoroalkynes. Because of the electron-deficient nature of these compounds, the use of KHF_2 alone does not completely fluorinate the boron atom. However, the preparation of several perfluoroalkynyltrifluoroborate salts could be achieved by the use of an aqueous solution of HF in addition to KHF_2, delivering the products in moderate to excellent yields.[19]

Bardin *et al.*[19] also showed that, depending on the base used for the deprotonation, different alkynyltrifluoroborate products were obtained from a single alkenyl bromide substrate (scheme 7).

Scheme 7. Influence of the base in the synthesis of perfluoroalkynyltrifluoroborates



Recently, our lab disclosed the synthesis of new alkynyltrifluoroborates.[17] We found that phosphine groups were compatible with the conditions for the introduction of the trifluoroborate moiety leading to the material shown in scheme 6 in moderate yield. To the best of our knowledge this constituted the first synthesis of alkynyltrifluoroborate with a heteroatom on the other side of the alkyne group.

3.2. Reactions of alkynyltrifluoroborates

The synthetic advantages of organotrifluoroborate salts are reflected in their combination of stability and reactivity. Before the discovery of those boron salts, functionalisation of alkynylboron reagents was challenging as those compounds were sensitive to basic, nucleophilic, oxidative conditions and so their chemistry was quite limited.

Therefore, the discovery of tetravalent organotrifluoroborate salts has had a positive impact in the chemistry of organoboron compounds.

3.2.1. Suzuki-Miyaura cross-coupling reaction

Over the years, the Suzuki-Miyaura cross-coupling reaction has become one of the most important carbon-carbon bond forming reactions in industry and academia. The first palladium catalysed Suzuki cross-coupling involving organotrifluoroborates was reported in 1997[20], as an efficient means of generating aryl-aryl bonds. Indeed, several groups have shown that aryltrifluoroborates were suitable replacements for organoboronic acid derivatives in this cross-coupling reaction.[21] More importantly, on several examples, the trifluoroborate substrates were more efficient than their organoboronic acid counterparts.[22]

Coupling of alkynyltrifluoroborates with aryl substrates

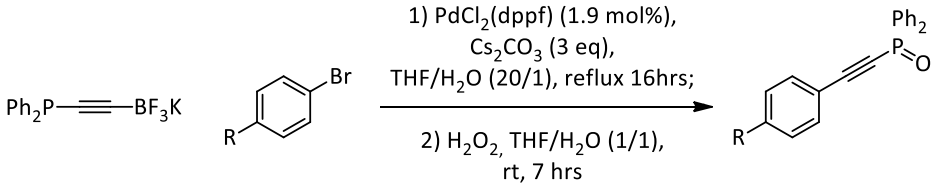
Molander *et al.* reported a catalyst system that allowed alkynyltrifluoroborate salts to participate in cross-couplings.[23] A variety of aryl and heteroaryl coupling partners bearing different functionalities such as nitrile, aldehyde, amine, ketone, hydroxyl group, halide and carboxylic acid were reacted in moderate to excellent yields under the same conditions. Interestingly a different order of reactivity was observed than when coupling alkyltrifluoroborates:[24] TfO > Br > I.

Kabalka *et al.* showed that the use of microwave irradiation was compatible with the trifluoroborate handle and that it also allowed for much shorter reaction times in the cross-coupling of aryl-iodides[25] and aryl triflates.[26] Both aryl- and alkyl-substituted trifluoroborates were well tolerated under the reaction conditions. Products were obtained in similarly excellent yields, compared to conventional heating methods with the structure of the borate salt having little effect. However, the use of electron rich triflates gave slightly lower yields. In

both cases, high chemoselectivity was achieved when chlorine or bromine handles were also on the substrates.

Finally, we have shown that the phosphine substituted alkynyltrifluoroborates could undergo Suzuki reactions[17] followed by subsequent oxidation in good yield (scheme 8).

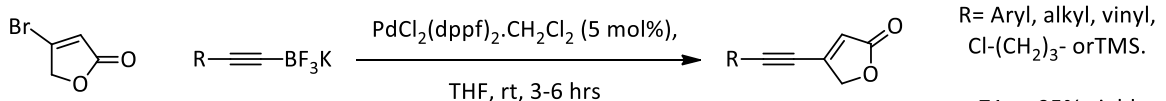
Scheme 8. Suzuki cross-coupling with phosphine substituted alkynyltrifluoroborate



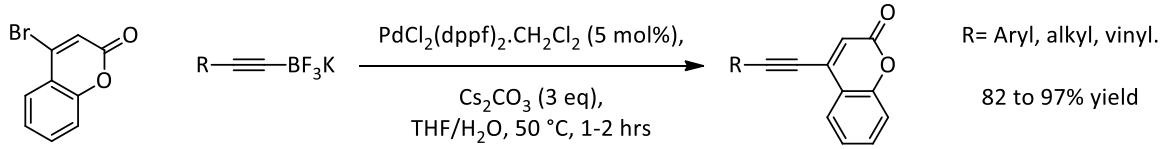
Coupling of alkynyltrifluoroborates with vinylic substrates

Using the conditions developed by Molander, Kabalka *et al.*[27] have synthesised functionalised α,β-unsaturated lactones by employing 4-bromo-2(*H*)-furanone and 4-bromocoumarin (scheme 9). These compounds are important targets in the synthesis of natural products and medicinal chemistry, and this coupling technique gave the desired products in good to excellent yields at room temperature.

Scheme 9. Cross-coupling of alkynyltrifluoroborates with 4-bromo-2(*H*)-furanone or and 4-bromocoumarine



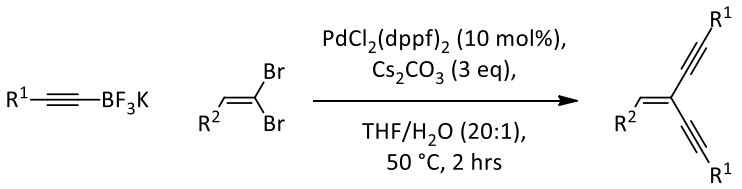
4-bromo-2(*H*)-furanone



4-bromocoumarine

With slight modifications to the above procedure, Kabalka and coworkers[28] applied this method to the synthesis of another important class of compounds: enediynes (table 2).

Table 2. Synthesis of enediynes via cross-coupling reaction



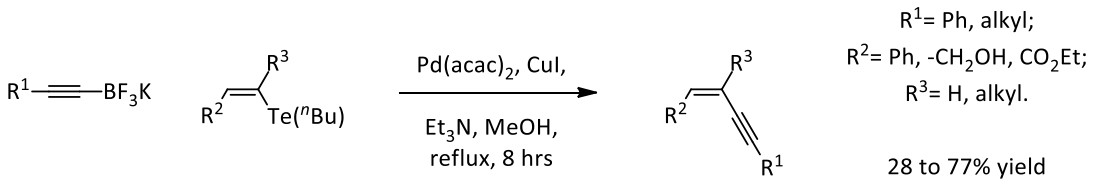
Entry	*R^1*	*R^2*	*Yield*
1	^{n}Bu	Ph	85%
2	$Cl(CH_2)_3$	Ph	82%
3	Isoprenyl	Ph	74%
4	Ph	Ph	73%
5	*p*-Me-Ph	Ph	76%
6	Ph	*p*-Cl-Ph	81%

Entry	*R^1*	*R^2*	*Yield*
7	$Cl(CH_2)_3$	*p*-Cl-Ph	73%
8	$Cl(CH_2)_3$	*p*-Me-Ph	76%
9	$Cl(CH_2)_3$	*o*-Me-Ph	66%
10	$Cl(CH_2)_3$	1-naphtyl	82%
11	$Cl(CH_2)_3$	*p*-NO_2-Ph	64%
12	Ph	C_8H_{17}	75%

Enediynes have various applications in fields such as non-linear optics,[29] macrocyclic ligands[30] as well as the synthesis of polycyclic aromatic hydrocarbons.[31] The enediynes were synthesised in good to excellent yields by coupling 1,1-dibromo-1-alkenes with alkynyltrifluoroborates, and this chemistry provided an alternate and faster route for the synthesis of those compounds as compared to other methods.

Finally, Stefani *et al.*[32] showed that potassium alkynyltrifluoroborates could be reacted with vinylic tellurides to afford the Suzuki cross-coupling products in moderate to good yields (scheme 10).

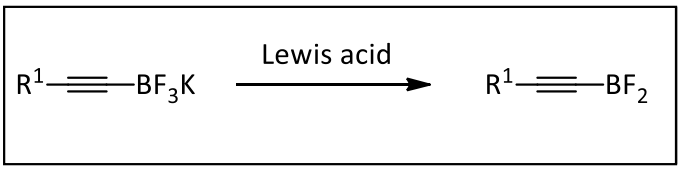
Scheme 10. Cross-coupling between alkynyltrifluoroborates and vinyl tellurides



The reactions proceeded in a stereoretentive manner. This synthesis of *Z*-1,3-enynes showed great functional group tolerance as products bearing a hydroxyl, methoxy or ester group, as well as double and triple bonds could be synthesised. However, reagents containing nitrogen atoms failed to provide product. The authors proposed the formation of a stable six-membered ring complex between the nitrogen, tellurium and palladium atoms in this case which prevented the formation of the desired products.[33]

Whereas Suzuki-Miyaura cross-coupling represents most examples for the use of alkynyltrifluoroborates, other interesting reactions have been disclosed.

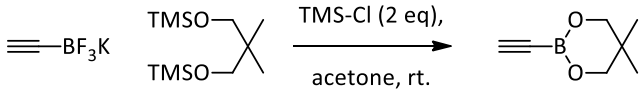
3.2.2. Generation of organodifluoroboranes



Soon after their discovery, potassium organotrifluoroborate salts were regarded as precursors to organodihaloboranes. The latter compounds are very efficient Lewis acids therefore they have to be generated *in situ* and used directly without isolation. The first example of this transformation was reported by Bir *et al.*,[34] whereby potassium organotrifluoroborate was treated with $BF_3.Et_2O$ to yield the difluoroborane in a quantitative manner. The authors reported only one example, and so a more in-depth study on the generation of organodifluoroboranes was needed.

The first detailed study on this subject was published by Vedejs *et al*.,[10] and they found that the most efficient reagent for the conversion of trifluoroborate salts to organodifluoroboranes was trimethylsilyl chloride, which offered a general method for this transformation. They provided an application for this reaction for the transformation of potassium trifluoroborate salts into boronic esters. TMS-Cl was used to transform the trifluoroborate into a difluoroborane which was then reacted with TMS-protected diol to yield the corresponding boronic ester in good yields (scheme 11).

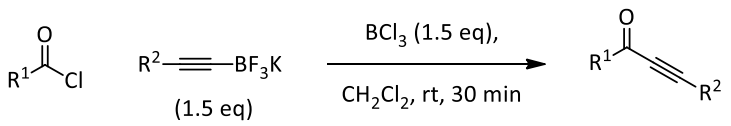
Scheme 11. Synthesis of boronic esters from trifluoroborate derivatives



74% yield

As another example of reactions going through the organodiborane species, in 2014, Bolshan's group published the Lewis acid catalysed formation of ynones.[35] Using boron trichloride, they reacted acyl chlorides and alkynyltrifluoroborates to synthesise ynones in average to excellent yields (scheme 12).

Scheme 12. Synthesis of ynones using alkynyltrifluoroborates



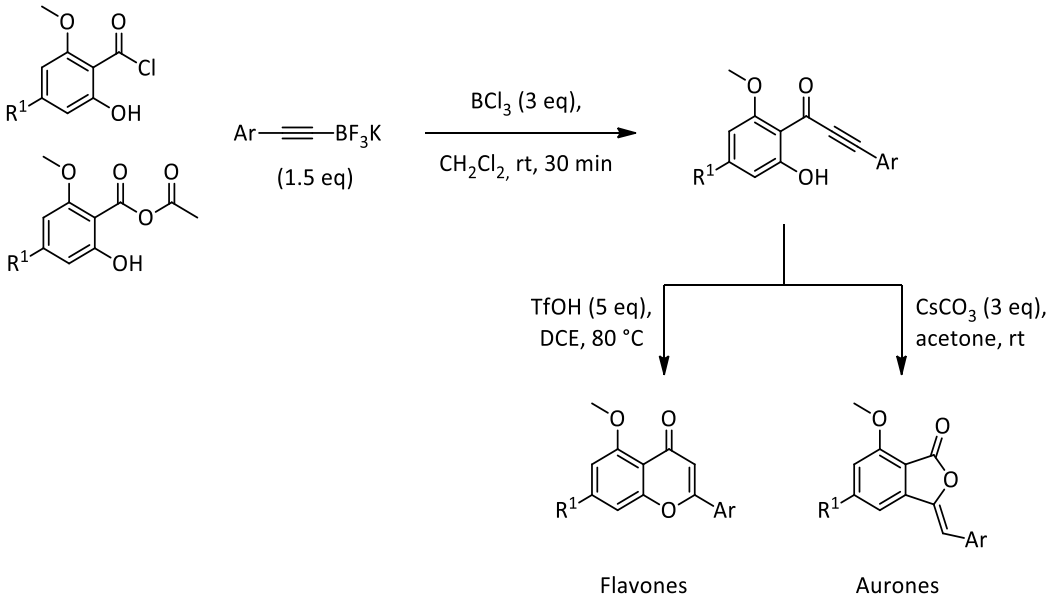
R^1= Aryl, cyclohexyl, cyclopropyl, ^{n}alkyl;
R^2= Aryl, cyclopentyl, ^{n}alkyl.

39 to 99% yield

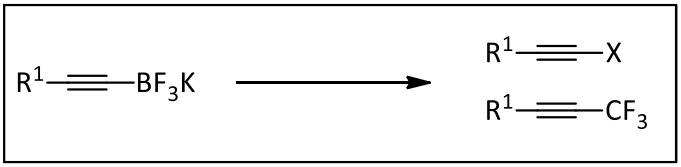
Acyl chlorides with electron-donating and -neutral susbtituents on the phenyl group gave excellent results whereas electron-withdrawing susbtituents tended to give lower yields. Alkyl-substituted acyl chlorides also gave average to good yields. Similarly, electron-rich and –neutral aryl trifluoroborates as well as alkyl trifluoroborates gave good to excellent yields in this reaction.

Later on, Bolshan's group[36] applied the above protocol to the synthesis of sterically hindered ynones towards the preparation of flavone and aurone derivatives (scheme 13).

Scheme 13. Synthesis of hindered ynones towards the synthesis of aurones and flavones

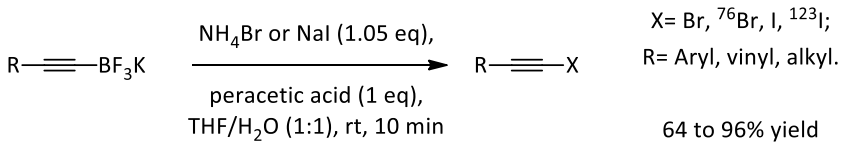


3.2.3. Halogenation reaction and trifluoromethylation



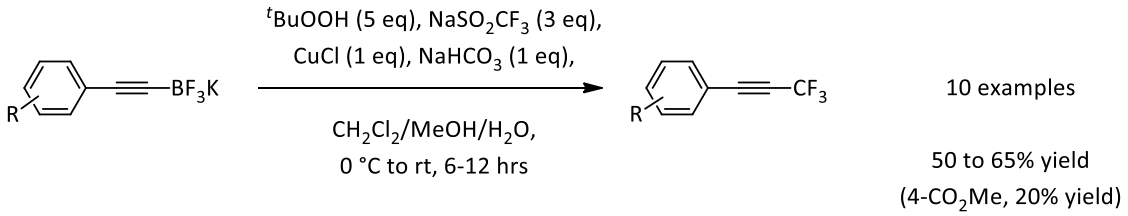
In 2004, Kabalka and Mereddy were the first to report the use of alkynylboron derivatives to synthesise iodo- and bromo-alkynes. They reported a dozen examples for the synthesis of both labelled[37] and unlabelled[38] iodo- and bromo-alkynes from potassium alkynyltrifluoroborates in excellent yields, highlighting that various substituents were well tolerated, including aryl, vinyl and alkyl groups (scheme 14). This easy and rapid conversion to labelled halo-alkynes represented a significant advance in the field of nuclear medicine imaging.

Scheme 14. Halogenation of alkynyltrifluoroborates using both labelled and unlabelled iodine and bromine



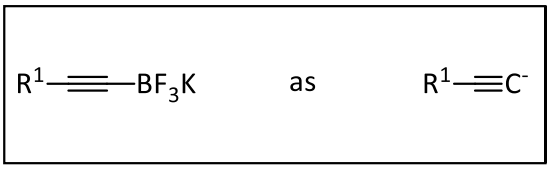
More recently, Dubbaka *et al.*[39] disclosed the copper mediated radical substitution reaction of a CF_3 moiety (scheme 15).

Scheme 15. Trifluoromethylation of trifluoroborates



Langlois reagent and *tert*-butylhydroperoxide were used to form the trifluoromethyl radical in the presence of copper which then reacted to give the trifluoromethylated products in average to good yields. The reaction accommodated *ortho*-, *meta*- and *para*-substituents on the arene ring. They showed that electron-neutral or -donating substituents performed much more efficiently than electron-withdrawing substituents. There was a thiophene example as well as a benzyl-, vinyl-, alkyl- and TMS-substituents which all gave satisfactory yields.

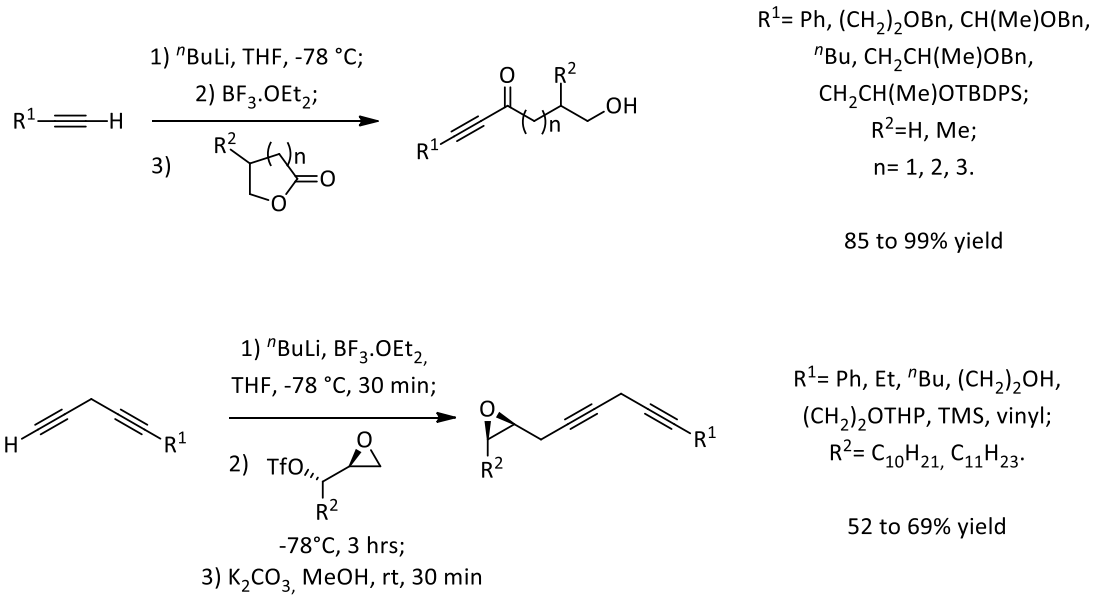
3.2.4. Alkynyltrifluoroborates as nucleophiles



Ring opening reactions

Lithium alkynyltrifluoroborates have been used for the nucleophilic ring opening of lactones and epoxides (scheme 16).

Scheme 16. Ring opening of lactones and epoxides using alkynyltrifluoroborates

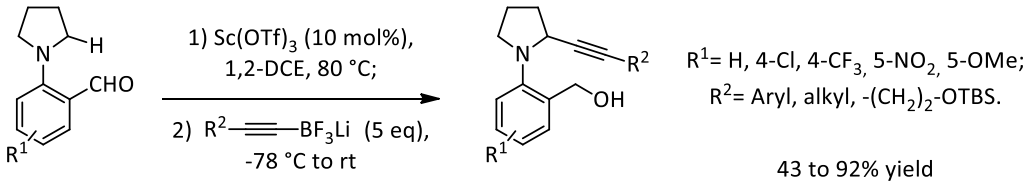


Koutek *et al.*[40] were the first to report the opening of five-, six- and seven-membered lactones using *in situ* generated lithium alkynyltrifluoroborates, yielding the desired products in excellent yields. Following the above conditions, Che and coworkers[41] published the epoxide opening by the addition of alkynyltrifluoroborates.

C-H functionalisation

Maulide *et al.*[42] have developed a redox-triggered C-H functionalisation of *ortho*-substituted aminobenzaldehydes using alkynyltrifluoroborates as nucleophiles (scheme 17). Indeed, under these conditions, the expected direct addition to the aldehyde group was not observed.

Scheme 17. C-H-functionalisation of *ortho*-substituted aminobenzaldehydes with alkynyltrifluoroborates

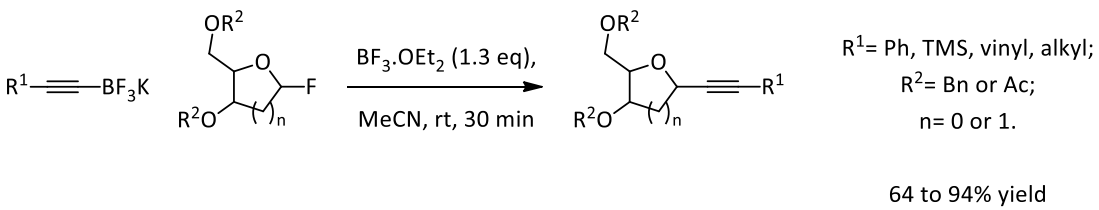


This one-pot sequence of Lewis acid promoted reduction / C(sp^3)-C(sp) bond formation gave the desired products in average to excellent yields with a remarkable tolerance regarding the substituent on the alkyne. Aryl as well as alkyl substituents were also well tolerated. More notably, silyl groups could be retained under those conditions.

C-glycosylation

C-Glycosides are a class of compounds possessing therapeutic applications,[43] they are also used as chiral building blocks and organocatalysts. And as compounds of the sugar family, their reactivity is governed by the specific properties of the anomeric carbon. Liu *et al.*[44] used this special reactivity to functionalise the anomeric carbon by alkynylation (scheme 18).

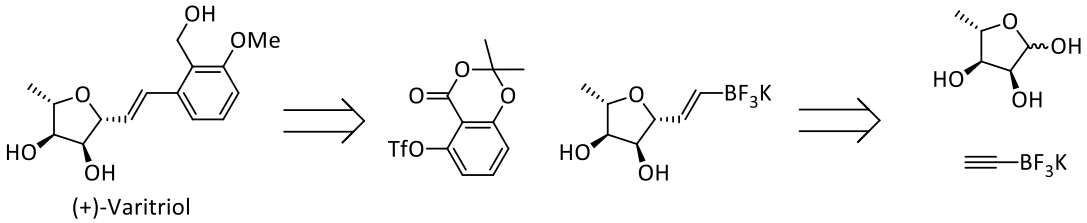
Scheme 18. Functionalisation of the anomeric carbon of furanoses and glucoses with alkynyl moiety



They described a direct method to capture electrophilic oxocarbenium ions (generated by treatment of furanoses and glucoses with a Lewis acid) with alkynyltrifluoroborates. After screening Lewis acids, solvents and various leaving groups at the anomeric carbon, they uncovered conditions giving the desired furanoses and glucoses in good yields (from 64 to 94%) with either aromatic or aliphatic substituted acetylides.

Furthermore, they proved the usefulness of their new method by using it in a key step of the synthesis of the natural product (+)-Varitriol (scheme 19).

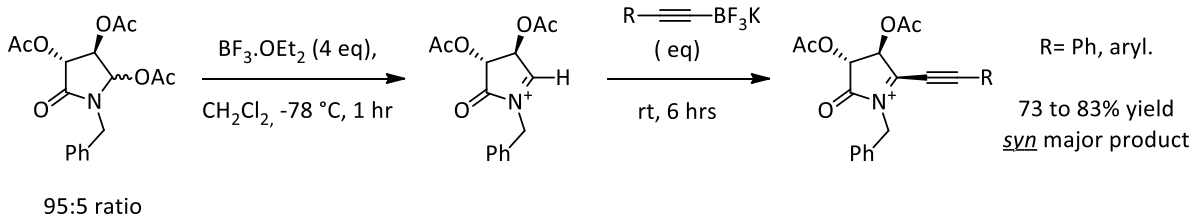
Scheme 19. Retrosynthesis of (+)-Varitriol



Nucleophilic addition

Similarly, Stephani *et al.*[45] used alkynyltrifluoroborates as carbon nucleophiles to synthesise α-functionalised cyclic amides. Like the oxocarbenium ion, *N*-acyliminium ions are well known to undergo reactions with nucleophiles. In their article, they reported the stereoselective one-pot addition of alkynyltrifluoroborates to *N*-acyliminium precursors (scheme 20).

Scheme 20. Addition of alkynyltrifluoroborates on *N*-acyliminium ions

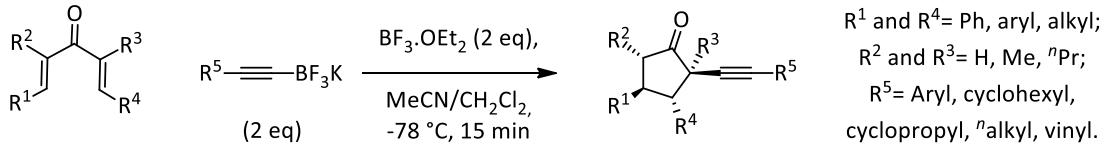


The enantiopure precursors (pyrrolidine derivatives) were synthesised following a 4-step procedure[46] from cheap and commercially available L-(+)-tartaric acid. Screening of Lewis

acids and optimisation allowed the formation of the desired products in excellent yields and diastereoselectivities (for the *syn*-isomer) for both aryl and alkyl substituted alkynyltrifluoroborate substrates. In this one-pot procedure, the Lewis acid is believed to have two roles: the transformation of the pyrrolidine into the acyliminium ion as well as the generation of the alkynyldifluoroborane from the trifluoroborate reagent.

Finally, Liu *et al.*[47] have shown that trifluoroborates could be used to trap intermediates of the Nazarov cyclisation, therefore publishing one of few examples using an α-carbon-based nucleophile in this reaction (scheme 21).

Scheme 21. Interrupted Nazarov cyclisation using carbon-based nucleophile

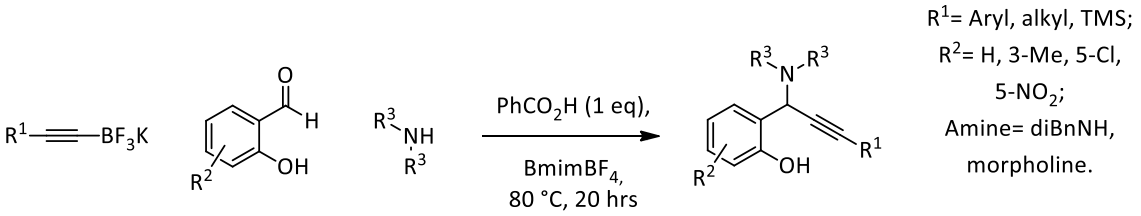


This reaction was proposed to operate via the difluoroorganoborane which formed a complex with the enone, allowing the trapping of the oxyallylcation intermediate and yielding the α-alkynylcyclopentanones in high yields.

3.2.5. Petasis reaction

A wide range of alkynyltrifluoroborates have been shown to participate in a multicomponent coupling reaction that generates propargylic amines. In this first reported example, Kabalka *et al.*[48] could synthesise benzylamine derivatives by reacting alkynyltrifluoroborates with amines and salicaldehydes (scheme 22).

Scheme 22. Petasis reaction yielding propargylamines

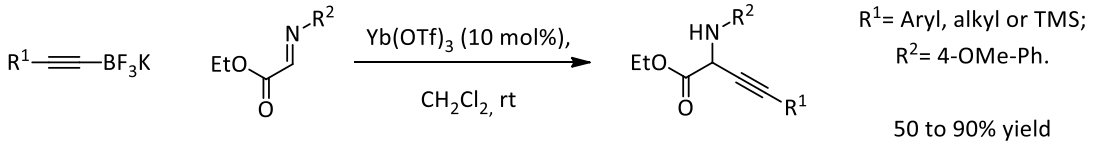


$BmimBF_4$ is an ionic liquid
(1-butyl-3-methylimidazolium tetrafluoroborate)

Interestingly, under the reaction conditions the TMS-group on the alkyne was not well tolerated yielding the desilylated product. The addition of benzoic acid (1 eq) was found to increase yields dramatically. The proposed explanation for this effect was that the benzoic acid promoted the condensation of the amine on the aldehyde, which was believed to be the first step. Investigations also showed that the 2-hydroxyl group was needed for the reaction to proceed and it was believed to direct the addition of the boron species to the C-N π-bond.

More recently, Lewis acid catalysed addition of potassium trifluoroborates to α-iminoesters was reported by Stefani *et al.*[49] (scheme 23).

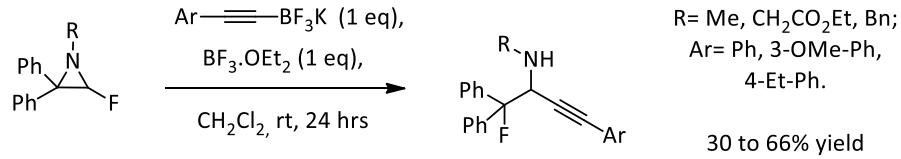
Scheme 23. Petasis reaction yielding α-ethylester propargylamines



The above reaction yielded the desired Petasis product, giving rise to the synthesis of a wide range of β-unsaturated-α-amino acid derivatives which can be used to synthesise a number of biologically active compounds. Various alkynyltrifluoroborate salts could be employed in this reaction: aryl substituents bearing both electron-donating and electron-withdrawing groups gave good to excellent yields. Alkyl substituents on the alkynyltrifluoroborates were also tolerated and gave even higher yields than the aromatic examples. Notably, this reaction proceeded well without the need for an *ortho*-OH directing group. Interestingly, despite the two possible reactive sites on the imino ester, only addition at the imine was observed.

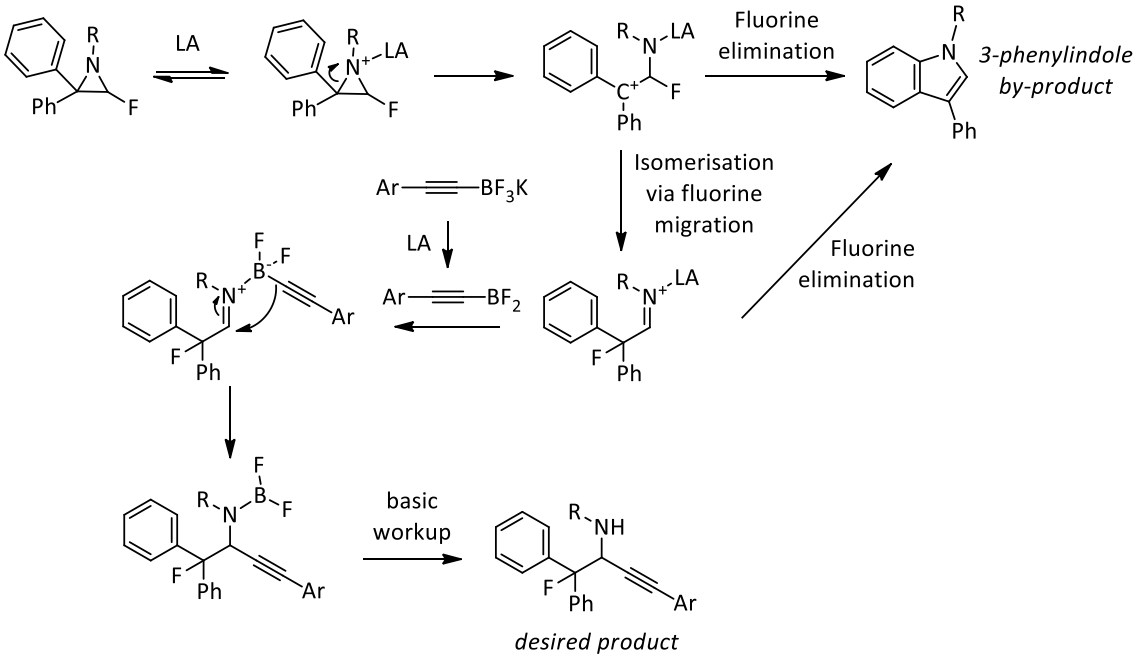
Finally, Konev and coworkers[50] have shown yet another application of the Petasis reaction for the synthesis of monofluorinated propargylamines, and they also assessed the bioactivity of the resulting products (scheme 24).

Scheme 24. Petasis reaction yielding β-fluoropropargylamines



Indeed, propargylamines have proven to be very useful intermediates for the synthesis of numerous drug compounds and natural products, and fluorine atoms are known to modify some biological properties of these molecules. Using aziridines as precursors of *in situ* generated imines, and various aryl substituted potassium alkynyltrifluoroborates, they devised the synthesis of β-fluoropropargylamines following a Petasis-like reaction mechanism. In all cases, the presence of an indole by-product (scheme 25) was observed but this did not prevent the isolation of the desired propargylamines, however it lowered the yields considerably (up to 1/1 ratio of product/by-product).

Scheme 25. Mechanism of the aziridine synthesis.

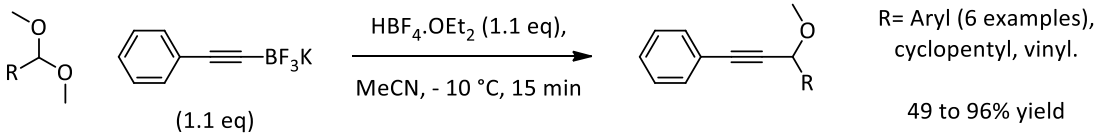


Good yields were obtained only when both the aziridine and the acetylides were substituted with electron-withdrawing groups. The authors believed the electron deficient nature of the nitrogen atom prevented the cyclisation of the intermediate in this case, and therefore diminished the amount of indole by-product formed.

3.2.6. Addition to acetals

Over the last couple of years, Bolshan's group has explored new reactions involving trifluoroborates. Reactions of trifluoroborates with Lewis acids to form the difluoroborane are very well-known. However, those compounds are unstable and very reactive, making them difficult to handle. This group however has been working on using Brønsted acids to carry out addition of trifluoroborates on acetal groups. They hypothesised that the reaction of an acid with an acetal would lead to the formation of the oxocarbenium ion which could then react with the trifluoroborates to give the addition product (scheme 26).[51]

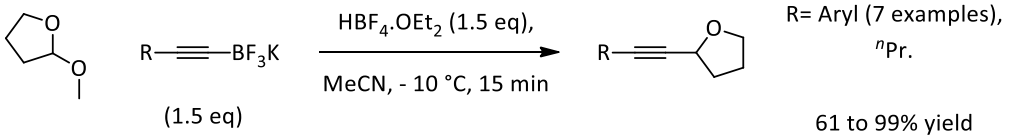
Scheme 26. Addition of trifluoroborates to dimethylacetal



Both electron-poor aryl and alkyl substituted acetals gave excellent yields (64 to 99%) except for the vinyl substituent which performed poorly (49%). Electron-rich acetals resulted in an overalkynylated product. They performed a short optimisation and found that lowering the temperature to -40 °C and changing the solvent to propanenitrile gave excellent selectivity for the mono-alkynylation product (90% isolated yield). Finally, they have shown that ketals could also undergo the reaction albeit in slightly lower yields (51 to 59%).

In a second publication the following year,[52] the same group disclosed the addition of trifluoroborates to asymmetrical acetals in order to form 2-alkynyltetrahydrofurans (scheme 27).

Scheme 27. Addition of trifluoroborates on tetrahydrofuran acetals



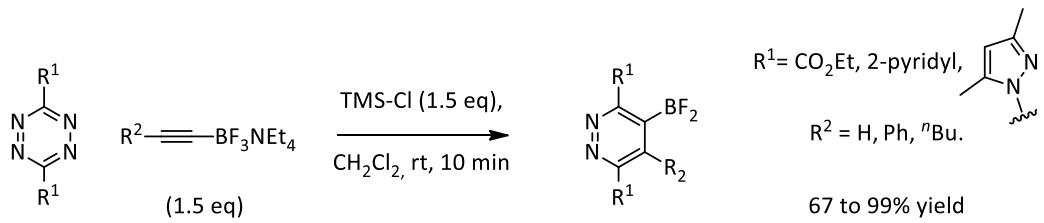
Using the same Brønsted acid, they could synthesise various tetrahydrofuran derivatives with alkynes bearing electron-rich and -poor aryl groups, as well as an alkyl substituted alkyne, in excellent yields (61 to 99%).

3.2.7. Cycloadditions

Alkynes are popular substrates for cycloaddition reactions. Our group has devised a Lewis acid/base pair promoted variant which allowed the reaction to be conducted at low temperatures and with complete control of regioselectivity.

The first example of this concept was using tetrazines and alkynyltrifluoroborates (scheme 28).[53]

Scheme 28. Cycloadditions of tetrazines and alkynyltrifluoroborates

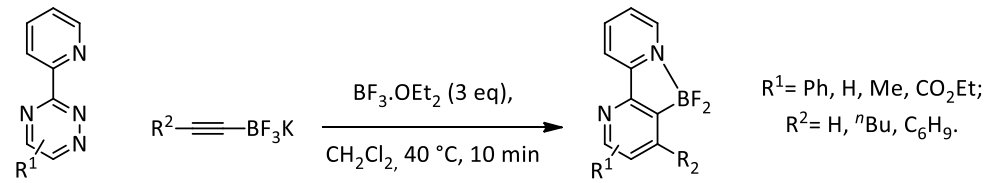


They showed that both aryl and alkyl substituted alkynes could undergo the cycloadditions under very mild conditions compared with their boronic ester derivatives (usually high temperatures 140 °C and several hours of reaction time). Finally, they showed

that a wide range of substituents on the tetrazine were tolerated, such as ester, pyridine and pyrazole.

Further studies have shown that several other types of molecules could undergo cycloadditions with alkynyltrifluoroborates. In 2014,[54] non-activated triazines and alkynyltrifluoroborates were reacted to yield a range of pyridine scaffolds (scheme 29) using pyridine as Lewis base and directing group. The regioselectivity of the reaction could be controlled via a *N*-heterocycle substituent on the tetrazine ring. Indeed, the nitrogen allowed for the formation of a Lewis acid/base complex with the boron group.

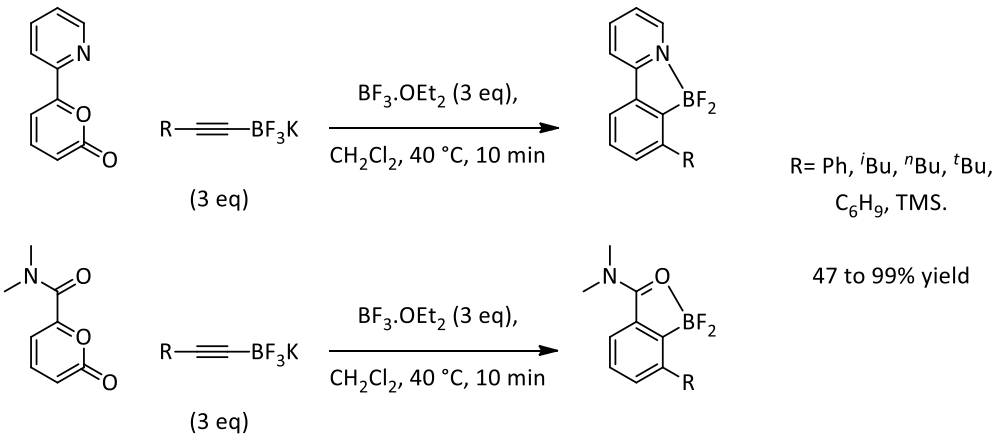
Scheme 29. Cycloadditions of triazines and alkynyltrifluoroborates



Vinyl and alkyl substituted trifluoroborates performed well (48 to 83% yield). Also, a wide substitution pattern on the triazine was tolerated and all gave the corresponding products in good to excellent yields in 10 to 20 minutes. Furthermore, we have shown that amides (NMe_2 and piperidine) could also be used as directing groups.

In addition, we have shown that pyrones could be used in similar reactions (scheme 30).[55]

Scheme 30. Cycloadditions of pyrones and alkynyltrifluoroborates



As above, the directing group could be either a 2-pyridyl or an amide group, the yields were generally excellent with aryl and alkyl substituted alkynes.

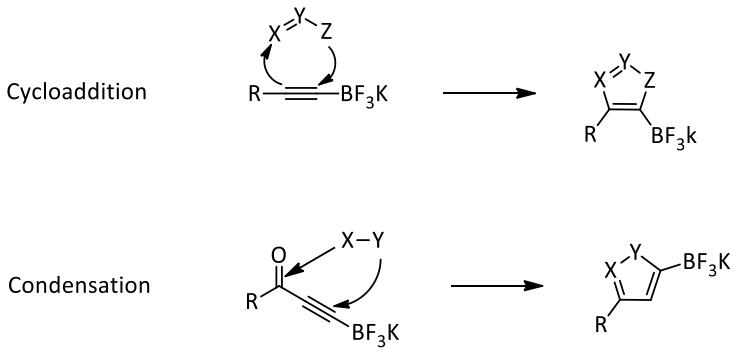
4. Conclusions and Outlook

Alkynyltrifluoroborates can be easily synthesised from the corresponding terminal alkynes via a 3-step one-pot sequence: a lithiation is then followed by a borylation and fluorination. Their purification is also quite straightforward since the products can be precipitated from solution using ethers as an anti-solvent.

Trifluoroborates also possess a good balance between reactivity and stability. First, they are air and moisture stable salts. They undergo cross-coupling reactions and in this regard, they are at least as effective as their boronic acids or esters derivatives. Furthermore, in some cases, they have been described as "protecting groups" for boronic acids or esters. In this instance, their stability allows for the chemoselective modification of various functional groups, under a range of conditions, while the trifluoroborate handle remains intact.

For the aforementioned reason, we were very interested in investigating such compounds. More precisely, we wanted to use such compounds as starting materials for the synthesis of various heterocycles. However, as we have shown in this chapter, there are few examples in the literature in which alkynyltrifluroborates are used in such a fashion. Our group has reported a small number of cycloaddition reactions that could accommodate the trifluoroborate handle. However, the scarcity of these reports has prompted us to look at the synthesis of heterocycles in a different way (scheme 31).

Scheme 31. Synthetic routes to heterocyclic structures



Whereas cycloadditions usually require harsh conditions, condensation reactions can be significantly milder. Therefore, we decided to prepare a series of ynone trifluoroborates, and to explore the ability of these compounds to generate heterocyclic boronic acid derivatives for organic synthesis.

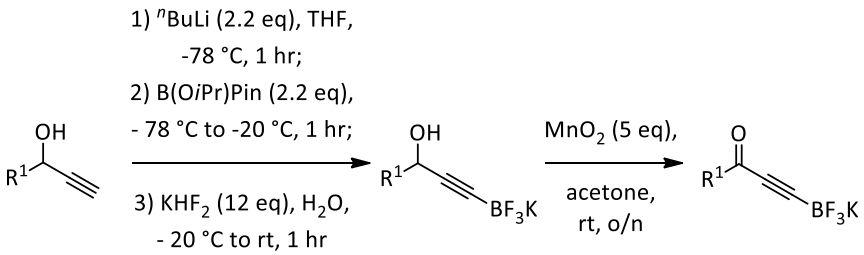
It should be noted that in the following report, all yields are given as isolated yields unless stated otherwise.

Chapter 2 – Ynone Trifluoroborates

1. ***Introduction***

Ynones have been the subject of active investigations because of their wide reactivity, therefore, there are many reported ways to synthesise them.[56] In 2012, our lab published conditions for the synthesis of such compounds,[57] bearing a trifluoroborate handle, using a modification of the standard conditions used for the synthesis of alkynyltrifluoroborates.[10] Kirkham *et al.*[57] have found that using *iso*propoxypinacolborane instead of typical trimethoxyborane, allowed borylated propargylic alcohols to be accessed in modest to excellent yields. Subsequent oxidation using manganese(IV) oxide provided the desired ynone trifluoroborates (table 3).

Table 3. Previously reported scope of ynone trifluoroborates



Entry	R^1	Yield borylation	Yield oxidation	Overall Yield
1	Ph	92%	80%	74%
2	Ph[a]	81%	61%	49%
3	*p*-$MeOC_6H_4$	42%	78%	33%
4	*o*-$MeOC_6H_4$	62%	83%	51%
5	*p*-$F_3CC_6H_4$	48%	93%	45%
6	Me	48%	60%	29%
7	^{n}Pr	80%	81%	65%
8	^{t}Bu	63%	91%	57%

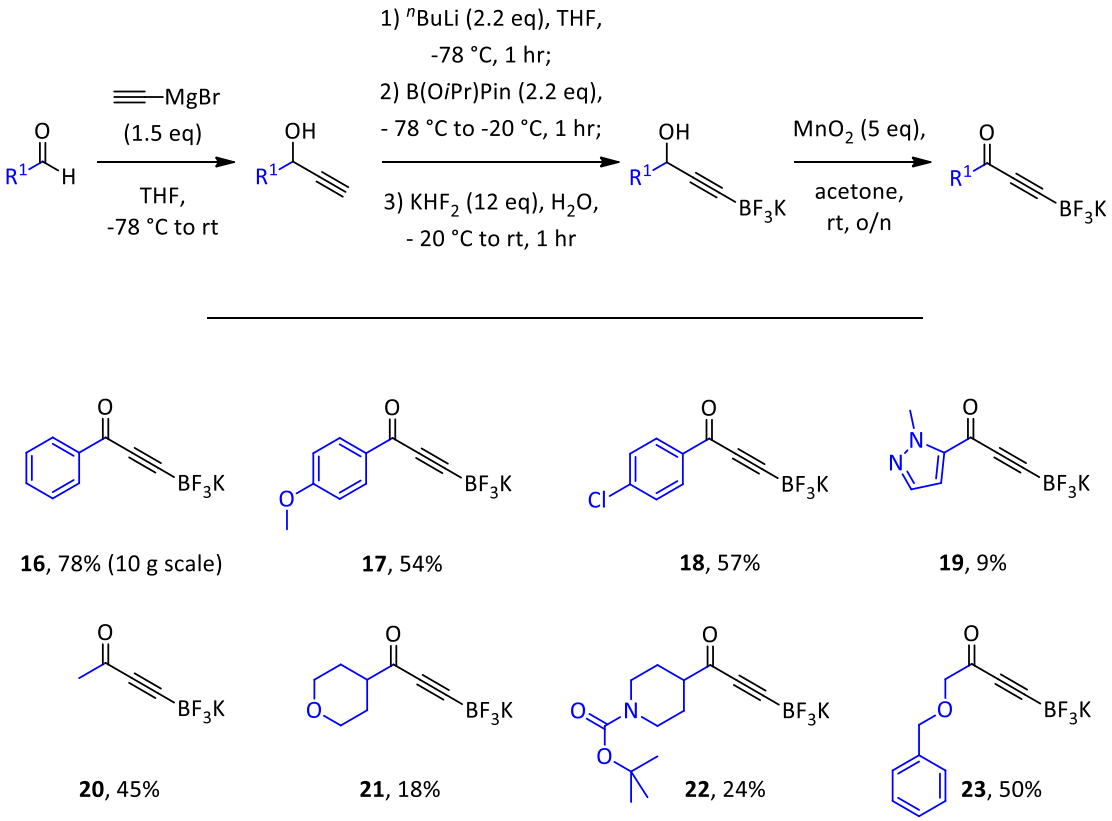
[a]On a 5 g scale.

The scope that was investigated showed that the reaction was tolerant of electron-neutral (entries 1 and 2), electron-rich (entries 3 and 4) and electron-poor (entry 5) aryl substituents. It also showed that *ortho*-substituents were tolerated (entry 4). Unfunctionalised alkyl substituted ynones could also be prepared in low to good yields (entries 6 to 8).

2. *Scope extension*

We were interested in further investigating the scope of this synthesis, to create new starting materials that could give more medicinal chemistry relevant scaffolds. Therefore, we mainly focused on functionalisable alkyl- and heteroaromatic- substituted propargylic alcohols. Due to the unavailability or excessive cost of the propargylic alcohols, we had to synthesise those compounds from the corresponding aldehydes. This could easily be achieved via addition to ethynylmagnesium bromide in THF. The results of our investigations are summarised in scheme 32.

Scheme 32. Scope of new ynone trifluoroborates



Several new ynones were synthesised using the optimised method. We could introduce a heteroaromatic group: pyrazole **19** which is a valuable scaffold from a medicinal chemistry point of view. Also, several alkyl substituents (**20** – **23**) were well tolerated, namely a pyran **21**, a Boc-protected piperidine **22** and a benzyl-protected alcohol **23** which provided evidence that these reactions could accommodate a wider scope of substitution than previously reported.

Importantly, the borylation and oxidation reactions were carried out until full conversion was reached according to ^{19}F NMR (products **8** to **15** have a broad signal at -131 ppm and ynones **16** to **23** have a well-defined quadruplet at -133 ppm).

Table 4. Stepwise yield for the synthesis of ynone trifluoroborates.

Entry	R	Grignard addition	Borylation	Oxidation	Overall
1	Ph	**1,** 100%	**8**, 98%	**16**, 80%	78%
2	*p*-$MeOC_6H_4$	**2**, 100%	**9**, 80%	**17**, 68%	54%
3	*p*-ClC_6H_4	**3**, 98%	**10**, 75%	**18**, 77%	57%
4	5-(*N*-Me-pyrazoyl)	**4**, 82%	**11, 37%**	**19, 30%**	9%
5	Me	X	**12**, 71%	**20**, 63%	45%
6	4-tetrahydropyranyl	**5**, 57%	**13**, 88%	**21, 36%**	18%
7	4-(NBoc-piperidyl)	**6**, 72%	**14**, 72%	**22, 46%**	24%
8	$BnOCH_2$	**7**, 92%	**15**, 94%	**23, 58%**	50%

Whereas optimised conditions for the synthesis of the borylated ynols **8** to **15** gave excellent yields in most cases, we have had some difficulties in precipitating the pyrazole-substituted ynol in good yield (table 4 - entry 4). This difficulty also continued through to the next step, yielding **19** in only small amounts.

It should be noted that alkyl substituted ynones (**21**, **22**) gave lower yields for the oxidation step compared to the aryl substituted substrates. Although the underlying reason for these lower yields is unclear, we noted that the mass balance recovery after filtration was quite low and that was reflected in the obtained yields. The case of the protected alcohol substrate **23** (entry 8) was slightly different as the mass balance after filtration was only slightly lower than the one expected. The crude ^1H NMR spectrum of the filtrate showed that multiple compounds were present. To reach completion, this oxidation required a much larger excess of manganese(IV) oxide.

We believe that the benzylic position was also prone to oxidation (figure 1).[58] Furthermore, we have observed evidence of protodeboration perhaps due to the large excess of manganese in suspension in the reaction mixture and the longer reaction time.

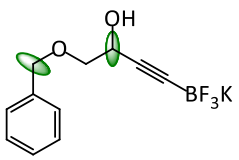


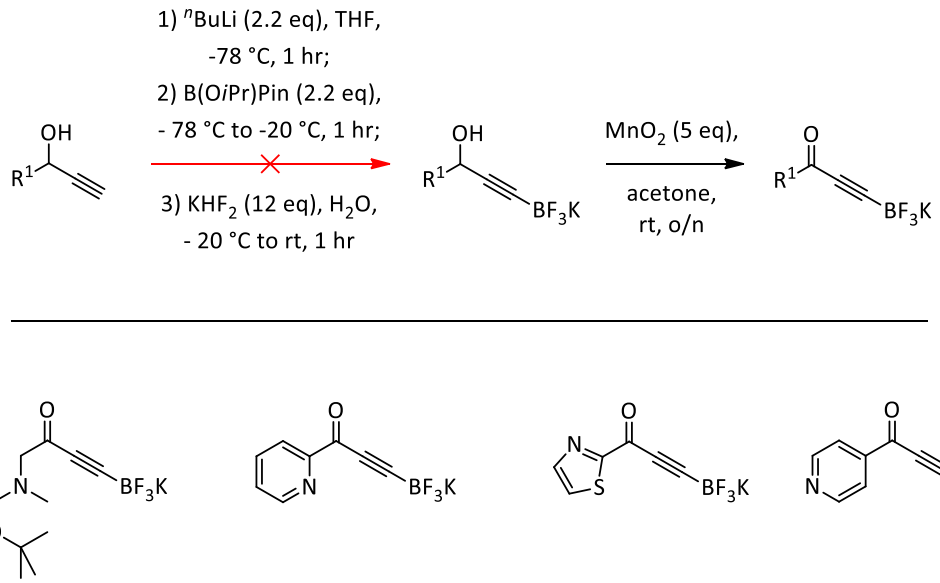
Figure 1. Possible oxidation positions on 15

We have also observed that the yields for the borylation and oxidation steps tends to be higher when the reactions were performed on a bigger scale: for the phenyl substituted example, borylation 55% yield on 1.4 g scale – 98% yield on 8.9 g scale; oxidation 53% yield on a 0.3 g scale – 80% yield on a 5.4 g scale. This was probably due to a more efficient precipitation from acetone and ether on larger scale.

3. *Scope and limitations*

Exploring the scope of the synthesis of ynone trifluoroborates showed us the limitations of this method. Indeed, the following substrates could not be synthesised (scheme 33) as in the following cases, the borylation step did not yield clean material.

Scheme 33. Limitation of the current method for ynone trifluoroborate synthesis



Regarding the *N*-Me carbamate, we believe the acidic proton *alpha* to the carbonyl group interferes with the base promoted borylation step (figure 2).

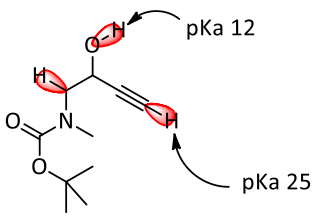
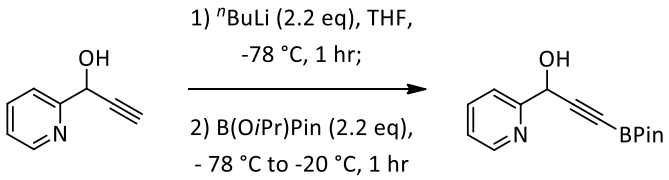


Figure 2. Possible deprotonation positions

For all heteroaromatic substituents, mass spectrometry analysis of the crude material showed the presence of mass ions of the expected products, however the

NMR spectra were inconclusive as no signal could be identified. In order to produce cleaner products, we tried increasing the equivalents of ^{n}BuLi and KHF_2 (to 3 and 4, then 6 and 6, respectively) without any improvement on the outcome. We wondered if the basic nitrogen atom was interfering with the acidic KHF_2 reagent, and so we tried to isolate the pinacolborane intermediate instead (scheme 34).

Scheme 34. Attempt to isolate the BPin intermediate



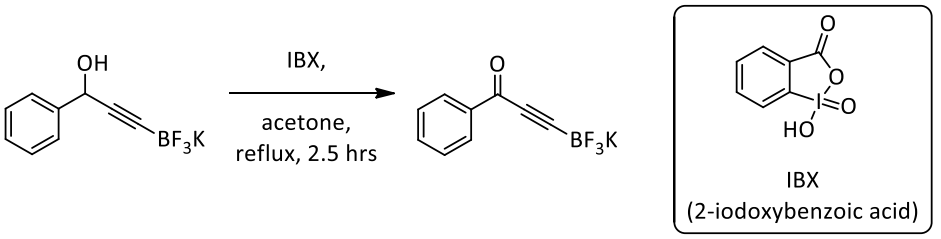
The mixture obtained from this reaction was purified by flash column chromatography on florisil, however we were unable to isolate the desired product. Finally, attempting a similar protocol with 4-pyridylpropargyl alcohol resulted in a similar outcome: mass spectrometry showed the expected mass ion but the NMR spectra were inconclusive.

To conclude, we were able to extend our synthetic approach to ynone trifluoroborates to include fragments bearing heteroatoms such as benzyl ethers, piperidines and pyrazole groups. These studies also uncovered some limitations that we have put down to sensitivity to over oxidation, and incompatibility with basic nitrogen atoms. In order to begin to address some of these limitations and to improve the yields more generally, we decided to investigate alternative methods for the oxidation step.

4. *Alternatives for the oxidation step*

Manganese(IV) oxide is a known selective oxidant for allylic alcohols.[59] In our case, we could observe variations in yield for the oxidation step for the substrates we examined. Therefore, we decided to investigate more reactive oxidants, and in this regard, Molander *et al.*,[19] showed that IBX was suitable for the oxidation of hydroxyl-substituted organotrifluoroborates, leaving the trifluoroborate group intact. We therefore set out to see if potassium alkynyltrifluoroborates could also be used as substrates (table 5).

Table 5. IBX oxidation of ynoltrifluoroborates.



Entry	IBX (eq)	Results[a]
1[19]	3	Complete conversion observed – 47% isolated yield
2	1.2	SM is the major product
3	1.5	50% estimated conversion
4	2	Complete conversion observed – no clean product isolated

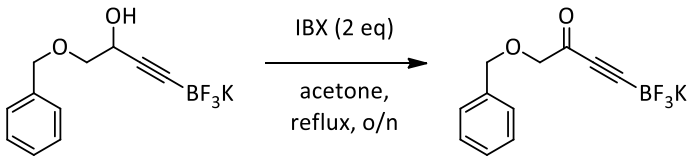
[a]Conversion followed by ^{19}F NMR spectroscopy.

Following the literature conditions[19] (entry 1), we observed complete conversion of the alcohol to the ynone after 2.5 hours at reflux. Unfortunately, the purification of the ynone product was not straightforward and we were unable to isolate clean product in a yield that was competitive with the manganese(IV) oxide method.

We attempted to decrease the amount of IBX added in the reaction (entries 2 to 4) to limit the amount of oxidant waste. We found that the minimum amount of IBX required for complete conversion in 2.5 hours was 2 equivalents (entry 3). Unfortunately, the same purification issues were also observed in that case: product could only be isolated as a mixture with IBX or its reduced form.

Having failed to improve the oxidation step of an otherwise successful substrate, we decided to repeat the study on a more challenging example and opted for the *O*-benzyl-ynol trifluoroborate that had performed poorly under MnO_2 oxidation (scheme 35).

Scheme 35. IBX oxidation of *O*-benzyl-ynol



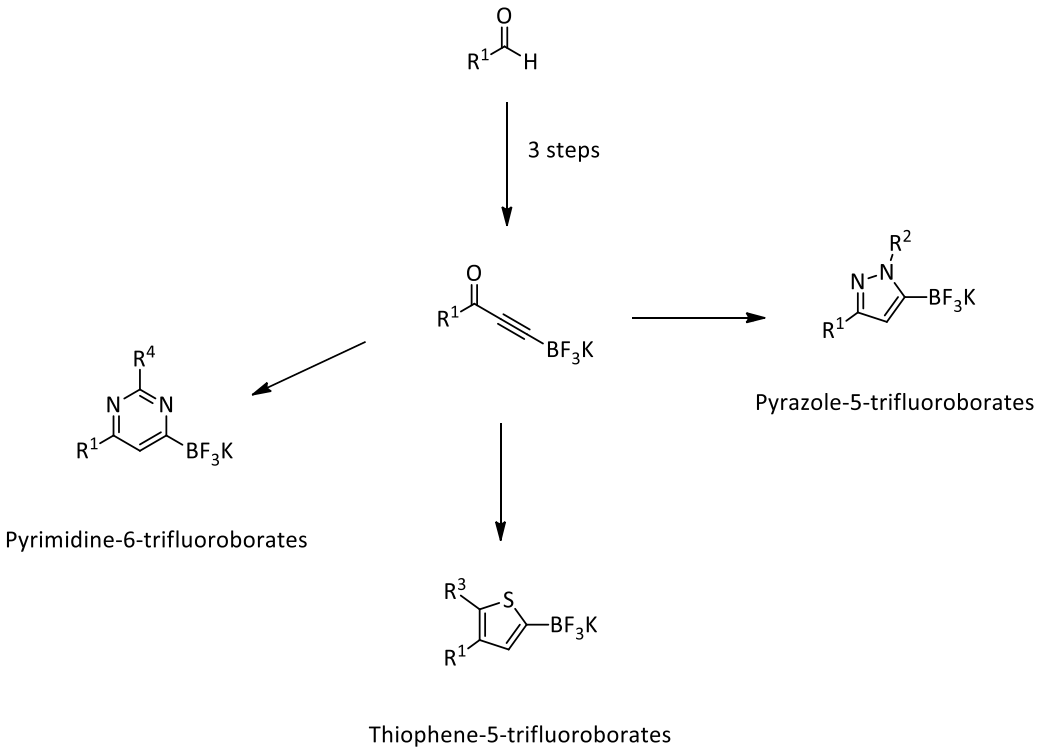
This reaction required overnight heating to reach completion (according to ^{19}F NMR spectroscopy). While we could assign signals corresponding to the expected product on the crude NMR, once again we were unable to isolate clean material.

5. ***Conclusions***

These experiments concluded our attempts to synthesise new ynone trifluoroborates. Using established conditions, we could synthesise various new ynones in modest to high yields in 3 steps from corresponding aldehydes. Interestingly, alkyl and heterocyclic substituents on the aldehyde were tolerated. We have also shown that there are some limitations to the established method such as the presence of a basic nitrogen as well as benzylic (or other oxidisable) positions on the molecules. Despite several attempts, we were unable to find a viable way to overcome these limitations. There are however, other potential synthetic strategies that remain to be investigated.

We now had several ynone trifluoroborates to work with and we set about exploring these as precursors to novel heterocycles bearing a trifluoroborate handle (scheme 36).

Scheme 36. Synthesis of heterocycle-trifluoroborates

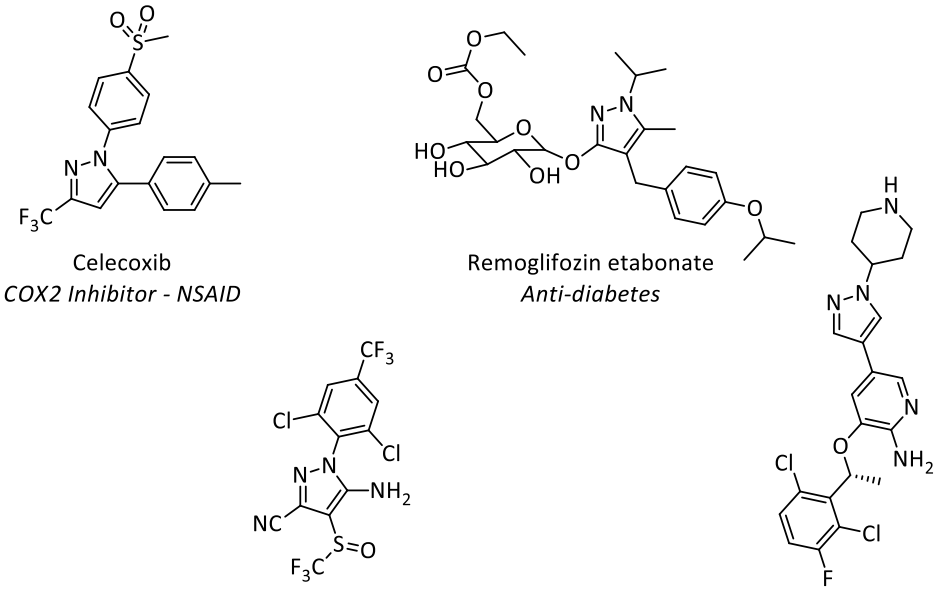


Chapter 3 – Pyrazole Trifluoroborates

1. Introduction

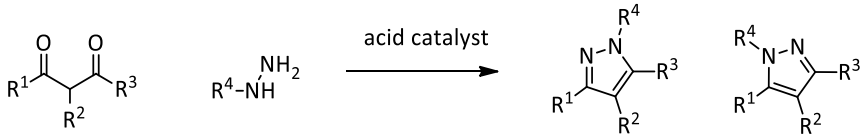
Pyrazoles are known to be valuable molecules. Whereas such scaffolds are utterly absent from the natural world, it has been demonstrated that they have privileged interactions with it. Indeed, pyrazoles have shown a wide range of biological activities (scheme 37) such as anti-inflammatory (Celecoxib),[60] anti-diabetes (Remogliflozin etabonate),[61] anticancer (Crizotinib)[62] and insecticidal (Fipronil)[63] to name only a few. Additionally, they are useful synthetic intermediates for the organic chemist.

Scheme 37. Various biologically active pyrazole-based molecules



The importance of pyrazoles in the chemical sciences has prompted synthetic chemists to devise many ways to access these products. Classical approaches for the formation of the pyrazole core often involve condensation reactions. The most famous of these is arguably the Knorr synthesis which was first disclosed in 1883 (scheme 38).[64]

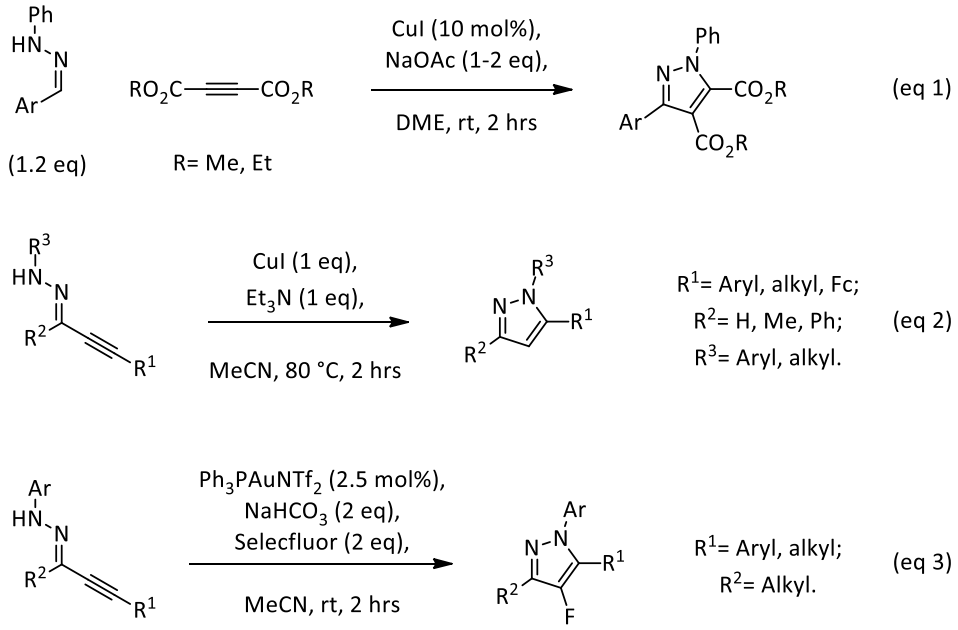
Scheme 38. Knorr pyrazole synthesis



Over the years, the scope of this reaction has been extended to not only diketones but also ketoesters, α,β-unsaturated ketones or aldehydes.[65] Similarly, hydrazone derivatives have shown great potential in condensation reactions to form pyrazoles.[65]

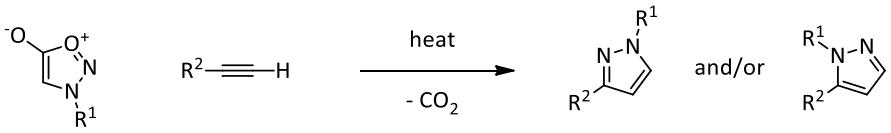
Later on, numerous examples of transition metal catalysed pyrazole synthesis have been reported. For example: amongst others, copper (eq 1,[66] eq 2[67]) and gold (eq 3[68]) proved efficient at promoting the cyclisation of hydrazones and alkynes whether in an intra- or inter-molecular fashion (scheme 39).

Scheme 39. Transition metal catalysed synthesis of pyrazoles



In the 1960's, Huisgen[69] described the use of a novel 1,3-dipole as a pyrazole precursor (scheme 40).

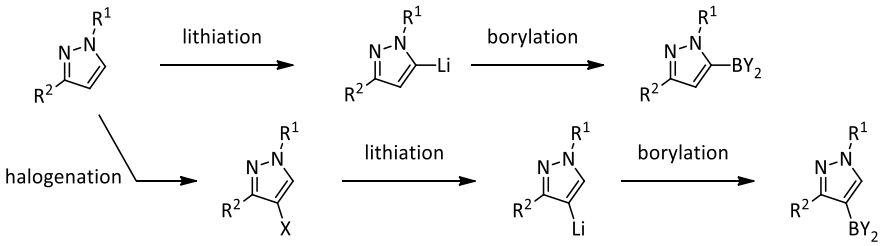
Scheme 40. [4+2] Cycloaddition of sydnones and alkynes



Using the above reagents, called sydnones, he could carry out [4+2] cycloadditions with alkynes in order to yield pyrazole scaffolds. However, due to the high temperatures (usually above 140 °C) and the long reaction times (often longer than one day), the reaction suffered from a limited scope. In the last decade, much effort has been made to overcome those issues: regioselectivity of addition (via the introduction of a directing group for example) and the harsh conditions (via the addition of promoters).

Usually, boron containing pyrazoles are synthesised in a stepwise fashion. First the pyrazole ring is formed using any of the abovementioned methods. Next the boron group is introduced either via a lithiation/borylation or the lengthier halogenation/lithiation/borylation sequence. The method of choice is often dependent on the required position for the boron group (scheme 41).

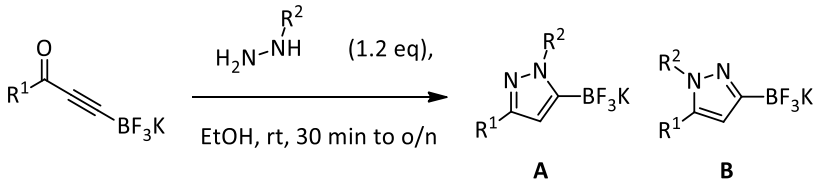
Scheme 41. Classical methods for the introduction of a boron group on a pyrazole ring



Despite some very elegant work on the regioselective functionalisation towards fully substituted pyrazoles, for example using a switchable metal directing group,[70] this process is time consuming and inefficient due to the high number of steps and reagents usually required.

Our group has developed a method for the synthesis of pyrazole boronic acid derivatives that involves the cycloaddition of sydnones and alkynylboronates.[71] To the best of our knowledge however, the use of condensation reactions to this end are very rare. In 2012, our group disclosed that ynone trifluoroborates could undergo condensation reactions with hydrazides to afford the corresponding pyrazoles.[57] The main advantage of this process over the cycloaddition approach was the mild conditions employed. The scope of this chemistry is shown in table 6.

Table 6. Synthesis of pyrazole trifluoroborates



Entry	R^1	R^2	Time (hours)	Yield	Ratio A:B
1	Ph	Me	4	96%	16:1
2	*p*-$MeOC_6H_4$	Me	2	63%	7:1
3	*o*-$MeOC_6H_4$	Me	3	92%	>98:2
4	*p*-$F_3CC_6H_4$	Me	0.5	98%	>98:2
5	Me[a]	Me	o/n	74%	9:1
6	^{n}Pr[a]	Me	o/n	78%	15:1
7	^{t}Bu	Me	o/n	92%	>98:2
8	Ph	**Ph**	o/n	88%	**<2:98**

[a]Reactions heated at 40 °C.

Aryl substituted ynones were well tolerated (entries 1 to 4) in the condensation reaction with methylhydrazine regardless of the electronic properties of the aryl ring: electron-neutral (entry 1), electron-rich (entries 2 and 3) and electron-poor (entry 4) examples all worked well. Simple alkyl chains also performed well under these conditions. A trend could be noted regarding regioselectivity which seem to increase with the steric bulk of the ynone substituent (entries 5 to 7).

Notably, changing the hydrazine reagent to phenylhydrazine (entry 8) led to an inversion in the regiochemical outcome, giving the pyrazole 3-trifluoroborate as the major isomer instead.

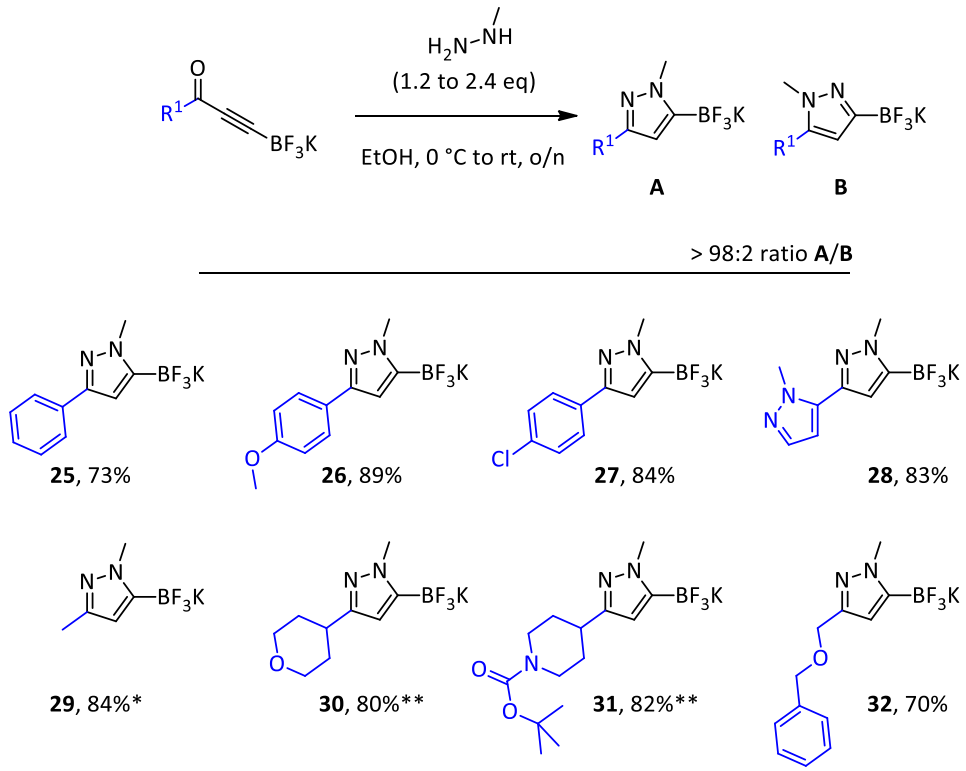
In this chapter, we will describe our efforts in the optimisation of the condensation of methylhydrazine with ynone trifluoroborates, followed by the scope extension to include fragments of value to drug discovery. We will also report our results in the investigations of the reactivity of the product pyrazole scaffolds and their employment in the synthesis of fully arylated pyrazoles.

2. *Synthesis of pyrazole trifluoroborates*

2.1. Improved synthesis of pyrazole-5-trifluoroborates

We began our studies by investigating the reaction of methylhydrazine and the ynone trifluoroborates prepared in the previous chapter. The preliminary report of this condensation by Kirkham *et al.*,[57] suggested that the ratios of regioisomers formed under these conditions spanned a wide range (table 6). Therefore, we set out to find more regioselective conditions that would favour the pyrazole-5-trifluoroborates. Pleasingly, we found that simply lowering the temperature of addition of the hydrazine reagent to 0 °C had a positive impact on regioselectivity and reproducibility of the results (scheme 42).

Scheme 42. Regioselective synthesis of pyrazole trifluoroborates

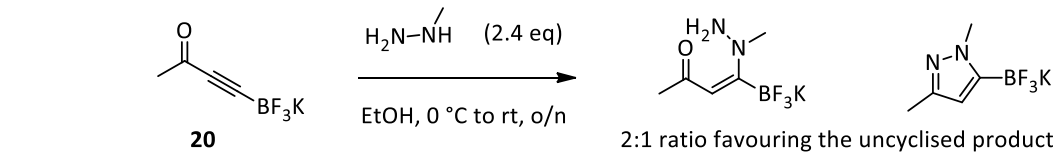


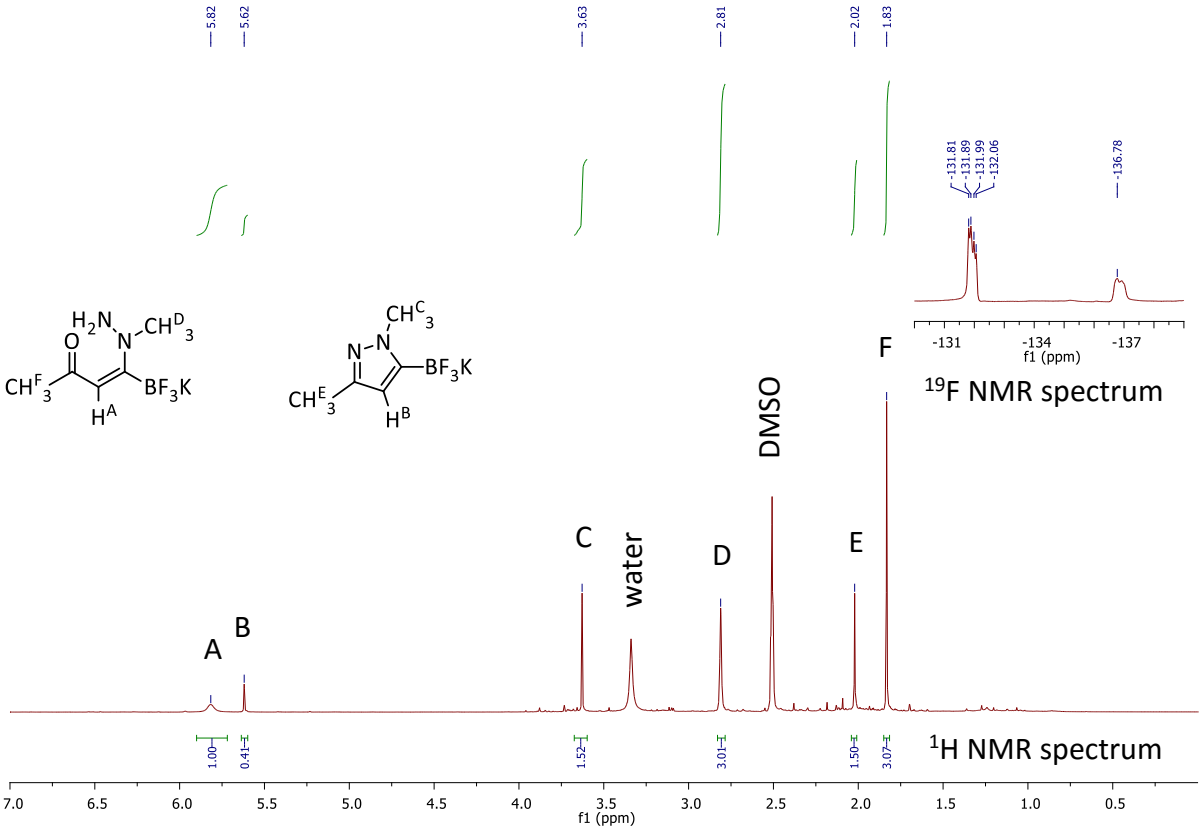
* Heated at 40 °C o/n. ** 90/10 ratio.

We have shown that the scope of the process was broad and all new ynones underwent the condensation reaction in high yields furnishing the desired pyrazoles with excellent regioselectivity. In fact, in only two cases did we see evidence of the formation of the second regioisomer: **30** and **31**.

When methylynone trifluoroborate **20** was submitted to the reaction conditions we could see evidence of the formation of a second product. After NMR analysis (scheme 43), we have tentatively assigned this product as being the 1,4-addition product of *N*-methylhydrazine on the ynone system. In this case, the intramolecular cyclisation requires heating to reach completion.

Scheme 43. NMR evidence for the enamide intermediate



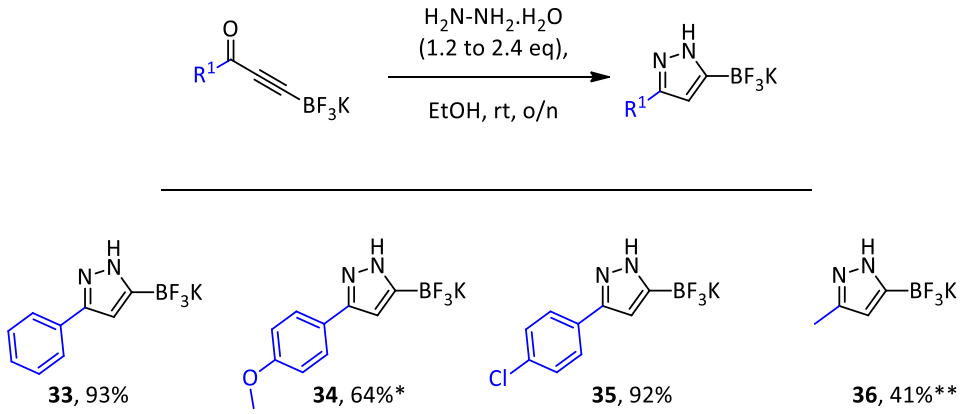


2.2. *N*-H pyrazoles

Having optimised the method to access *N*-methylpyrazoles bearing a trifluoroborate moiety, we next decided to perform the condensation with hydrazine, as the products could then undergo *N*-alkylation to further increase the scope of pyrazoles that could be obtained.

Firstly, we set out to find conditions for the condensation of hydrazine hydrate with a selection of ynone trifluoroborates (scheme 44).

Scheme 44. Synthesis of *N*-H pyrazole trifluoroborates

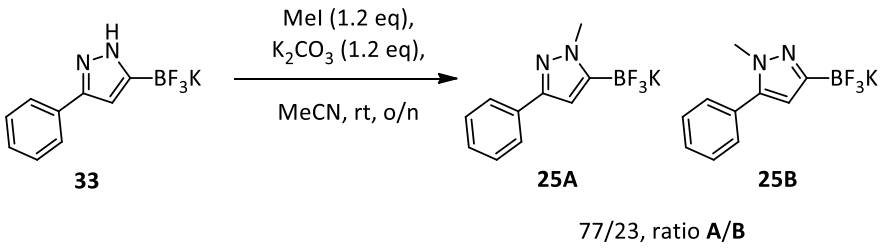


* Heated at 40 °C, o/n. ** Heated at reflux, 2 days.

Since regioselectivity was no longer an issue, we carried out the reactions at room temperature. Both aryl and alkyl substituted ynones underwent the condensation reaction in average to excellent yields. Both electron-rich aryl **34** and alkyl **36** substituted pyrazoles required higher temperatures, 40 °C and 80 °C respectively, as well as longer reaction times to reach complete conversion (as judged by ^{19}F NMR spectroscopy).

Having successfully designed conditions for the synthesis of *N*-H pyrazole trifluoroborates, we then attempted *N*-alkylation (scheme 45).

Scheme 45. *N*-methylation of pyrazole trifluoroborates

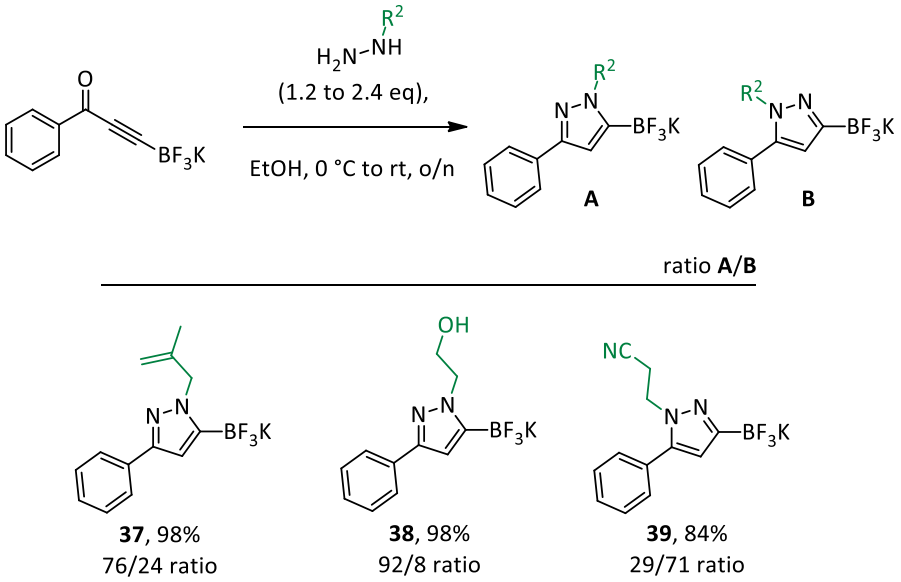


Using methyl iodide as the alkylating agent, we carried out the above reaction. The solid isolated after stirring overnight at room temperature was a mixture of both possible isomers **A** and **B** in a 77/23 ratio, determined by ^{1}H NMR spectroscopy (C-$H_{pyrazole}$ signal 6.58 ppm for isomer **A** and 6.07 ppm for isomer **B**). Considering the poor selectivity resulting from the alkylation compared to the excellent results obtained when condensing methylhydrazine (> 90:10), we decided not to pursue this strategy any further.

2.3. Scope of hydrazide reagents

All synthesised pyrazoles were so far substituted by a methyl group or a proton at *N*1. Facing the low selectivity obtained from the alkylation reaction, we decided to further explore the scope of hydrazides that could be used in the condensation reaction, as well as investigating the impact of different hydrazides on the regioselectivity. Since the above results (scheme 42) seemed to indicate that changing the ynone substituent had little impact on the regioselectivity, we decided to use the phenylynone trifluoroborate **16** as the model substrate for this study (scheme 46).

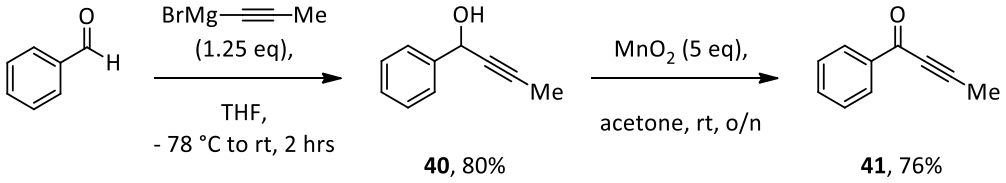
Scheme 46. Scope of hydrazides (major isomer shown in each case)



We choose hydrazines that possessed functionalisable handles in order to produce synthetically useful scaffolds. As expected, changing the hydrazide reagent had a significant impact on the regioselectivity, giving the desired products with good to excellent selectivities (determined by ^{1}H NMR spectroscopy). Interestingly, free alcohols were not only tolerated in the reaction but gave both excellent yield and regioselectivity (compound **38**).

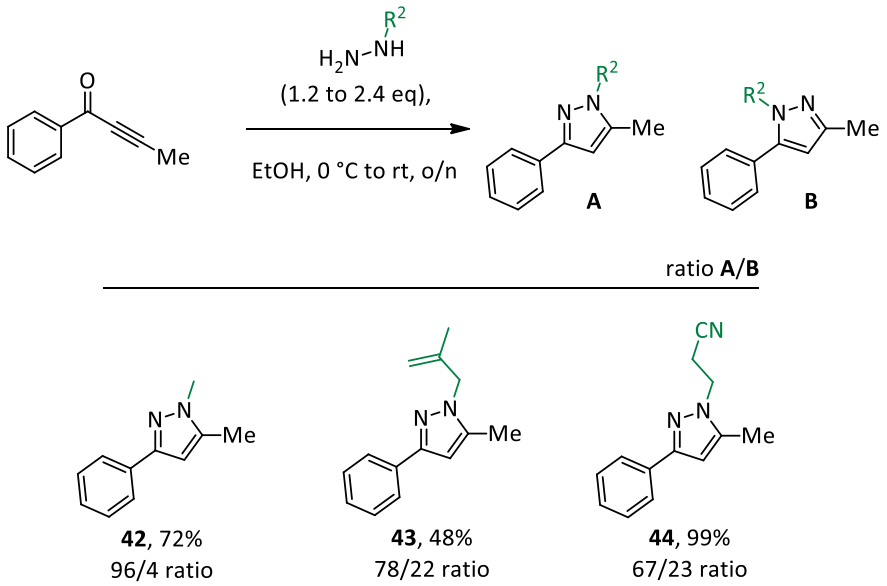
To our surprise, we observed an inversion in the regioselective outcome when using a nitrile substituted hydrazine (compound **39**). We have been so far unable to provide a rationale for this result, although it appears that the borate group plays a role in influencing the regiochemical outcome. Specifically, we synthesised the phenylynone with a methyl group to replace the trifluoroborate moiety as they would have similar size and spatial conformation (scheme 47).

Scheme 47. Synthesis of 1-phenylbut-2-yn-1-one



Next, we carried out the synthesis of the pyrazoles using the same conditions as those employed with the trifluoroborated ynones (scheme 48).

Scheme 48. Synthesis of 5-Me-pyrazoles (major isomer shown in each case).



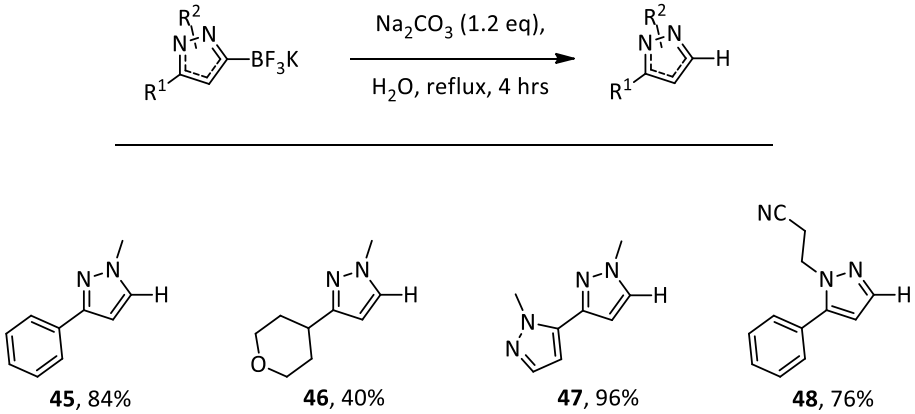
Comparing the results of the 5-Me and 5-trifluoroborate pyrazoles that we had synthesised, we could observe that the ratios (determined by ^{1}H NMR spectroscopy) are very similar if not the same. However, isomer **A** was the major product in all cases when using the boron-free derivative (scheme 48, compound **44**).

2.4. Structure elucidation

The case of the nitrile substituted hydrazine gave us an unexpected regiochemical outcome, prompting us to closely examine our structural assignments. In the first publication on the use of ynone trifluoroborates for the condensation reaction, Kirkham *et al.*[57] had removed the boron handle so as to perform nOe NMR experiments to assign the structure of the major isomer that they had obtained.

We have performed the same reaction on some of our new substrates (scheme 49) so as to compare with literature precedent when possible.

Scheme 49. Protodeborylation of pyrazole trifluoroborates



The spectrum recorded for compound **45** matched literature data,[57] therefore, by analogy, a similar correlation could be made with compounds **46** and **47**. For compound **48**, we found that unfortunately, the drawn isomer had no literature precedent. However, its regioisomer **48A** had been synthesised before and below are its NMR data, together with the data for the isolated compound:

Published as isomer **48A**:[72] ^{1}H NMR (200 MHz, $CDCl_3$), ppm: 3.00 (t, 2H), 4.42 (t, 2H), 6.57 (d, *J* = 3.0 Hz, 1H), 7.30-7.47 (m, 3H), 7.52 (d, *J* = 3.0 Hz, 1H), 7.78 (m, 2H).

Isolated product **48**: ^{1}H NMR (400 MHz, $CDCl_3$), ppm: 2.94 (t, *J* = 7.0 Hz, 2H), 4.37 (t, *J* = 7.0 Hz, 2H), 6.31 (d, *J* = 2.0 Hz, 1H), 7.42 -7.40 (m, 2H), 7.50 – 7.44 (m, 3H), 7.60 (d, *J* = 2.0 Hz, 1H).

From the above data, clear differences could be observed when comparing the two spectra. Indeed, while the protons of the alkyl chain showed almost no changes (0.05 ppm difference which could be explained by the difference in frequency for the two measurements), the same cannot be said for the other signals. The most downfield C*H*$_{pyrazole}$ signal was only slightly shifted, the second C*H*$_{pyrazole}$ signal moved upfield by 0.15 ppm in the second set of data. Finally, the most significant change was observed for the C*H*$_{phenyl}$ signal which showed an upfield shift from 7.78 ppm to the 7.42-7.40 ppm range. The aforementioned observations were the first evidence we had gathered which supported the structural assignment we had proposed.

We have also found it possible to assign the regiochemistry directly using nOe NMR experiments without the need to remove the boron handle. To do so, we first had to compare

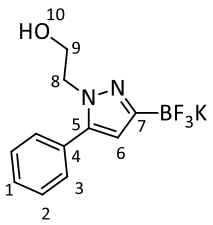
the nOe spectra of both isomers of the same molecule. We had observed that in the case of *N*-methylhydrazine, we could not separate the individual isomers (which arose when performing the reaction at room temperature). However, we were fortunate to find that the isomers of pyrazole **38** were efficiently separated by trituration in acetone. Upon filtration and NMR analysis we discovered that the solid was the pure minor isomer **38B**. After removal of the acetone under vacuum, the residue was dissolved in the minimum amount of acetone and pure isomer **38A** could be precipitated from ether. Separate analysis of both isomers was now possible and the results are detailed below.

Amongst the analyses that we carried out on **38B**, HSQC was first measured to assign protons and carbon atoms on the molecule (table 7).

Table 7. Proton and carbon assignments for 38B (minor isomer)

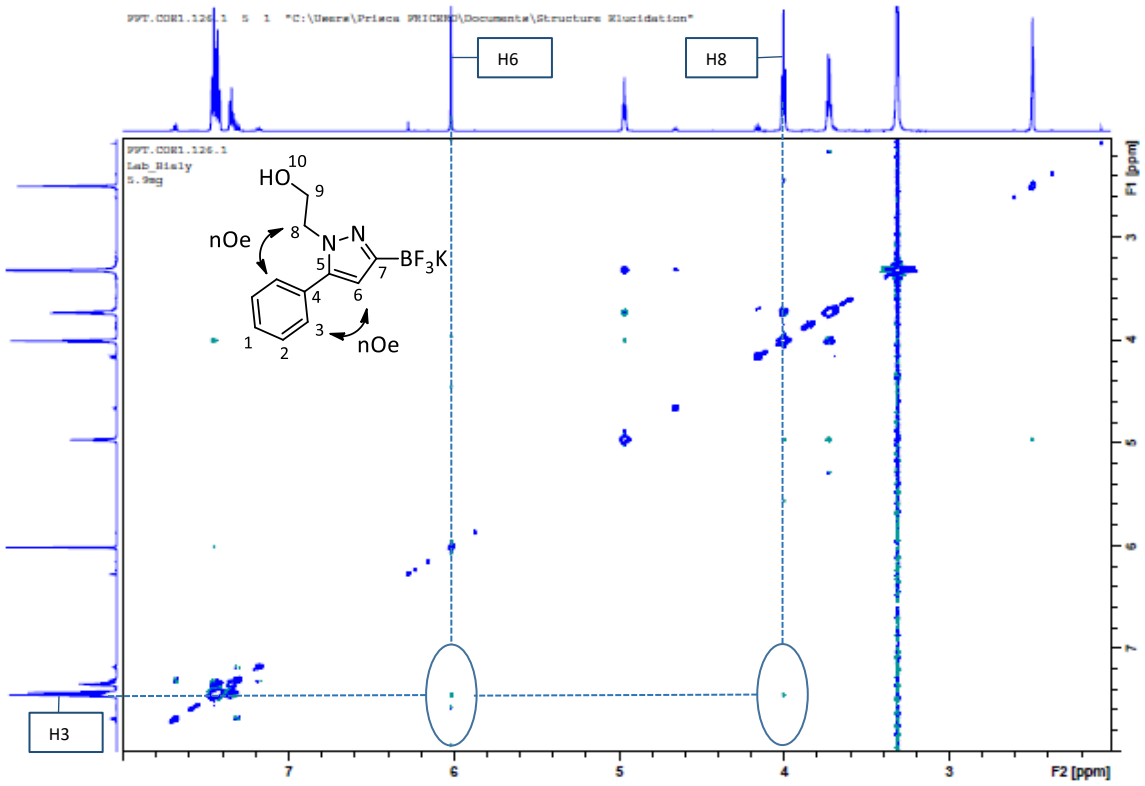
Position	**^{1}H (ppm)**	**^{13}C (ppm)**
1	7.35	127.3
2	7.43	128.44
3	7.46	128.43
4	-	132.1
5	-	141.5
6	6.02	109.3
7	-	ns*
8	4.01	50.3
9	3.73	60.6
10	4.97	-

*ns: not seen due to broadening arising from the quadrupolar relaxation effect.



Then, the nOe experiment was next performed (spectrum 1).

Spectrum 1. nOe of pyrazole 38B



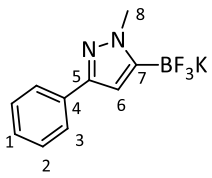
On this spectrum, we have highlighted the areas of interest. Coupling between the *H*6 and *H*3 proton as well as *H*8 and *H*3 are visible. The latter indicates that the substituted nitrogen of the pyrazole core is close to the phenyl substituent which tends to confirm the structure of **38B** as the minor isomer.

We then turned our attention to a substrate which structure had already been assigned.[57] When we measured the nOe spectrum of potassium 1-methyl-3-phenyl-5-trifluoroboratepyrazole **25**, we could observe the absence of signal between the CH_3 and the phenyl ring (table 8 and spectrum 2).

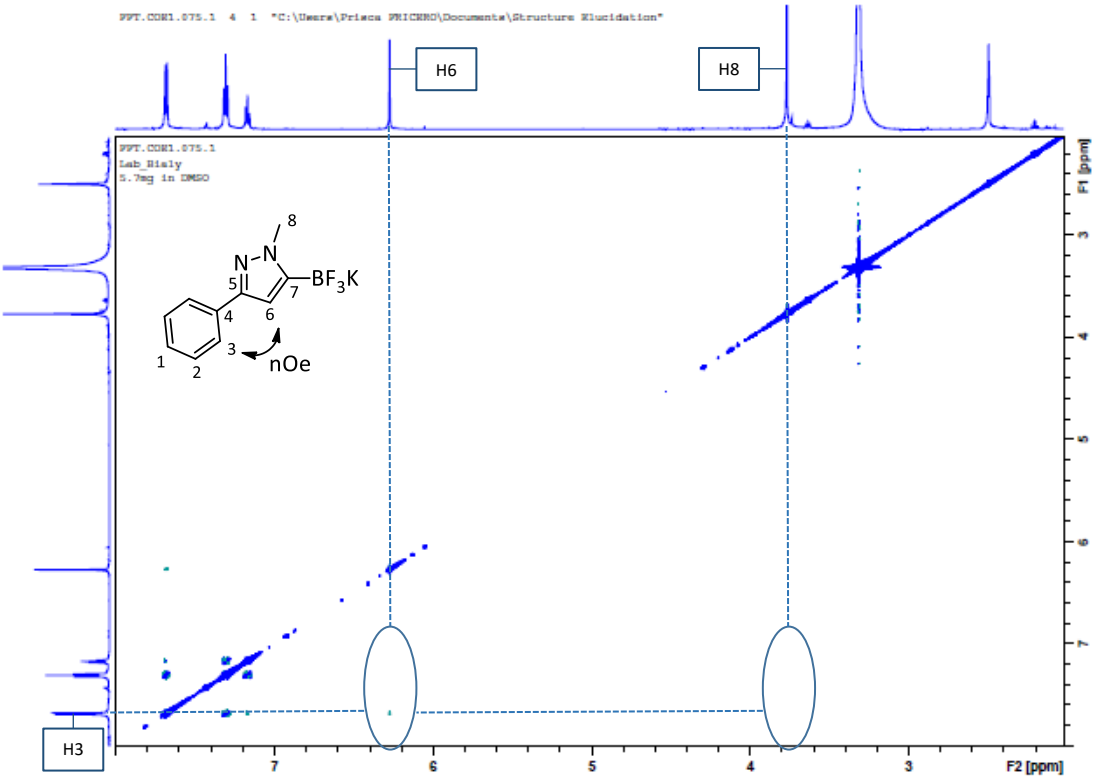
Table 8. Proton and carbon assignments for 25 via HSQC

Position	^{1}H (ppm)	^{13}C (ppm)
1	7.17	126.1
2	7.31	128.3
3	7.68	124.7
4	-	135.0
5	-	147.5
6	6.27	105.4
7	-	ns*
8	3.65	38.0

*ns: not seen due to broadening arising from the quadrupolar relaxation effect.



Spectrum 2. nOe of pyrazole 25



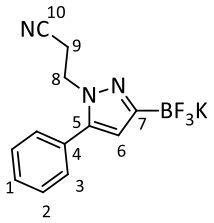
This lack of interaction between the proton at *C*3 of the pyrazole and the *N*-CH_3 was also observed in the remaining pyrazoles that we had chosen to investigate, namely: **28** and **30**.

We also measured the data for the major isomer of the condensation of *N*-ethylcyano-hydrazine **39B** where we had observed an unusual regioselectivity (table 9 and spectrum 3).

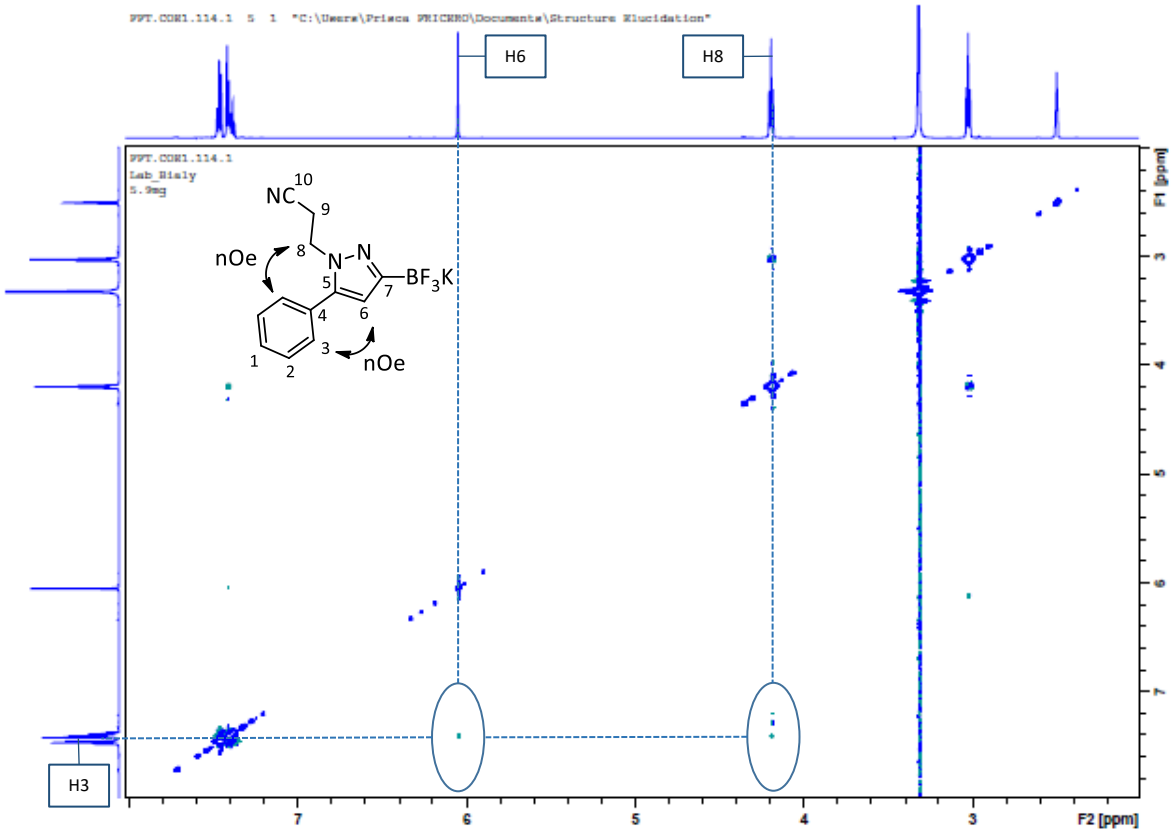
Table 9. Proton and carbon assignments for 39B (major isomer)

Position	^{1}H (ppm)	^{13}C (ppm)
1	7.38	127.63
2	7.46	128.62
3	7.41	128.49
4	-	131.56
5	-	141.65
6	6.05	109.86
7	-	ns
8	4.19	43.67
9	3.02	18.31
10	-	118.90

*ns: not seen due to broadening arising from the quadrupolar relaxation effect.



Spectrum 3. nOe experiment on isomer 39B

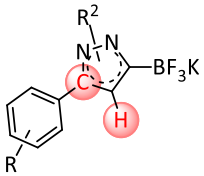


The presence of interactionS between *H*3 and *H*6 as well as *H*3 and *H*8 are consistent with our contention that this condensation reaction displays inverted regioselectivity, as compared to other hydrazine substrates.

Finally, upon analysis of the NMR spectra, we found that it was possible to determine which isomer was obtained by looking at two signals on the 3-aryl substituted pyrazoles. Indeed, by tabulating the NMR data of those two signals a trend can be observed. The pyrazole-5-trifluoroborates have a C-^{1}H signal around 6.30 ppm and a ^{13}C-aryl signal between 147 and 148 ppm making them more downfield compare to the pyrazole-3-trifluoroborates which have respectively a C-^{1}H signal between 6.00 and 6.10 ppm and a ^{13}C-aryl signal around 142 ppm (table 10).

Table 10. Proton and carbon assignments for pyrazole borates

Pyrazole	Pyrazole C-^{1}*H* (ppm)	Pyrazole ^{13}*C*-aryl (ppm)
25	6.27	147.5
26	6.31	147.9
27	6.31	146.9
37A	6.30	148.8
38A	6.29	147.9
37B	6.10	141.8
38B	6.03	141.5
39B	6.06	141.7



In conclusion, these NMR correlations and the nOe experiments have allowed us to rationally assign the structure of the isomers that we have obtained when condensing hydrazide reagents and our ynone trifluoroborates. We could now study the derivatisation of these substrates in order to build complexity and exploit unexplored chemical space.

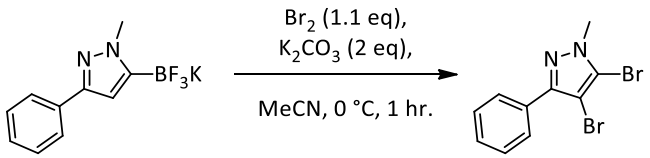
3. Reactivity of pyrazole-5-trifluoroborates

3.1. Towards fully substituted pyrazoles

Our method allowed us to readily access 1,3,5-trisubstituted-pyrazoles bearing a trifluoroborate handle at *C*5. This handle can be further functionalised through various well-known methods. Position *C*4 of our substrates remained unfunctionalised, but we recognised the potential to carry out a halogenation at this site. So, we set out to test conditions to assess the feasibility and compatibility of pyrazole halogenation in the presence of the trifluoroborate handle.

Our first attempt, using a common set of conditions, yielded an unexpected product (scheme 50): the 4,5-dibrominated pyrazole **49**.

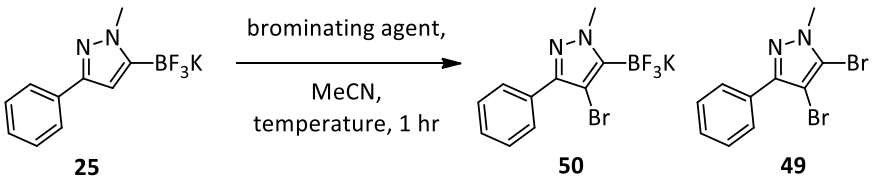
Scheme 50. Bromination of *N*-Me-pyrazole trifluoroborates



25 **49**, 95%

Although bromination at the *C*4 position had occurred, the trifluoroborate handle seemed to be incompatible with this brominating agent. We hypothesised that milder conditions might better accommodate the boron moiety, and so we chose *N*-bromosuccinimide as the brominating agent and set out to conduct a brief optimisation of the reaction conditions (table 11).

Table 11. Optimisation of bromination reaction of 25



25 **50** **49**

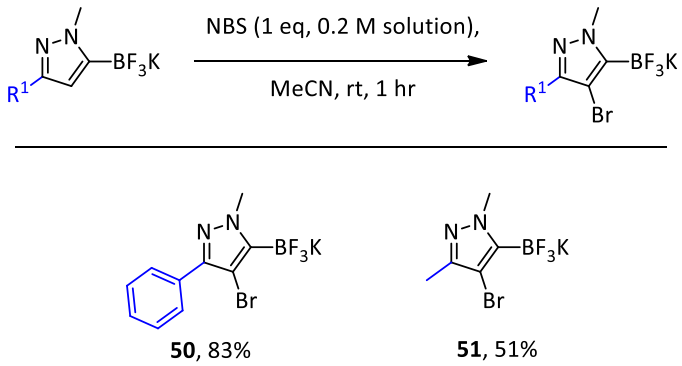
Entry	**Brominating agent, Additive (eq)**	**Temperature**	**Ratio[a] 50/49**
1	Br_2 (1.1), K_2CO_3 (2)	0 °C	**Only 49 isolated**
2	NBS (1)[b]	rt	ratio 4/1
3	NBS (1)[b]	10 °C	ratio 3.2/1
4	NBS (1)[b]	0 °C	ratio 2.5/1
5	NBS (1)[b]	-10 °C	ratio 4.5/1
6	**NBS (1)[c]**	**rt**	**ratio 14/1**
7	NBS (1)[d]	rt	ratio 10/1
8	NBS (2)	rt	**Only 49 isolated**

[a]Ratios determined by ^{1}H NMR spectroscopy of the crude. [b]NBS added as a 0.4 M solution in MeCN. [c]NBS added as a 0.2 M solution. [d]NBS added as a 0.1 M solution.

We observed that using stoichiometric amount of brominating agent led to the synthesis of the desired monohalogenated compound as the major product (entry 2) albeit only in limited chemoselectivity. Our attempts at lowering the temperature showed no visible impact on the chemoselectivity (entries 3 to 5). However, we observed that the concentration of the solution of NBS (entries 6 and 7) was an important parameter, and controlling this aspect allowed us to identify optimum conditions (entry 6) giving excellent selectivity for the monobrominated product **50**. We also showed that, as expected, using an excess of NBS leads to dibromination (entry 8).

We next investigated the scope of the reaction under optimal conditions (scheme 51).

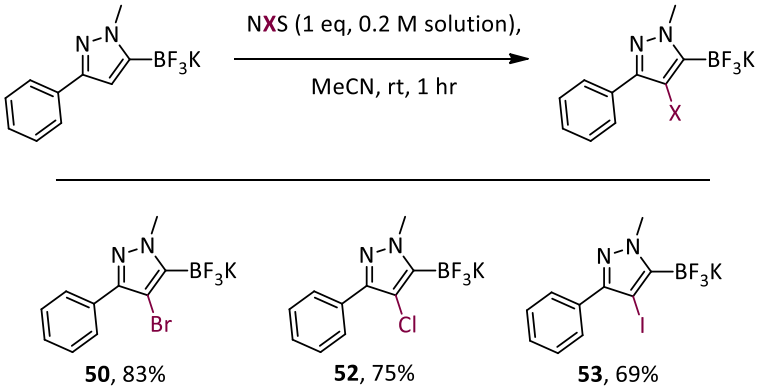
Scheme 51. Bromination of pyrazole-5-trifluoroborates



50, 83% **51**, 51%

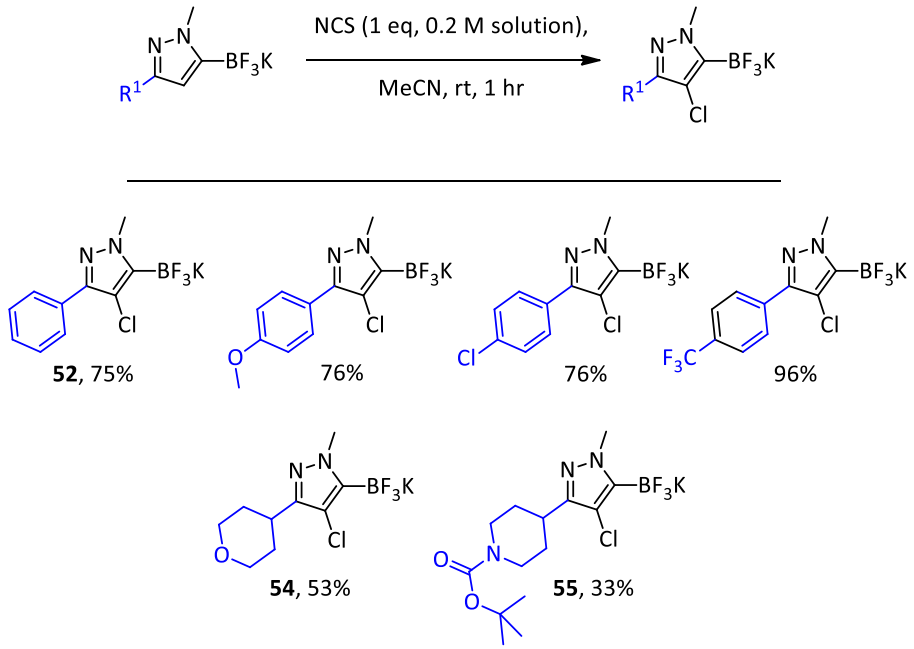
We found that the bromination reaction was compatible with both 3-phenyl and 3-methyl-*N*-methyl-substituted pyrazoles (compounds **50** and **51**). Notably, the reaction conditions that we developed were not only very efficient for the selective introduction of a bromine group at *C*4 but, changing the reagent to *N*-chloro and *N*-iodosuccinimide resulted in the highly selective introduction of a chloride or iodide at the same position (compounds **50**, **52** and **53** – scheme 52) in excellent yields.

Scheme 52. Halogenation of 3-phenylpyrazole



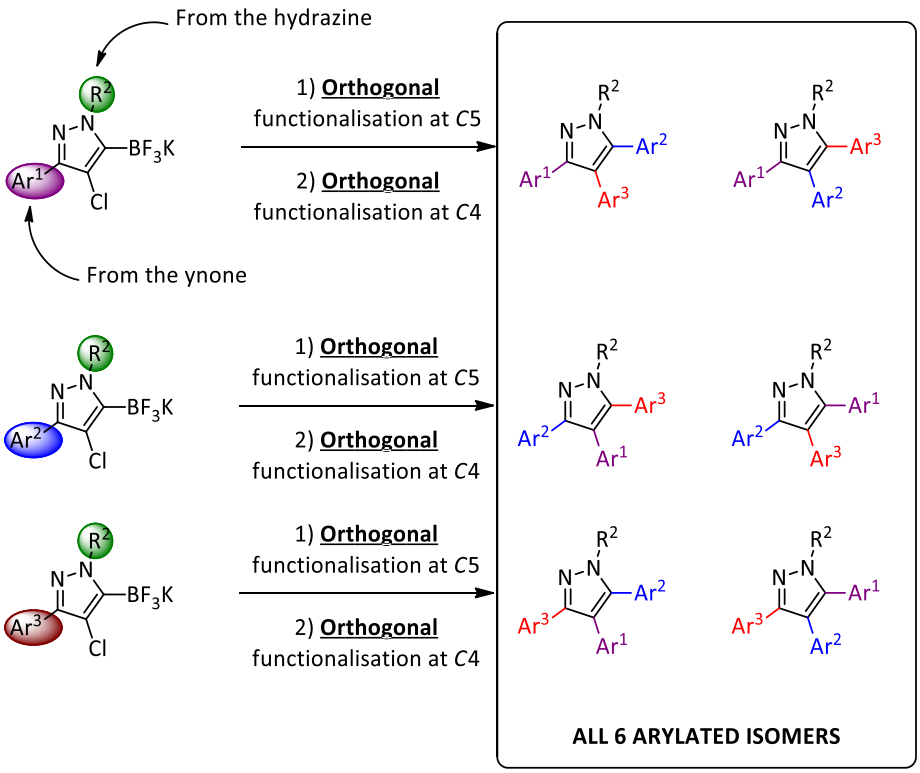
Furthermore, we elaborated the scope for the chlorination across a range of pyrazole-5-trifluoroborates (scheme 53), these proceeded in good to excellent yields in all but one case.

Scheme 53. Chlorination of pyrazole-5-trifluoroborates



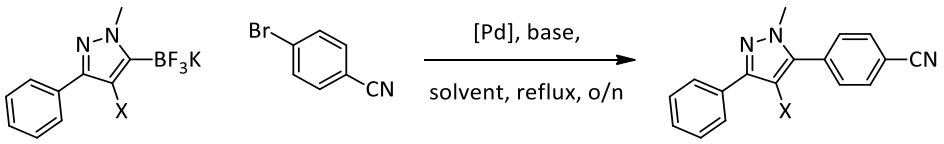
With access to a wide variety of fully functionalised pyrazoles, our next goal was to demonstrate that we could make fully arylated pyrazoles with a short sequence. With specific regard to 3,4,5-trisubstituted pyrazoles, there are six possible isomers that could be synthesised. Our method allowed the easy, two-step access to bifunctional compounds where the substituent at *C*3 is fixed by the ynone reagent used in the first step. If we were able to orthogonally functionalise both *C*4 and *C*5 then we would be able to synthesise all possible fully arylated pyrazole isomers with complete regiocontrol (scheme 54).

Scheme 54. Orthogonal functionalisation of bifunctional pyrazoles



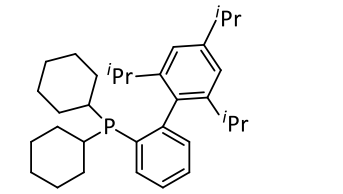
Our easy access to 4-halo, 5-boryl pyrazoles suggested that the Suzuki-Miyaura cross-coupling would be the method of choice for obtaining these fully arylated targets. Of course, we foresaw several issues arising from this strategy. The biggest to overcome was that both reactive handles involved in Suzuki reaction, namely a boron and a halogen moiety, could potentially undergo self-coupling reactions. Indeed, our preliminary experiments using the brominated pyrazole **50** generated complex mixtures of unidentifiable compounds, even after catalyst screening (table 12).

Table 12. Suzuki-Miyaura cross-coupling on pyrazole-5-trifluoroborates

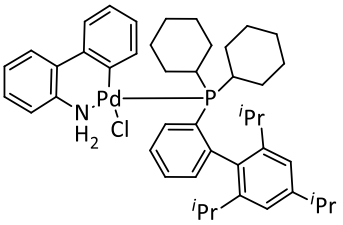


Entry	X group (eq)	Palladium catalyst (mol %)	Base (eq)	Solvent	yield
1	H (1.15)	$Pd(OAc)_2$ (3), XPhos (6)	Na_2CO_3 (2)	EtOH	36%
2	Br (1.14)	$Pd(OAc)_2$ (3), XPhos (6)	Na_2CO_3 (2)	EtOH	< 8%
3	Br (1:1.5)	PdXPhosG2 (10)	Na_2CO_3 (2)	DME/H_2O (1:1)	0%

Using a set of conditions that proved efficient on simple pyrazole trifluoroborates[57] (entry 1), we attempted to couple bromopyrazole **50**. However, although we could isolate the desired compound, the yield was much lower than expected. Changing the solvent, temperature and the catalyst system did not improve matters.



XPhos
ligand

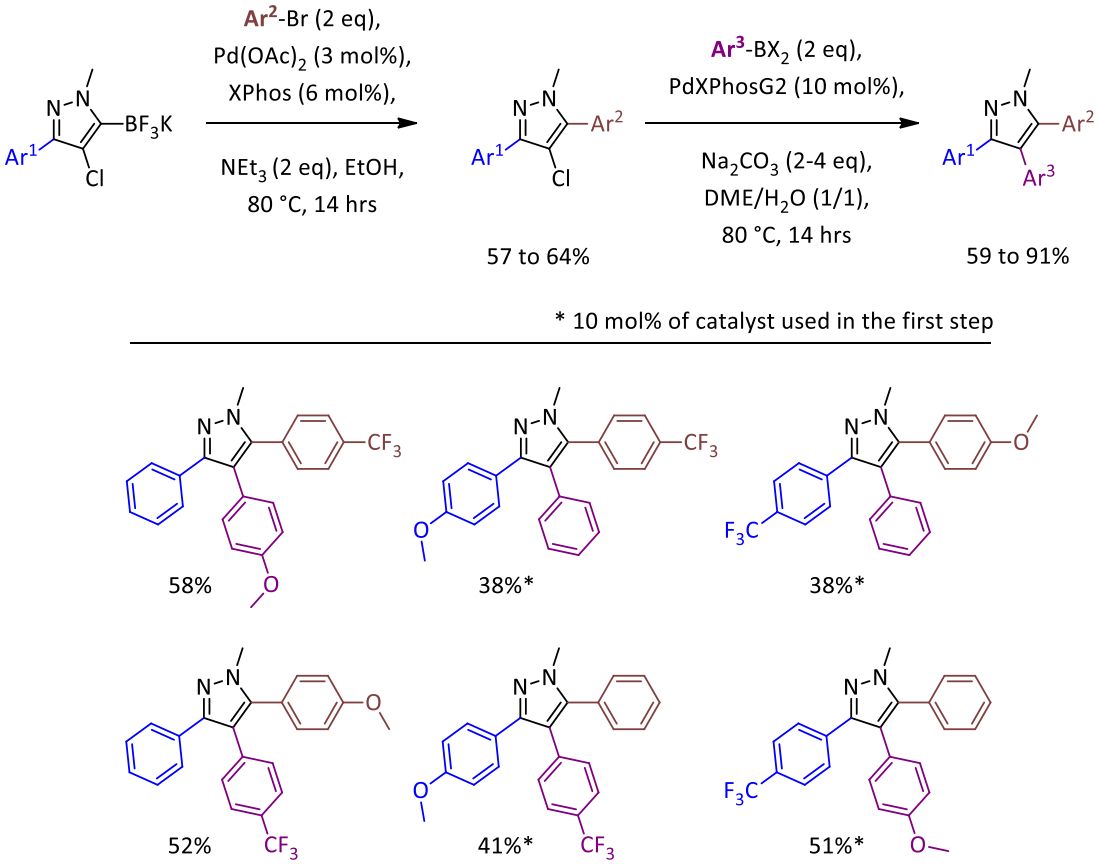


PdXPhosG2
2nd generation precatalyst

Figure 3. Structure of reagents in table 12

Fortunately, the solution to our problem came from the versatility of the halogenation reaction. Specifically, as shown in scheme 52, we coulkd easily introduce various halides at *C*4 making the reactivity at this position tunable. With this hypothesis, the project was handed to Andy Brown, a fellow student, who was able to exploit this aspect of the chemistry to successfully develop conditions for the orthogonal functionalisation of both handles (scheme 55).

Scheme 55. Orthogonal Suzuki reactions at *C*5 and *C*4 on our pyrazoles-5-trifluoroborates



As shown in scheme 55, he was able to develop conditions that allowed to first react the carbon-boron bond at *C*5 and, in a second Suzuki reaction, insert another aryl group at *C*4. Indeed, the lower reactivity of the chloride, as compared to the bromide, allowed for the selective reaction at the boron moiety in the presence of the $Pd(OAc)_2$/XPhos catalyst system. All six precursors to fully arylated pyrazoles were isolated in high yields regardless of the electronic properties of the brominated coupling partner (electron-rich or -poor). In most cases however, the desired compounds were isolated together with a small amount of the protodeborated by-product.

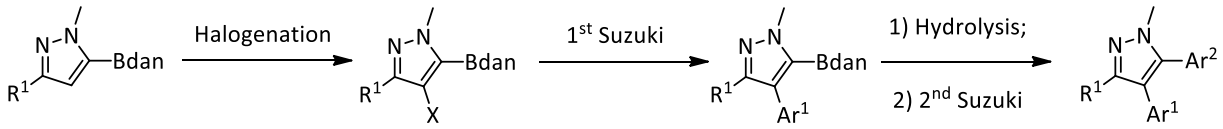
In the second step, he designed efficient conditions for the reaction of the chloride at *C*4 using the Buchwald precatalyst PdXPhosG2 and sodium carbonate as base. He also found that changing the solvent for a 1/1 mixture of DME and water gave the best results.

In conclusion, following our method, 1,3,5-trisubstituted pyrazoles could be synthesised in one-step from the condensation of ynone trifluoroborates and *N*-methylhydrazine. Furthermore, despite the boron handle present on these compounds, we could selectively halogenate the *C*4 position in excellent yields. Finally, we developed conditions to orthogonally conduct Suzuki-Miyaura cross-coupling reactions giving rise, in only 4 steps, to all 6 possible isomers of these fully arylated pyrazoles.

3.2. Ligand exchange on the boron atom

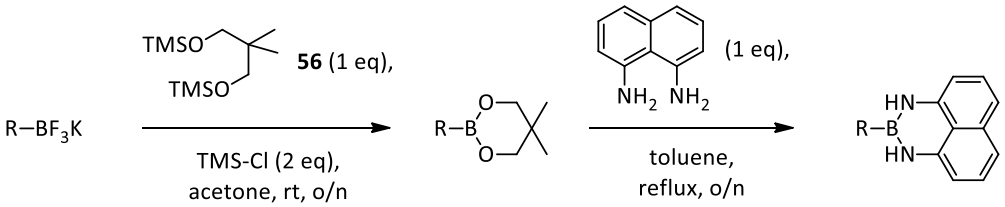
At the same time as trying to develop a pathway to fully arylated pyrazoles, we were investigating the possibility to change the boron handle to facilitate the orthogonal functionalisation that would follow. We therefore turned to the boronamide functional group as the Bdan group has been presented as being inert to transmetalation.[73] We envisioned that if we could synthesise pyrazoles bearing this Bdan handle instead of the trifluoroborate one, then halogenate the *C*4 position, we could prepare a complementary class of bifunctional reagents. Specifically, these compounds would first react at the halide and then the borate group would be activated towards coupling in a subsequent step (scheme 56).

Scheme 56. Plans behind the synthesis of Bdan derivatives



When we started our investigations, the only known way to transform trifluoroborates into Bdan derivatives was a two-step process according to the sequence in scheme 57.[74]

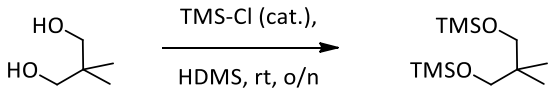
Scheme 57. Ligand exchange from BF_3K to Bdan



This sequence is inconvenient as it requires the synthesis of a boronic ester before carrying out the ligand exchange to the boronamide. Also, whereas the 1,8-diaminonaphthalene is commercially available, the diprotected diol used for the first step is not.

Nonetheless, we began by following the two-step literature method. Accordingly, the disilyl ether was synthesised in acceptable yield after some optimisation (table 13).

Table 13. Synthesis of the di-TMS protected diol

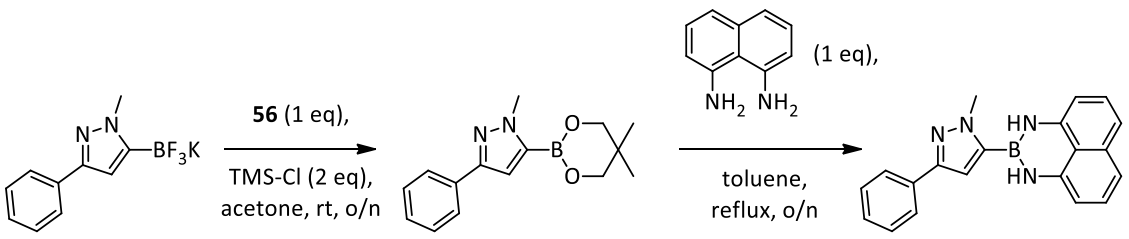


56

Entry	HMDS	Isolated yield
1[75]	1 eq	59%
2	1.2 eq	42%
3	1.5 eq	55%

Product **56** was found to be very volatile, meaning some product was inevitably lost when evaporating fractions after flash chromatography. However, the reaction could be scaled up to 2 g yielding enough product to continue with the synthesis (scheme 58).

Scheme 58. Ligand exchange from trifluoroborate to boronamide

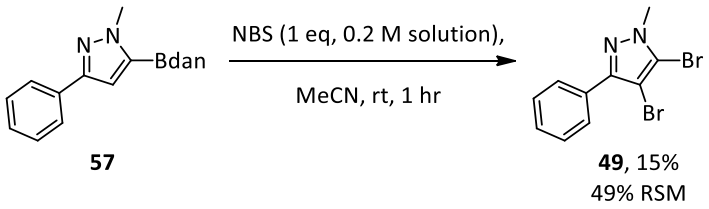


25 not isolated **57**, 42%

As described in the literature,[75] we could synthesise the desired product albeit in low yield. Our attempt at isolating the boronic ester intermediate yielded 27% of pure product, which could mean that the product was unstable on silica column. We could not reasonably

tell which step had to be optimised. Furthermore, we observed, when attempting to brominate Bdan pyrazole **57**, that the Bdan handle was even less stable to halogenation then the trifluoroborate handle (scheme 59), as it showed only 50% conversion and the 4,5-dibrominated product **49** as the only isolated product of this reaction.

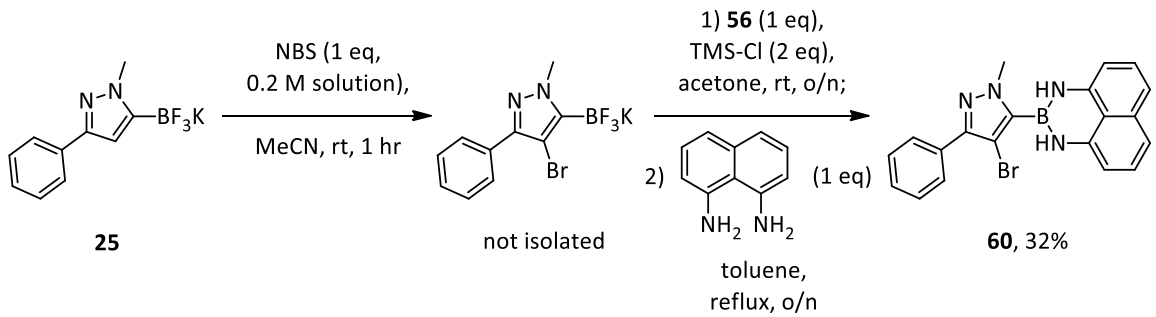
Scheme 59. Bromination of pyrazole-5-Bdan



57 **49**, 15%
49% RSM

To solve this problem, we decided to switch the order of these reactions, meaning, first carrying out the bromination of the pyrazole-5-trifluoroborates followed by ligand exchange to produce the desired 4-bromo-5-Bdan pyrazoles (scheme 60).

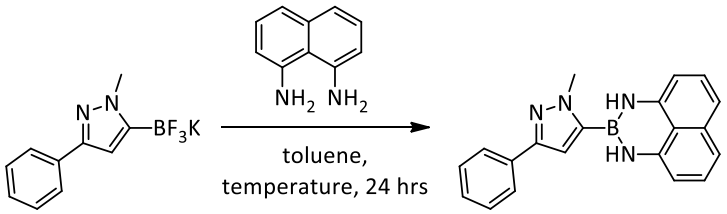
Scheme 60. Synthesis of 4-bromo-5-Bdan pyrazole



25 not isolated **60**, 32%

Following this sequence of reactions provided the desired 4-bromo-5-Bdan pyrazole **60**. However, the issue of the low yield was not solved. As the yields from the bromination were usually very high (see scheme 51), we believed the problem was likely to originate from the ligand exchange step, and so investigated this step further (table 14).

Table 14. Optimisation of the Bdan ligand exchange



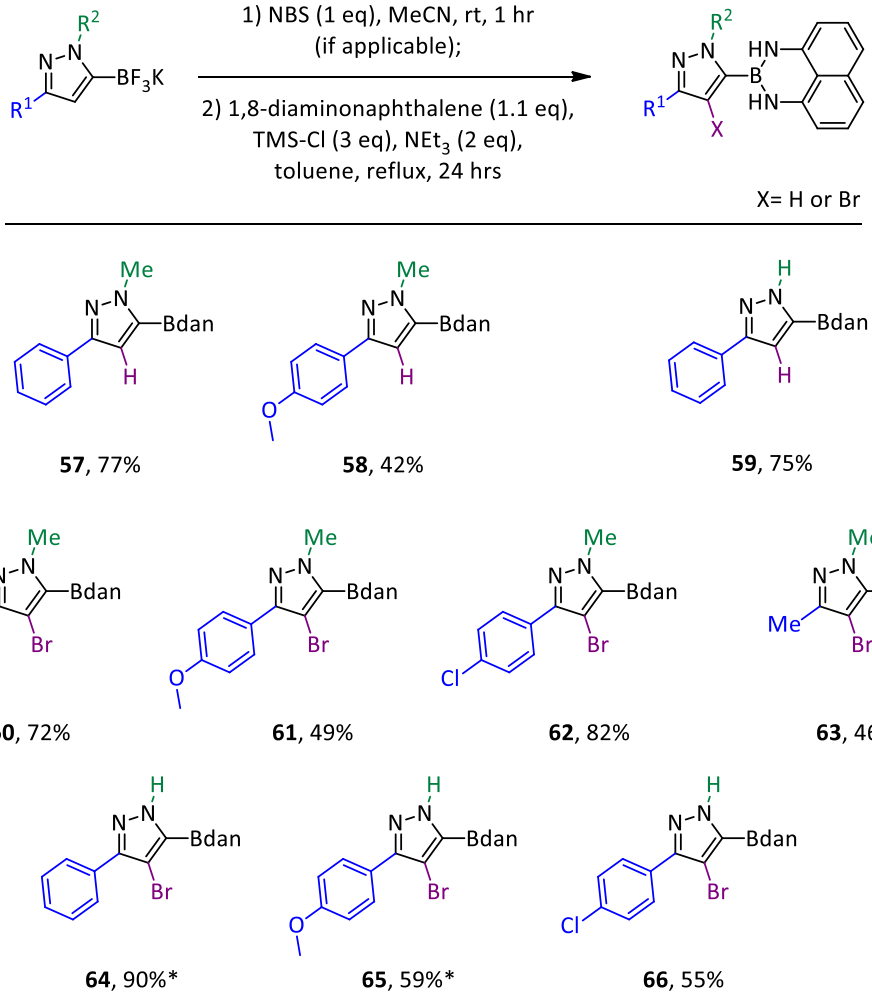
25 **57**

Entry	1,8-dan (eq)	Additive (eq)	Solvent, temperature (°C)	Yield
1	1.1	TMS-Cl (2)	Toluene, reflux	23%[a]
2	**1.1**	**TMS-Cl (3), NEt_3 (2)**	**Toluene, reflux**	**77%**
3	1.1	TMS-Cl (3), NEt_3 (2)	Toluene, rt	37%
4	1.1	TMS-Cl (3), NEt_3 (2), $^nBu_4NI$ (0.1)	Toluene, rt	47%
5	2	TMS-Cl (3), NEt_3 (2), $^nBu_4NI$ (0.1)	Toluene, rt	55%

[a]Mass balance consisted of protodeborylated material.

Using only the Lewis acid and the diamine in the reaction (entry 1) was successful but generated a significant amount of protodeborated material. We believed this to be due to the formation of Brønsted acid, and so we introduced a base in the reaction mixture (entry 2). Indeed, adding a base improved the yield dramatically up to 77%. Decreasing the temperature (entry 3), however proved detrimental to the reaction. We also tried adding tetrabutylammonium iodide (entry 4) in order to exchange the potassium for a tetrabutylammonium counterion, to improve the solubility of **25** in common organic solvents. Finally, adding an excess of diamine (entry 5) did not show any substantial improvement in the yield and it also proved significantly more difficult to isolate the product free of the unreacted 1,8-diaminonaphthalene. We had therefore developed highly efficient conditions for the ligand exchange from pyrazole-5-trifluoroborates to 5-Bdan analogues and we wanted to investigate the scope of this reaction (scheme 61).

Scheme 61. Synthesis of 5-Bdan pyrazole derivatives



* Inseparable mixture with succinimide

We have shown that this new method of ligand exchange was compatible with a wide range of substituents at *C*3 as well as *N*-H pyrazoles. Notably, the electron-rich pyrazoles **58**, **61**, and **65** were synthesised in lower yield compared to the rest of the scope. 3-Alkyl substituted pyrazole **63** seemed to also suffer from a reduced reactivity. Nevertheless, we could reach a wide variety of bifunctional compounds: bearing a halogen at *C*4 and a protected boron moiety at *C*5.

We did not pursue our investigations into the selective functionalisation of both handles for two reasons: first, in early 2015, Churches and coworkers,[76] published a similar reaction for the ligand exchange between trifluoroborates and Bdan species. He showed that aryl, ethylenic, allylic and alkyl trifluoroborates could undergo the desired transformation using two equivalents of TMS-Cl as Lewis acid, two equivalent of potassium carbonate as a base in acetonitrile at rt. Secondly, we had shown that there was no need to "protect" the trifluoroborate handle, making it inert to transmetalation, to perform selective palladium catalysed reaction at *C*5 and *C*4 (see section 3.1.).

4. Conclusions

We had designed a novel four-step synthesis of fully arylated pyrazoles. Such synthesis included the condensation of our ynone trifluoroborate susbtrates with hydrazine reagents to yield a wide scope of pyrazoles bearing a boron handle that was readily installed. Following this reaction by a chlorination using *N*-chlorosuccinimide as a mild halogenating agent proceeded chemoselectively. The final two steps were the orthogonal Suzuki cross-couplings at *C*4 and *C*5.

Through our investigations, we have conducted experiments proving the structure of the major isomer obtained for each condensation of ynone trifluoroborates and hydrazides. We have also shown the versatility of our halogenation conditions, as it allows the introduction of bromine, chlorine as well as iodine at *C*4. Finally, we have developed a method to convert trifluoroborated pyrazoles into their boronamide derivatives.

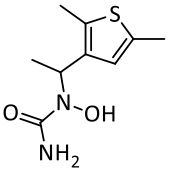
We next decided to follow up on the excellent results obtained in the condensation reaction of our ynone trifluoroborate substrates.

Chapter 4 – Thiophene Trifluoroborates

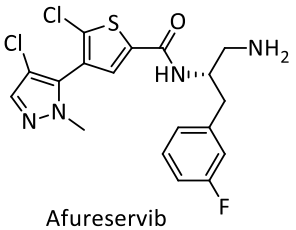
1. Introduction

In line with many other heteroaromatic scaffolds, thiophenes are very valuable compounds in the chemical sciences. They have demonstrated potent biological activities such as anti-inflammatory,[77] anticancer (Afuresertib)[78] properties, and in the treatment of Alzheimer's disease (Begacestat)[79] to name a few (scheme 62).

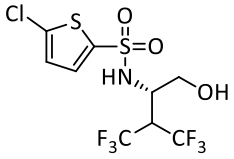
Scheme 62. Biologically active thiophene based compounds



Anti-inflammatory



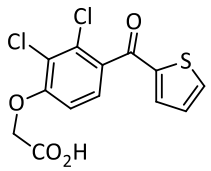
Afureservib
Cancer treatment



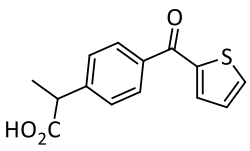
Begacestat (GSI-930)
Alzheimer's disease

However, over the years, the thiophene ring has become a structural alert on drug candidates because of its demonstrated tendency for bioactivation, in other words, the thiophene is transformed in the body into another active molecule, often with adverse effects.[80] Indeed, there are many reported examples of drug candidates or marketed thiophene-based drugs which, despite their high potency, were withdrawn or never made it to the market. For example, Tienilic acid[81] and Suprofen[82] (scheme 63) which are respectively, non-steroidal anti-inflammatory and diuretic molecules, proved to be toxic to humans and animals because of their metabolic bioactivation.

Scheme 63. Drugs removed from the market because of metabolic bioactivation



Tienilic acid

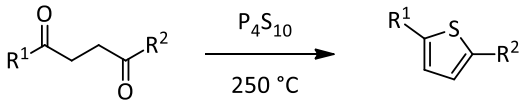


Suprofen

Thiophene rings also have other diverse uses such as their incorporation into a wide range of polymers for material science[83] (semi-conducting polymers for example[84]) and coordination chemistry[85].

Thiophene rings are usually synthesised through condensation reactions. Historically, the first example was published by Paal and Knorr. It involved the condensation of 1,4-dicarbonyl compounds with a source of sulfur (scheme 64).

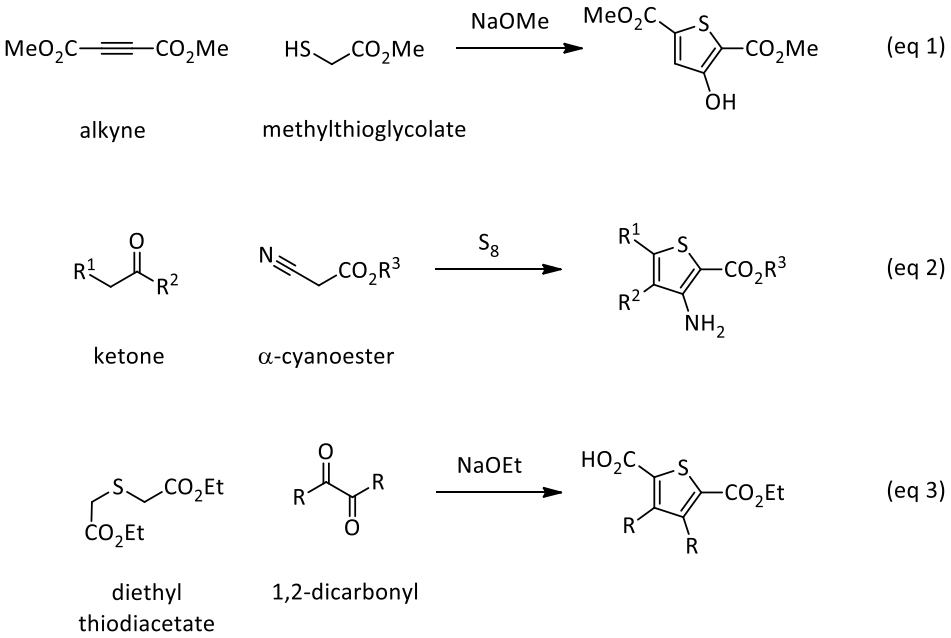
Scheme 64. Paal-Knorr thiophene synthesis



Over the years, other sulfiding agents have been used in place of phosphorus pentasulfide, Lawesson's reagent and bis(trimethylsilyl)sulfide being two examples.

Scheme 65 describes three commonly established synthetic approaches to thiophenes: Fiesselmann (eq 1), Gewald (eq 2) and Hinsberg (eq 3) reactions.

Scheme 65. Fiesselmann, Gewald and Hinsberg reactions



In the reactions mentioned above, regioselectivity represents an issue when using unsymmetrical reagents. In the last few decades a lot of work has been undertaken to address this issue. In this regard, functionalised alkynes appear to hold significant promise.

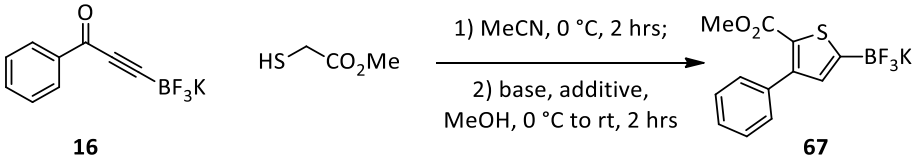
There are now a number of strategies available to convert alkynes into thiophenes.[86] The specific examples that attracted our attention were the Fiesselmann-type condensations. Indeed, these involve the reaction of an ynone and a functionalised methanethiol reagent. We envisaged that our ynone trifluoroborates could be potentially suitable substrates for this reaction, offering access to a novel and functionalisable scaffold. Additionally, studies on the Fiesselmann reaction were largely restricted to methylthioglycolate as the source of sulfur, which gave us room to extend the scope in this direction.

We report in this chapter our results on expanding the scope of this Fiesselmann-type condensation regarding both substrates (ynone and methanethiol), as well as showing the synthetic utility of our new thiophenes bearing a readily installed trifluoroborate handle.

2. *Synthesis of 2-CO_2Me-thiophenes*

Obretch was the first to report the Fiesselmann-type condensation of ynones with methylthioglycolate to give highly substituted thiophenes.[87] In considering how this chemistry might be adapted for the synthesis of trifluoroborate salts, we were concerned that the required use of a base in this reaction could cause protodeboration in our substrates/products.

Table 15. Synthesis of thiophene trifluoroborates



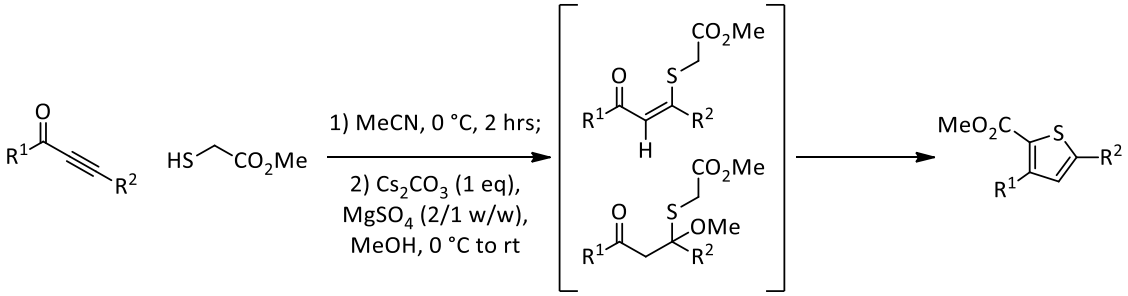
16 **67**

Entry	thiol (eq)	Base (eq)	Additive	Results
1	1	Cs_2CO_3 (1)	$MgSO_4$	50% conversion[a]
2	1.1	Cs_2CO_3 (2)	$MgSO_4$	50% yield
3	1.1	K_2CO_3 (2)	$MgSO_4$	40% yield
4	1.1	K_2CO_3 (2)	none	75% yield

[a]Determined by ^{19}F NMR spectroscopy.

Fortunately reproducing the published conditions (entry 1) did not show sign of protodeboration, however, we could observe two distinct signals. According to the mechanism described by Obretch *et al.*,[87] we believed that one signal corresponded to the desired product and the other might belong to the proposed reaction intermediate (in brackets in scheme 66).

Scheme 66. Proposed reaction mechanism.

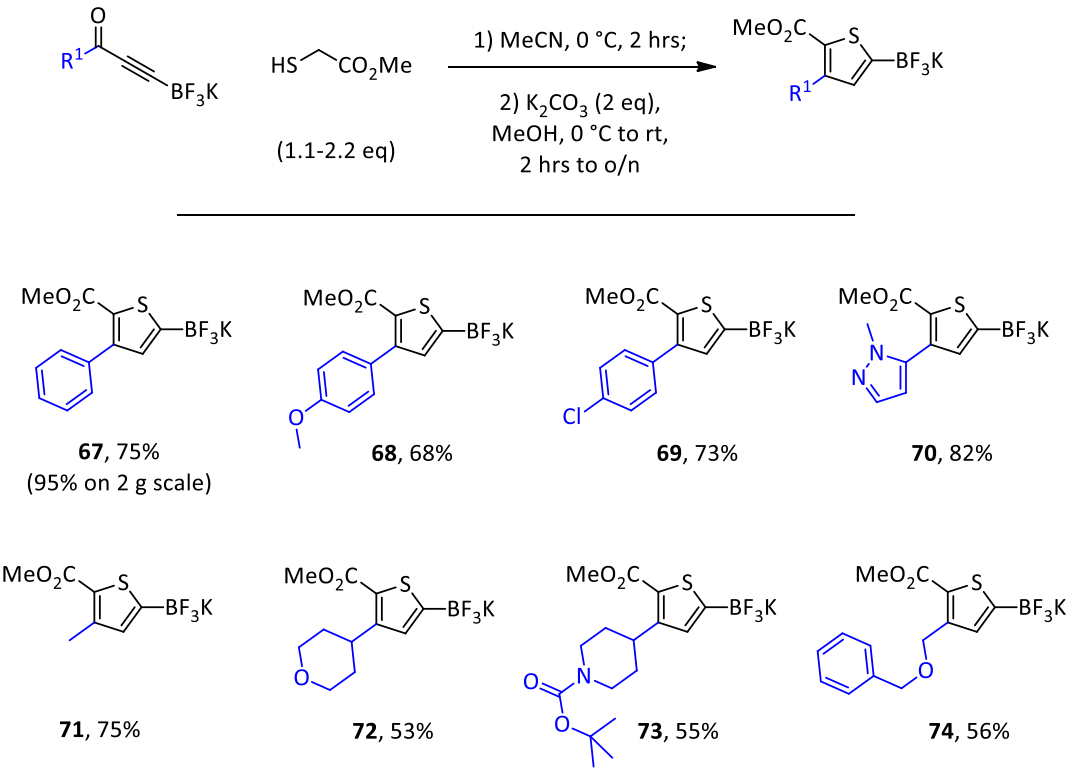


The optimisation of the reaction conditions (table 15) allowed us to find that a two-fold excess of base was required for the reaction to reach completion within two hours (entry 2). Out of concern for potential counterion exchange, we decided to assess the efficiency of potassium carbonate to replace cesium carbonate (entry 3) and we were happy to see that it performed similarly driving the reaction to completion. Finally, upon investigating the use of the drying agent, we found that not only was magnesium sulfate unnecessary for the reaction to proceed, but also that removing the additive seemed to facilitate the isolation of pure

material resulting in higher isolated yields.

As we had now developed suitable conditions for the condensation of methylthioglycolate and our model ynone, we could show the extent of the scope using the range of ynone substrates we had previously synthesised (scheme 67).

Scheme 67. Scope of ynone trifluoroborates for the synthesis of thiophene-5-trifluoroborates



As shown in the above scheme, all ynones were well tolerated and gave high to excellent yields. Notably, we could scale up the synthesis of **67** up to 2 grams where we saw an increase in the isolated yield, which was probably due to a more efficient precipitation during purification. Indeed, from our observations, this method tended to give higher yields when the reactions of trifluoroborates were carried out on a larger scale, which was consistent with previous observations (see chapter 2). In line with the earlier work on the condensation to form pyrazoles (see chapter 3), alkyl substituted ynones were less reactive than their aryl substituted analogues. The reaction time had to be extended from 2 to 20 hours in order to reach completion. Finally, the lower isolated yields could be explained by the observed propensity of such compounds to coordinate with solvent (water or acetone) making their

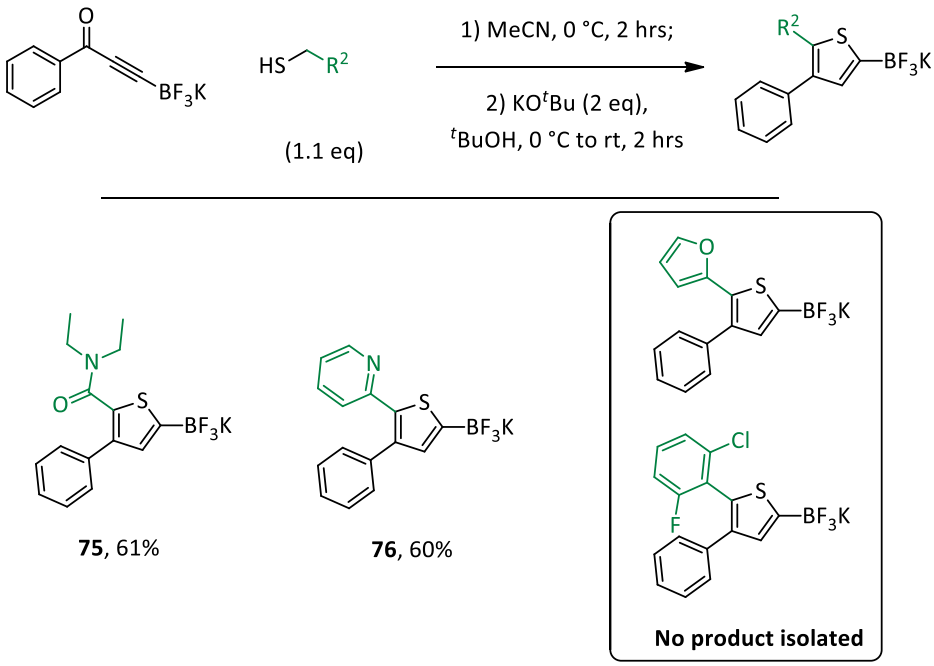
isolation as dry solids quite challenging. Thankfully, freeze-drying the oily samples under high vacuum gave the desired solids.

As a result of the condensation reaction, we could synthesise a wide range of 2,3,5-trisubstituted thiophenes bearing a trifluoroborate handle at the *C*5 position. Having used methylthioglycolate as the model thiol for the optimisation, we then set out to test the extent of the scope of thiols that could be used in this reaction.

3. *Scope of methanethiol tolerated in the condensation with ynone trifluoroborate*

To our surprise, the variety of methanethiols used in these condensation reactions reported in the literature was very limited. Essentially, all reports described the use of methylthioglycolate, with one exception that highlighted the use of benzazolemethyl substituted thiols.[88] In the event, we found that subjecting a selection of other methanethiol derivatives to our optimised conditions failed to furnish the desired thiophenes (to be discussed in section 4.). However, we were able to modify the conditions, using a stronger base for the condensation step, and this did promote cyclisation in a few cases (scheme 68).

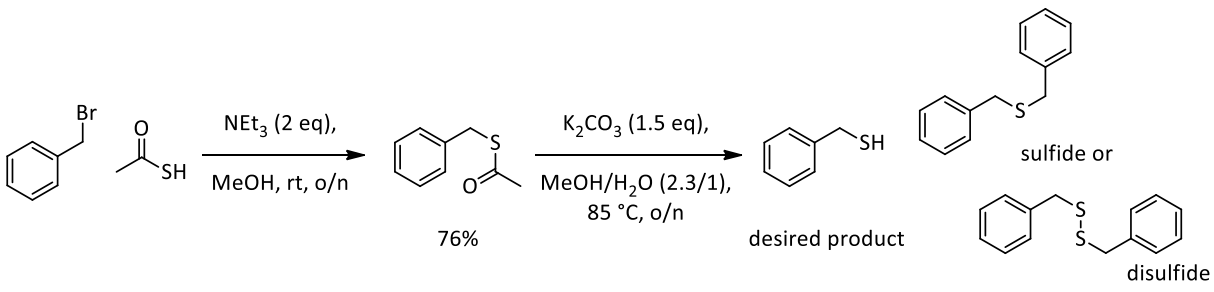
Scheme 68. Scope of commercial thiols



During this part of our investigations, we became aware of the relative scarcity of commercially available methanethiols and had to resort to synthesising some of these. There are several pathways to synthesise methanethiols from corresponding methylhalides, and we have investigated some of these on a model substrate: benzylbromide.

The first method that we investigated was through the synthesis of the corresponding thioester (scheme 69).[89]

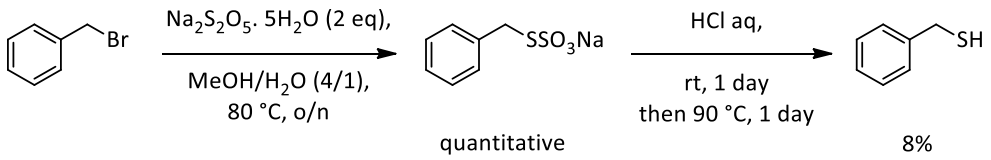
Scheme 69. Synthesis of benzylmercaptan through the benzylthioester



Whereas the synthesis of the thioester performed well, the hydrolysis of the ester performed less efficiently giving a mixture of products which were identified by ^{1}H NMR as the desired thiol and a dimer by-product (sulfide or disulfide) in a 1/3 mixture.

Facing the mixture of products and the unpleasant smell and toxicity of the reagent, we examined another method which goes through the synthesis of a thiosulfate reagent, namely Bunte salt (scheme 70).

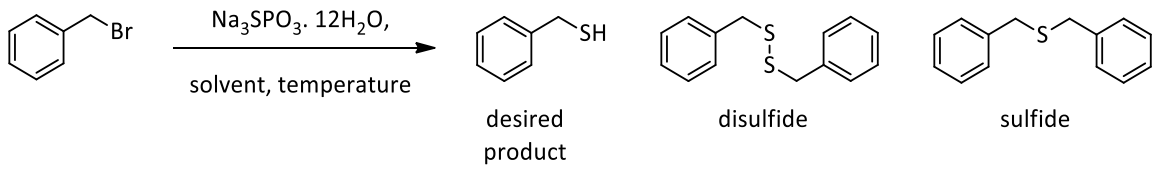
Scheme 70. Synthesis of benzylmercaptan through the benzylthiosulfate



Following a method developed by Muhannad Al-Saedy (unpublished results), we noted that, the first step to transform benzylbromide into the corresponding Bunte salt gave quantitative conversion into the desired product. However, despite acid hydrolysis of Bunte salts into thiols being described in literature,[90] upon treating our substrate with hydrochloric acid, first at rt then at 90 °C, we were unable to form reasonable quantities of benzylthiomercaptan.

We were next attracted to an alternative publication which used a salt of a different nature as an intermediate towards thiol derivatives: thiophosphate salts. In this publication, Bieniarz *et al.*[91] disclosed two methods for the transformation of bromide and chloride compounds to their thiols counterparts (table 16).

Table 16. Optimisation of the synthesis of methanethiols



desired product | disulfide | sulfide

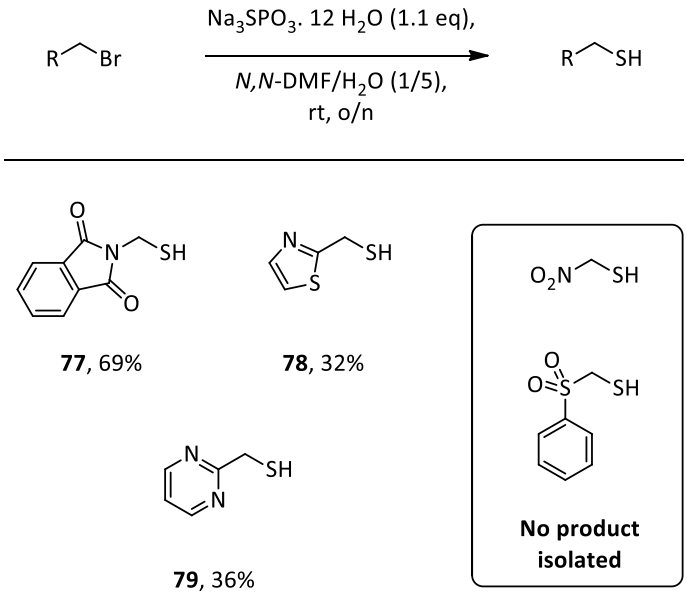
Entry	$Na_3SPO_3.12H_2O$ (eq)	Solvent	Conditions	Ratio desired product/ by-product[a]
1	2	MeOH	reflux, o/n	1/2 ratio – both by-products observed
2	2	MeOH	reflux, o/n[b]	1/2.6 ratio – only one by-product observed
3	2	*N,N*- DMF/H_2O (1/5)	rt, o/n	80% estimated yield – only desired product

[a]Determined by ^1H NMR spectroscopy. [b]Under N_2.

Method A in MeOH at reflux yielded a mixture of three compounds (entry 1) that we had tentatively identified as the desired thiol, the disulfide oxidation by-product as well as the sulfide by-product. We believe that the latter resulted from the reaction of the thiol product and the starting material. Carrying out the reactions under inert atmosphere suppressed the formation of one by-product (entry 2), but it was still not particularly selective for formation of the desired thiol. Fortunately, we have found that method B (entry 3) gave the desired thiol in good yield and good selectivity.

Having found suitable conditions for the synthesis of methanethiols we tested the scope of substrate that could successfully undergo the reaction (scheme 71).

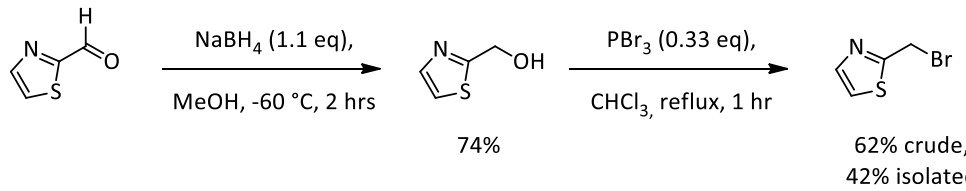
Scheme 71. Synthesis of methanethiols



According to our designed reaction, we could reproduce the synthesis of the phthalamide product in high yield.[91] We could also synthesise two novel methanethiols, bearing a thiazole and a pyrimidine group, respectively **78** and **79**, in average yields. However, we found that a nitro or a phenylsulfone group were not compatible.

In the case of the thiazole compound **78**, we had to synthesise the brominated starting material. Following a known reaction sequence,[92] we could easily transform commercial thiazole-2-carboxaldehyde into thiazole-2-bromomethane in two steps (scheme 72).

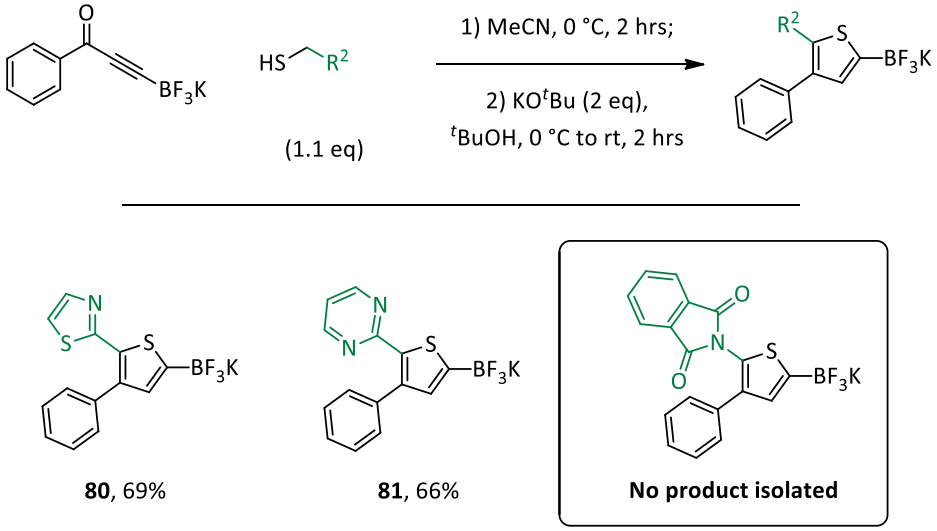
Scheme 72. Synthesis of thiazole-2-bromomethane



As mentioned in the article,[92] thiazole-2-bromomethane was unstable, therefore its purification by silica column resulted in a very low yield. Comparison of the ^{1}H NMR spectra of the crude and purified batches suggested that the crude material was clean enough to use directly in the next step. In the event, this afforded the desired thiol derivative in acceptable yield (see scheme 71).

Through this reaction, we had now three additional methanethiols to further investigate the scope of the condensation with our ynone trifluoroborates (scheme 73).

Scheme 73. Further scope extension of the condensation of ynone trifluoroborates and methanethiols



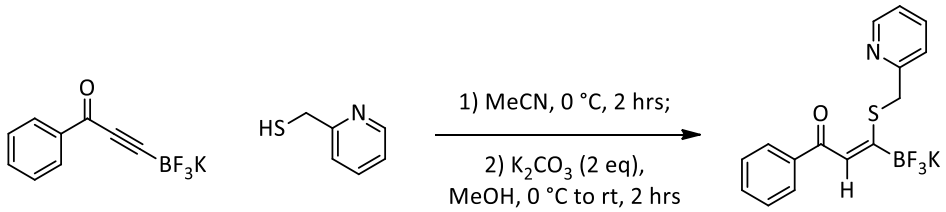
We were delighted to see that two of our non-commercial methanethiols underwent the transformation in high yields. It seemed however that the phthalimide substrate was unsuitable for this transformation as it failed to react, yielding only starting material under these conditions.

During our investigations into the scope of methanethiols we discovered that the condensation of our ynone trifluoroborates and methanethiols was not as general as we first thought. These observations led us to take a closer look into the reaction mechanism. Indeed, whereas Obretch[87] had published proposed intermediates for the reaction, he did not offer any analytical evidence in support of their formation. Furthermore, to the best of our knowledge, the mechanism for this transformation has never been studied.

4. Mechanism

During our first approach of this condensation reaction, we had observed the formation of a potential reaction intermediate (table 15), that was assigned as a trifluoroborate salt as it had a clear signal on the ^{19}F NMR spectrum. We did not pursue the characterisation of this intermediate at the time. However, when we reacted the phenylynone trifluoroborate **16** and 2-pyridylmethanethiol in the presence of potassium carbonate in acetonitrile and methanol, we noted complete conversion to a new product that was not the desired thiophene (scheme 74).

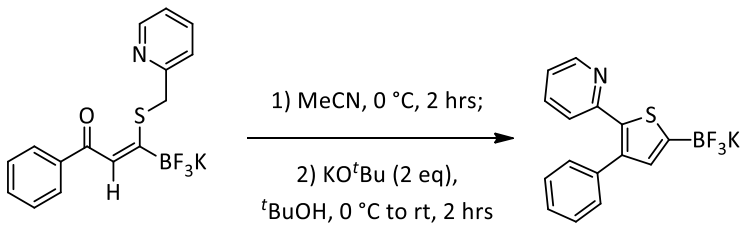
Scheme 74. Isolation of the reaction intermediate



16 (1.1 eq) **82**, 64%

NMR spectra of the crude as well as the isolated material were consistent with the isolation of a single product (one set of proton signals as well as one fluorine and boron signal). Therefore, product **82** was tentatively identified as one of the reaction intermediates proposed by Obretch.[87] However, we had to gather evidence that this compound could be an intermediate in the thiophene forming process. Therefore, we submitted this compound to our second set of optimised conditions and showed that it did cyclise into the desired thiophene (scheme 75). We believe that this experiment provided good support for the 1,4-adduct **82** being a synthetic intermediate in this condensation reaction.

Scheme 75. Cyclisation of the reaction intermediate

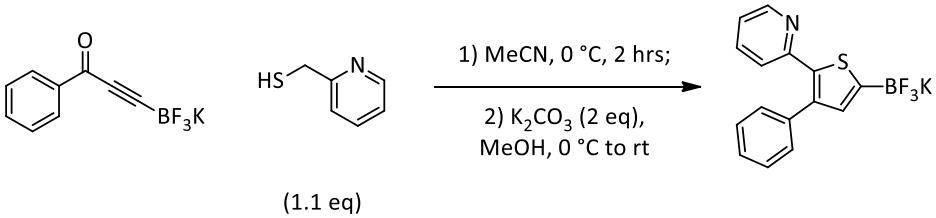


82 **76**, 62%

Having conducted the above experiments, we now had a better understanding of the reaction mechanism: we believed that the reaction started with the deprotonation of the thiol with subsequent nucleophilic attack of the thiolate on the triple bond followed by quenching by the protic solvent leading to the formation of the isolated reaction intermediate. A second deprotonation step at the α-position to the sulfur atom would then lead to the cyclisation and in turn to the formation of the desired thiophene.

Further control experiments (table 17) revealed that both the base and the protic solvent were necessary for the cyclisation reaction to take place.

Table 17. Control experiments on the condensation reaction

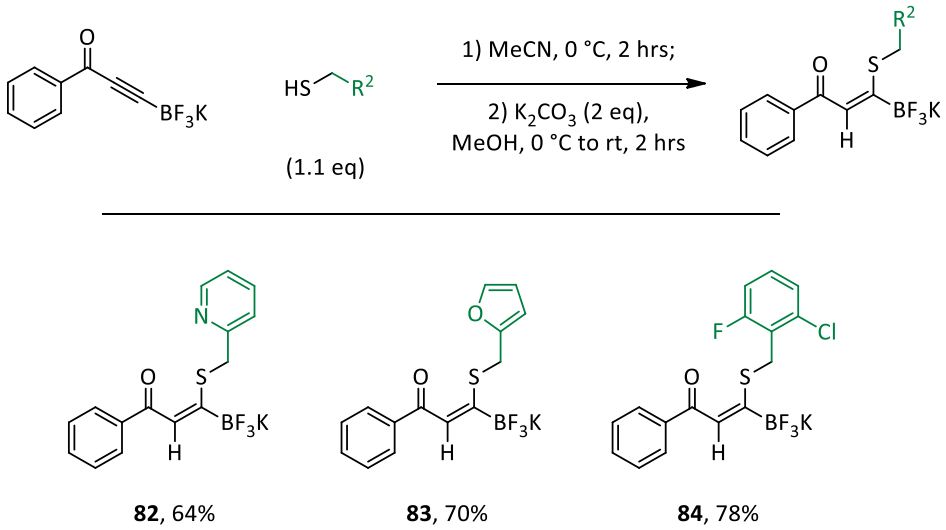


Entry	**Conditions for 2nd step**	**Results[a]**
1	**no base**, MeOH	Only starting material recovered
2	KO^{t}Bu, **no solvent**	Only starting material recovered

[a]Reactions followed by ^{19}F NMR spectroscopy and stirred at rt for 2 days.

Whereas the above experiments gave us further insights on the reaction mechanism, the difference in reactivity between the thiols remained to be explained. First, we have shown that the observations made with the 2-pyridyl substrate were also true for the methanethiols which failed to give the thiophene product (scheme 76).

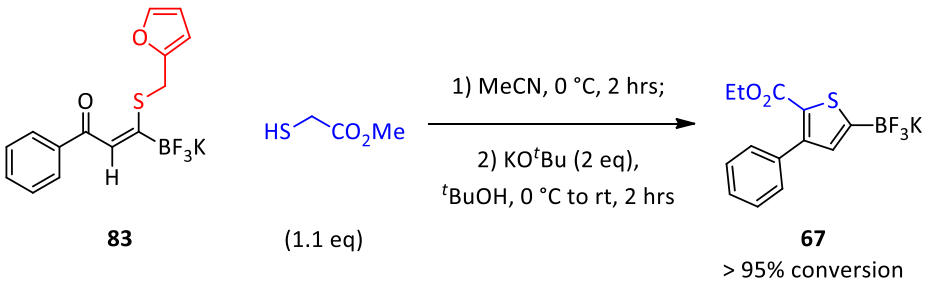
Scheme 76. 1,4-addition of methanethiol on ynone trifluoroborates



As we could isolate in excellent yields all the above intermediates, we now had evidence that the conjugate addition step was probably quite general for all methanethiols. We therefore hypothesised that those substrates which failed to deliver thiophene products, must not undergo the deprotonation/cyclocondensation step.

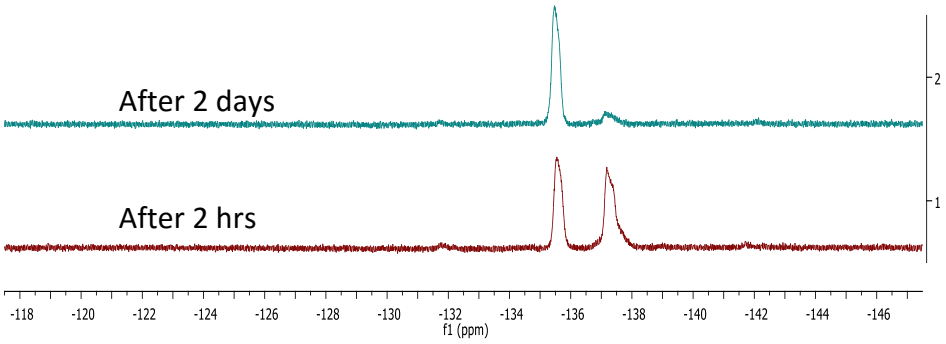
As a final control experiment, we reacted intermediate **83** with methylthioglycolate under our strong basic conditions (scheme 77).

Scheme 77. Control experiment on reaction reversibility



The reaction was followed by ^{19}F NMR spectroscopy (scheme 78).

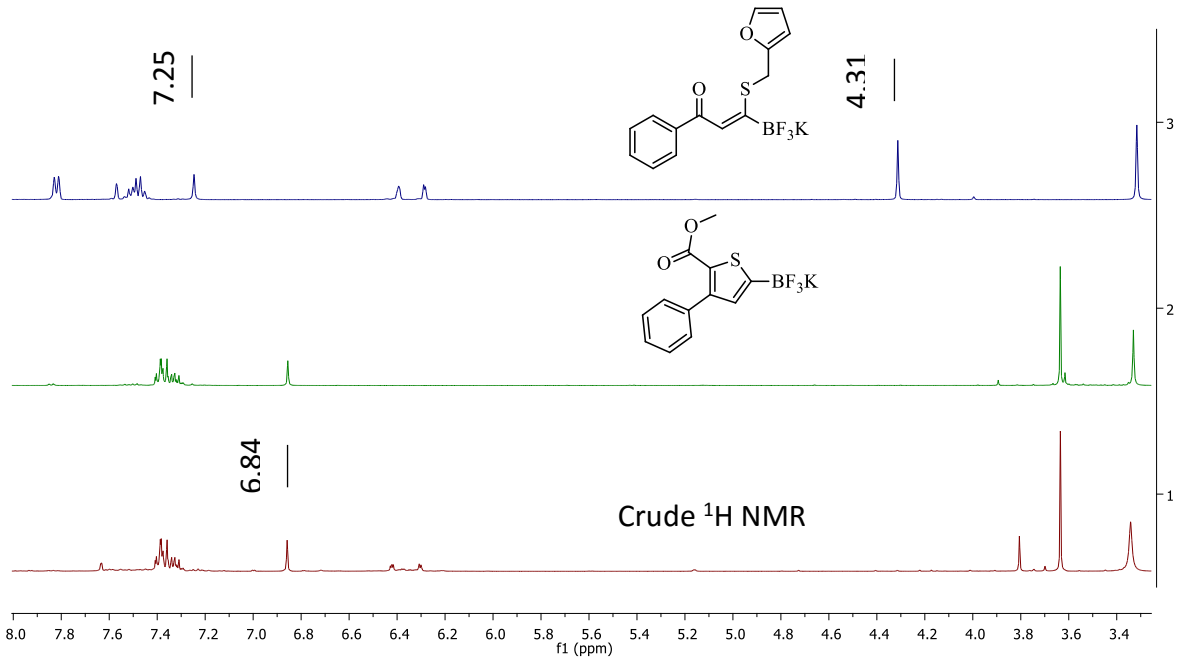
Scheme 78. Evolution of the reaction by ^{19}F NMR



After 2 hrs (red spectra), the signal corresponding to starting material **83** (-137 ppm) has slowly disappeared in favor of the cyclised product (-135 ppm). This trend continues with time and after 2 days, only one fluorine signal could be observed.

After treatment to remove the inorganic by-products, the ^{1}H NMR clearly shows that the starting material was completely consumed in favor of the thiophene product where the furfuryl mercaptan has been exchanged for the methylthioglycolate (scheme 79).

Scheme 79. Analysis of the ^{1}H NMR of the crude of the reaction



When comparing the crude NMR (red spectrum) with the starting material (blue spectrum) we could observe the complete disappearance CH_2 signal at 4.31 ppm as well as a significant upfield shift of the CH_{alkene} from 7.25 ppm to 6.84 ppm. When comparing the crude

NMR with the product we were expecting (green spectrum), we could see a clear match between the signals. We had therefore shown evidence of the thiol exchange and that when given the option, the reaction favors the thiophene product over the 1,4-adduct over time.

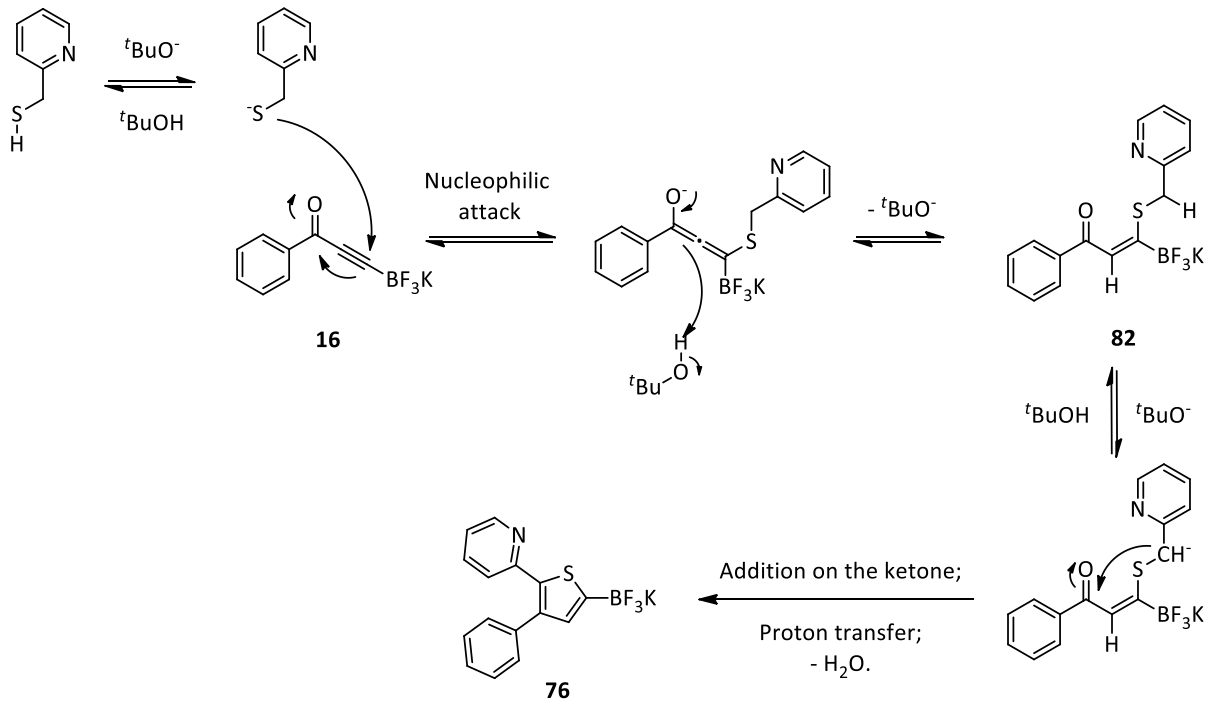
The other signals observed in the crude NMR (scheme 79) have been tentatively attributed to the difurfuryl disulfide which results from the oxidation of furfuryl mercaptan after comparison of our data with the ^{1}H NMR data in the literature (see below).

Published as difurfuryl disulfide[93]: ^{1}H NMR (400 MHz, $CDCl_3$), ppm: 3.69 (s, 4H), 6.22 (d, *J* = 2.5 Hz, 2H), 6.33 (dd, *J* = 2.5, 2.0 Hz, 2H), 7.39 (dd, *J* = 2.0, 1.0 Hz, 2H).

^{1}H NMR (400 MHz, DMSO-d_6), ppm: 3.81 (s, 4H), 6.30 (d, *J* = 3.0 Hz, 2H), 6.42 (dd, *J* = 3.0, 2.0 Hz, 2H), 7.63 (dd, *J* = 2.0, 1.0 Hz, 2H).

From the above experiments and observations, we could propose two possible mechanisms for the synthesis of thiophenes trifluoroborates (scheme 80).

Scheme 80. Reaction mechanism, first proposal



As mentioned above, the first equivalent of base is used to deprotonate the thiol. The resulting thiolate then acts as a nucleophile and adds on the triple bond, sequential quenching by the protic solvent leads to the synthesis of the reaction intermediate that we had isolated.

We believe that until this point, the abovementioned reactions are reversible. A second deprotonation forms a carbanion which attacks the carbonyl group. A sequence of proton transfer and water elimination then leads to the formation of the thiophene product.

According to this hypothesis, we rationalised the non-cyclisation of some intermediates as follows. As depicted in figure 4, these conjugate addition products have two available sites for deprotonation. Deprotonation at the red site would lead to the formation of the desired product.

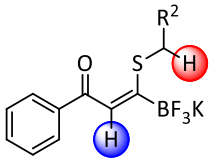
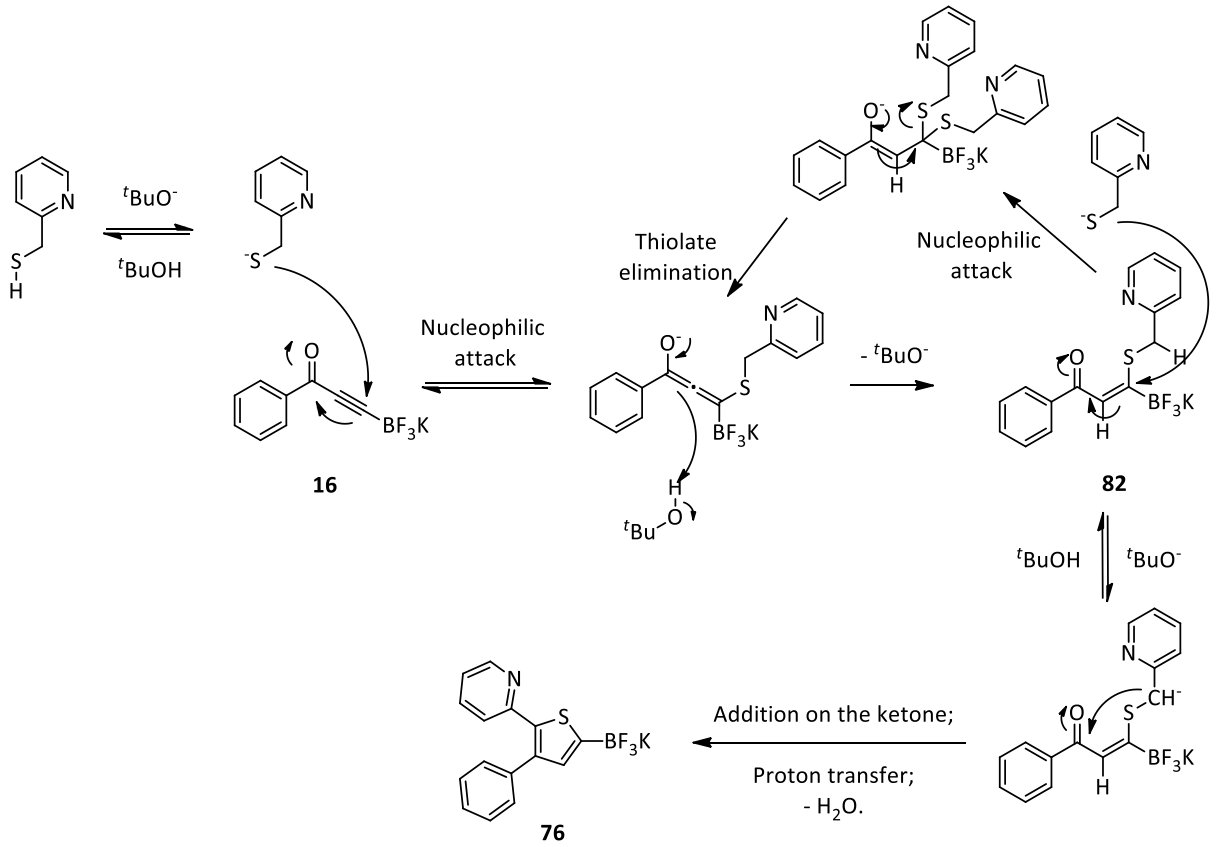


Figure 4. Possible deprotonation positions

When the proton α to the sulfur is not acidic enough to be deprotonated by the base (potassium *tert*-butoxide), as for intermediates **83** and **84**, the base could be strong enough to deprotonate the ethylenic proton instead (blue site) leading back to the ynone starting material via the elimination of the thiolate. The latter hypothesis was supported by ^{19}F NMR evidence. When attempting the cyclisation of the above molecules (**83** and **84**) into the thiophenes, we could see on the ^{19}F NMR spectrum the appearance of the signal matching the ynone starting material. According to these observations, we believed the first part of the condensation mechanism was reversible.

Our second proposal for the mechanism for the thiophene synthesis differed from the previous one by the reversible nature of the quenching step. Indeed, this previous mechanism relies on the hypothesis that potassium *tert*-butoxide is basic enough to deprotonate the ethylenic proton (see figure 4 above). However, the reaction intermediates are enones and could therefore undergo another 1,4-addition of the thiolate giving rise to an enolate. The elimination of a thiolate moiety would then lead back to the allene compound as depicted on scheme 81.

Scheme 81. Reaction mechanism, second proposal



We had now synthesised an extended scope of thiophene-5-trifluoroborates. By doing so we have shed some light onto the reaction mechanism and provided a rationale for the failure of some thiols to give the expected thiophene products. Indeed, if the protons α to the sulfur atom are not acidic enough on the intermediate, then the reaction will not yield the desired thiophene and the elimination of the thiolate will dominate. However more investigations are needed to determine exactly which of our proposed mechanism is actually taking place.

Furthermore, it should be noted that the structure of the isolated 1,4-adduct intermediates was assigned according to Obretch proposed compounds.[87] However, quenching of the allene intermediate could lead to the formation of two different products (figure 5)

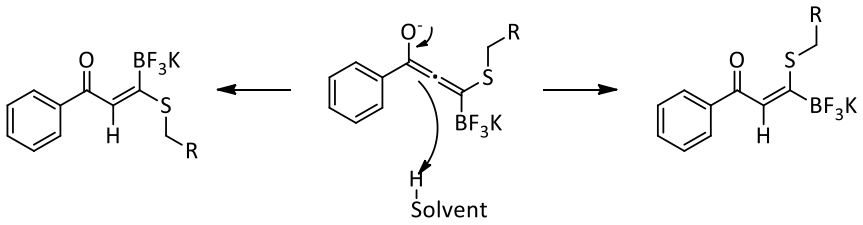


Figure 5. Quenching of the allene intermediate.

Whereas the compound on the right leads after deprotonation to the desired thiophene product, the compound on the left cannot cyclise. At this stage, we cannot exclude the formation of the latter product. Further analysis must be performed on the isolated intermediates (compounds **82**, **83** and **84**) to determine its exact structure: nOe spectroscopy for example.

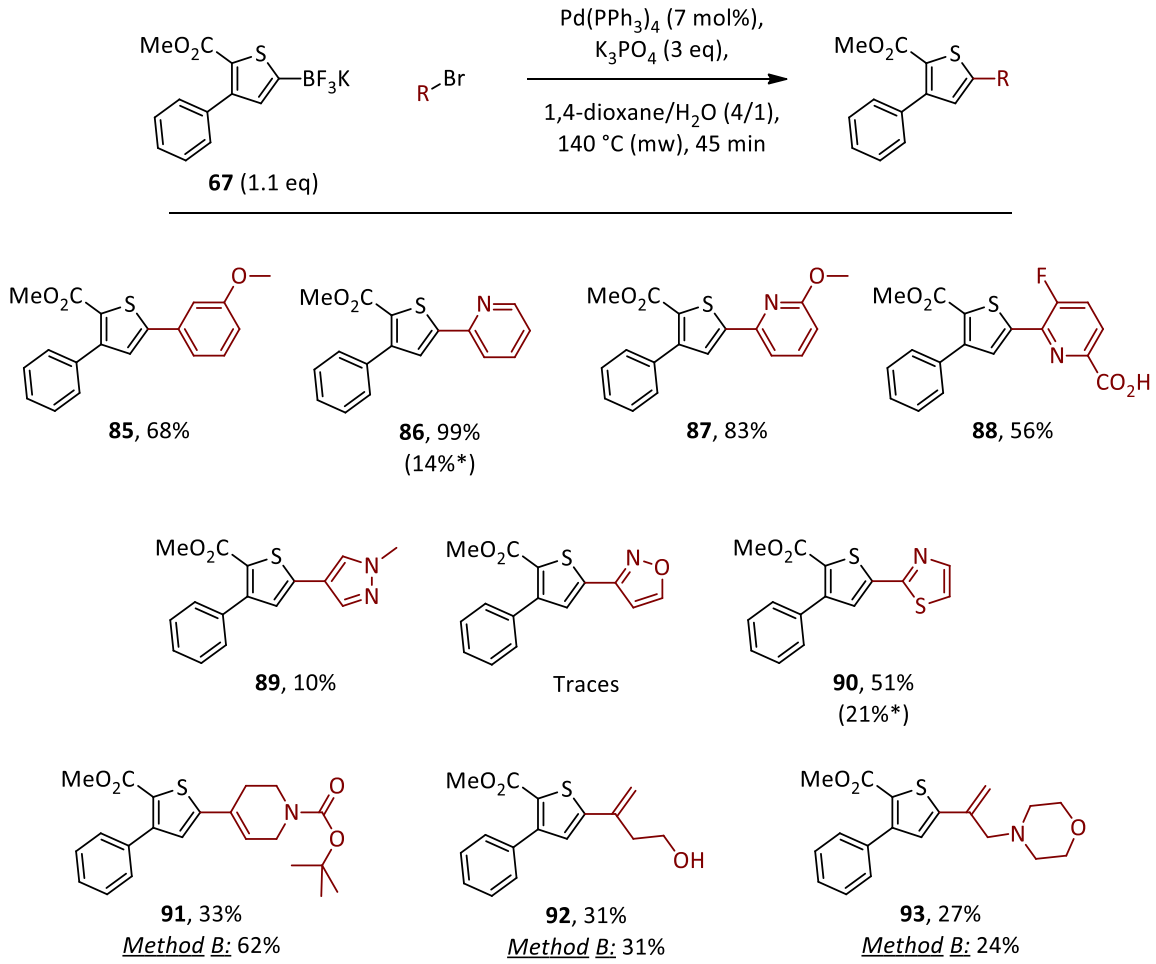
5. Derivatisation

Showing that we could efficiently synthesise various thiophene compounds bearing a boron handle at *C*5, we then exemplified the potential of these compounds as substrates for further derivatisation.

5.1. Suzuki-Miyaura cross-coupling

The boron handle is most commonly used in palladium catalysed aryl-aryl bond formation, therefore, our first idea was to test how our substrates performed in this reaction (scheme 82).

Scheme 82. Suzuki-Miyaura cross-coupling



* Conventional heating: 100 °C, o/n

Method B: PdSPhosG2 (7 mol%), Na_2CO_3 (2 eq), EtOH, 120 °C (mw), 45 min

As evidenced in the above scheme, we could couple a wide scope of halide partners, ranging from electron-rich aryl to both electron-rich and electron-poor six-membered heteroaromatic rings as well as 5-membered heteroaromatics. Most substrates performed well under our optimised set of conditions: $Pd(PPh_3)_4$ and K_3PO_4 in a 4/1 mixture of 1,4-dioxane and water.

Tetrakis-(triphenylphosphine)palladium ($Pd(PPh_3)_4$) being unstable to air, moisture and heat, we also tested Buchwald catalyst derived from $Pd(OAc)_2$, XPhos in this reaction. Unfortunately, LC-MS analysis of the crude mixture after the reaction showed that protodeboration was the major product on our six-membered ring partners.

Interestingly, only a limited range of 5-membered heterocycles were tolerated under the optimised conditions. Whereas the thiazole gave **90** in average yield, *N*-methylpyrazole and isoxazole coupling partners gave respectively **89** in low yield and the coupled isoxazole product in traces amounts.

Notably, all the above results came from reactions under microwave irradiation. When carrying out the synthesis of **86** and **90** under conventional heating (overnight at reflux), protodeboration became the major reaction pathway yielding respectively 14 and 21% yield of desired coupled products, compared to 99 and 51% yield under microwave irradiation.

Finally, we also attempted to couple vinylic bromides. We could isolate the desired products **91**, **92** and **93** in low yields. Fortunately, we could find another set of conditions that could give high yield for product **91** (method B). Unfortunately, such increase in yield was not observed with the other two examples (**92** and **93**) we investigated.

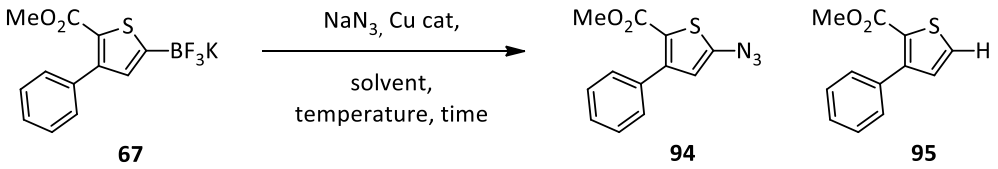
5.2. Azidonation

The azidonation of boron functional groups was first documented by Pinhey *et al.*.[94] They showed that the transformation of arylboronic acids into aryl azides could be carried out over two steps. First by treating said arylboronic acids with lead(IV) tetraacetate and catalytic amounts of mercury(II) acetate in chloroform,[94a] leading to an aryl-lead triacetate derivative, which was then reacted with sodium azide in dimethylsulfoxide[94b] to generate the azide product. However, the use of toxic mercury-based reagent for this transformation was not optimal. In 2007, a significant improvement in the conditions was developed. Indeed, Tao *et al.*[7] showed that this transformation could be performed using copper catalysts in place of toxic mercury salts. Even more recently, this reaction was demonstrated on aryltrifluoroborates by Grimes and coworkers.[95]

The versatility of azides prompted us to apply Grimes' conditions[95] to our thiophene trifluoroborate substrates (table 18 – entry 1). We could only isolate 8% of the desired azide, furthermore, analysis of the crude ^{1}H NMR spectrum showed only a 20% conversion of starting material. It should be noted that this set of conditions had proven efficient on pyrazole

trifluoroborates (99% yield for the transformation of **25**),[57] therefore highlighting the difference in reactivity between these heterocyclic trifluoroborates. Changing to an aprotic solvent (entry 2) resulted in no reaction at all, an observation which was consistent with the literature.[7]

Table 18. Optimisation of the azidonation of thiophene 67



67 **94** **95**

Entry	*NaN_3 (eq)*	*Copper cat (eq)*	*Conversion*	*Result*
1	1.5	$Cu(OAc)_2$ (0.1)	20%	**8% isolated yield**
2	1.5	$Cu(OAc)_2$ (0.1)[a]	0%	RSM
3	1.5	$CuSO_4.5H_2O$ (0.1)	20%	
4	1.5	$CuSO_4.5H_2O$ (1)	100%	1/6 ratio **94/95**
5	3	$CuSO_4.5H_2O$ (1)[b]	0%	RSM
6	1.5	$CuSO_4.1H_2O$ (1)	100%	1/10 ratio **94/95**
7	1.5 (1.2 M in H_2O)	$CuSO_4.5H_2O$ (1)	75%	1/1.6 ratio **94/95**
8	1.5 (1.2 M in H_2O)	$CuSO_4.5H_2O$ (1)[c]	100%	1/4 ratio **94/95**
9	1.5 (1.2 M in H_2O)	$CuSO_4.5H_2O$ (1)[c,d]	100%	Only **95**
10	1.5 (1.2 M in H_2O)	$CuSO_4.5H_2O$ (0.1)	77%	2.3/1 ratio **94/95**
11	1.5 (1.2 M in H_2O)	CuBr.DMS (0.1)	88%	1/1 ratio **94/95**
12	*1.5 (1.2 M in H_2O)*	*$[Cu(MeCN)_4]BF_4$ (0.1)*	*81%*	*11.2/1 ratio **94/95***

Conditions: Unless specified otherwise, thiophene **67** was dissolved in methanol (0.22 M) then NaN_3 was added followed by the copper catalyst, the mixture was then heated to 55 °C and left o/n. [a]In acetonitrile. [b]Under inert atmosphere (N_2). [c]Heated at 70 °C. [d]In water. Conversion and ratio **94**:**95** determined by ^1H NMR spectroscopy.

Changing the catalyst from $Cu(OAc)_2$ to $CuSO_4.5H_2O$ (entry 3) did not drive the reaction to completion, however using a stoichiometric amount of copper salt (entry 4) gave complete

conversion of the starting material albeit with protodeboration being the major product. Under inert atmosphere (entry 5), interestingly, the reaction only gave back starting material.

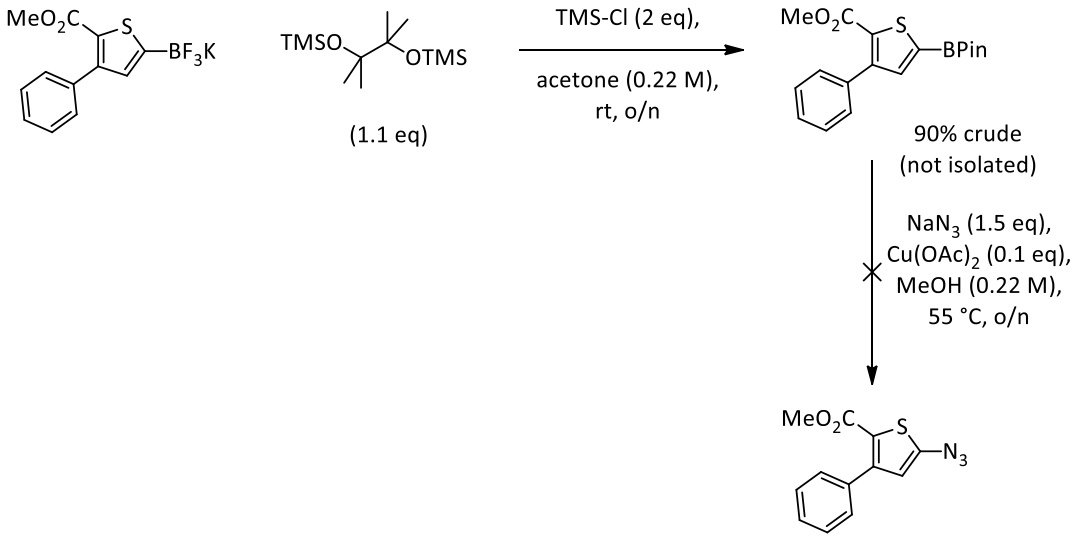
We were interested in assessing the influence of water on the reaction. We dried the copper salt under vacuum to yield a grey solid which we believed to be $CuSO_4.1H_2O$.[96] When performing the reaction using this copper source (entry 6), the conversion was satisfactory however we observed a dramatic increase in protodeboration. Since removing water appeared to promote protodeboration, we thought of dissolving the sodium azide reagent in water before(entry 7), as a result, the amount of protodeboration was significantly reduced. Unfortunately, heating the reaction to a higher temperature (entry 8) or performing the reaction in water alone (entry 9) favoured again the protodeboration pathway. Finally, lowering the copper loading to 0.1 equivalent whilst adding water to the reaction mixture (entry 10) finally gave the desired product as the major compound, albeit with a significant amount of protodeboration product.

Therefore, we next screened copper(I) catalysts under our optimised conditions. Although CuBr.DMS (entry 11) only gave a 1/1 ratio of desired product and protodeborated starting material, $[Cu(MeCN)_4]BF_4$ (entry 12) yielded for the first time a large excess of desired product in a reproducible manner.

Unfortunately, when we attempted to isolate the desired product from the crude mixture, we could only obtain a considerably lower yield (23% of a mixture of product and protodeborated by-product in a 1/2 ratio) than the one expected from analysis of the crude NMR spectrum. These observations led us to believe that the azide **94** was not stable on silica.

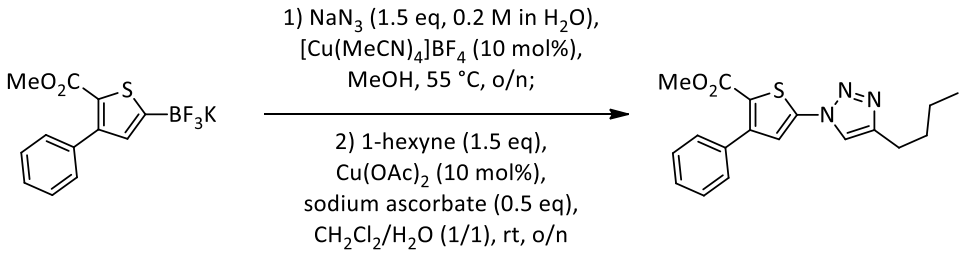
Following the successful azidonation of boronic esters,[95] we decided to investigate the conversion of the trifluoroborate salts to their corresponding pinacol esters. We could observe the formation of the desired thiophene pinacol ester but attempt at isolating said product failed to yield sufficient amount. Therefore, the crude mixture was reacted using literature conditions.[95] Unfortunately this reaction only yielded protodeborated product **95** (scheme 83).

Scheme 83. Conversion of the trifluoroborate moiety into a pinacolborane group followed by its azidonation for thiophene 67



As we had hypothesised that the azide compound was unstable to silica gel purification, we attempted to trap this compound by reacting the crude azidonation mixture with an alkyne in order to synthesise the corresponding triazole. Therefore, we decided to employ conditions that had been successfully used on pyrazole trifluoroborates previously (scheme 84).[57]

Scheme 84. Triazole formation using copper acetate

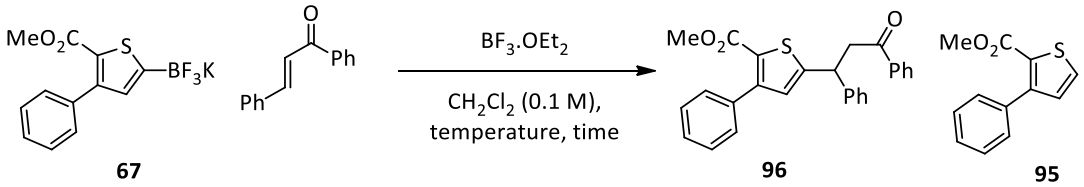


Unfortunately, while we could detect product formation (upon LC-MS analysis), the reaction produced a complex mixture of products and we were unable to isolate the desired triazole compound cleanly. Further optimisation, following a second set of literature conditions,[97] failed to deliver clean azide products or derivatives and so this chemistry was discontinued.

5.3. 1,4-addition to enones

As our next potential functionalisation reaction of the boron handle, we decided to investigate the compatibility of our thiophene trifluoroborate salts with a Lewis acid promoted conjugate addition reaction. Accordingly, we carried out the reaction using thiophene **67** under literature conditions (table 19).[98]

Table 19. Optimisation of the 1,4-addition to enones



67 **96** **95**

Entry	***67****/enone*	*$BF_3.OEt_2$*	*Conditions*	*Isolated yield of* **96**
1	2/1	1.5 eq	rt, 2 hrs	Trace amounts
2	2/1	1.5 eq	reflux, o/n	66%
3	1/1	0.75 eq	reflux, o/n	56%
4	3/1	2.25 eq	reflux, o/n	89%[a]
5	1/1.2	0.5 eq	reflux, o/n	No conversion
6	1/1.2	1 eq	reflux, o/n	No conversion

[a]as a 1/4 mixture **96**/**95**.

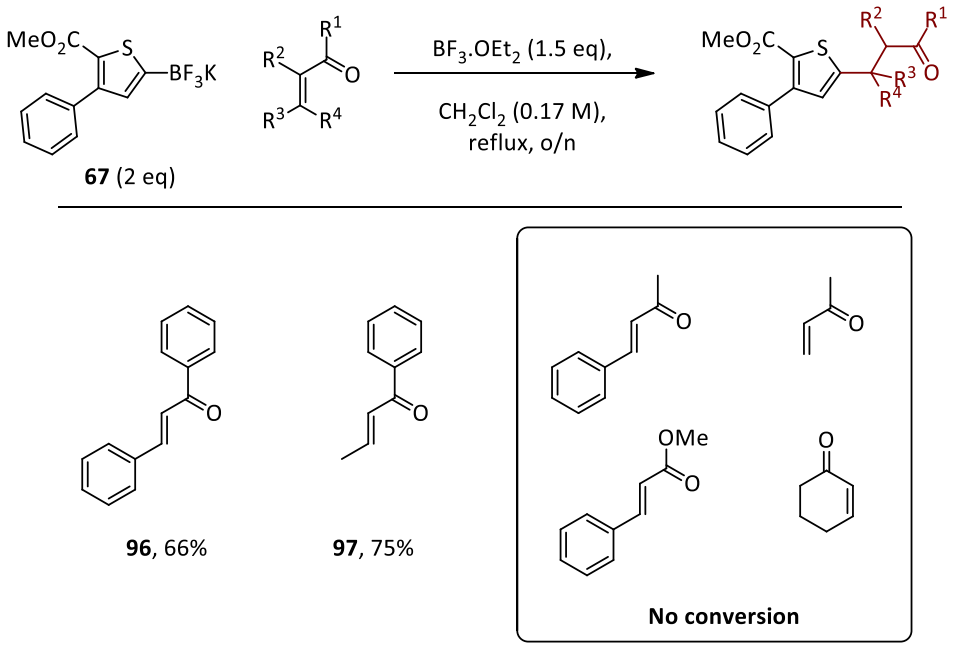
As we had seen with the pyrazole chemistry, at rt (entry 1) the reaction was very slow but trace amounts of product could be observed on the ^{1}H NMR spectrum. Encouraged by this observation, we attempted heating the reaction and leaving it for a longer period of time (entry 2). To our delight, such conditions gave the desired product **96** in high yield.

However, under these conditions an excess of trifluoroborate reagent was used, therefore we attempted to examine the influence of the stoichiometry on the outcome of the reaction (entries 3 and 4). Using a 1/1 ratio (entry 3), the reaction was incomplete after being left overnight, but still gave the desired product in a good yield. As expected, the use of a 3/1 ratio of **67**/enone (entry 4) drove the reaction to completion after 18 hr. However, as it proved difficult to separate the protodeborated compound **95** from the product (1/4 ratio of **96**/**95** determined by ^{1}H NMR integration in the isolated fractions), our next attempts focused on

making the trifluoroborate salt the limiting reagent (entries 5 and 6). Unfortunately, this failed to give the desired product.

As we had a set of optimised conditions, we could now investigate the scope of the reaction using various enones (scheme 85).

Scheme 85. 1,4-addition of enone thiophene trifluoroborates

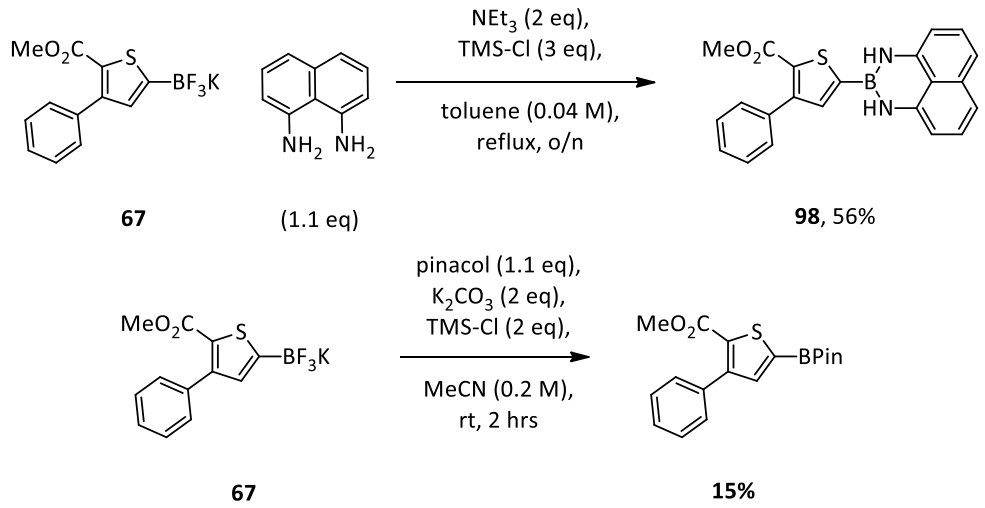


Noteworthy, the scope of enone compatible with this chemistry seemed to be limited to non-enolisable enones. Indeed, both non-enolisable enones yielded the desired adducts **96** and **97** in high yields, whereas 1-methyl-3-phenylenone gave no conversion. It should be noted that α,β-unsaturated esters and cyclic enone also failed to react under our optimised conditions.

5.4. Ligand exchange on the boron group.

Using our pyrazole substrates (see chapter 3), we had developed an efficient method to transform the trifluoroborate handle directly into a boronamide functional group. Applying these conditions to the thiophene substrate, we were pleased to find that we could also transform the trifluoroborate handle into its boronamide counterpart (scheme 86).

Scheme 86. Ligand exchange on the boron atom



67 (1.1 eq) **98**, 56%

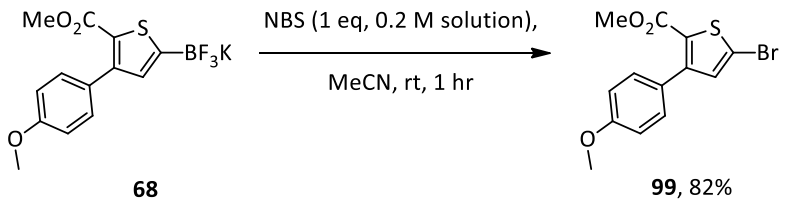
67 **15%**

Indeed, we were able to isolate the desired boronamide **98** in good yield after purification by flash chromatography. The ability to carry out this transformation offered a solution to purification issues that can arise in the case of some 3-alkyl substituted thiophene salts (see section 2.), where the only option for purification is precipitation. Moreover, this method is more efficient than the conversion to the corresponding pinacol ester because of its instability towards chromatographic purification.

5.5. Bromination

Finally, as we had successfully brominated pyrazoleborate derivatives (see chapter 3), we wanted to test the same conditions on our thiophene substrates to see whether we could also make fully substituted thiophenes (scheme 87).

Scheme 87. Bromination of thiophene-5-trifluoroborate



68 **99**, 82%

Conducting the bromination using NBS showed that starting material was completely consumed after one hour (as judged by ^{19}F NMR spectroscopy). However, after workup, we did not detect the presence of the expected product. Instead we isolated in excellent yield the bromodeborated product **99**.

Whereas this result differs from what we had observed on the pyrazole scaffolds, it was not completely unexpected. Indeed, we had already observed bromodeboration in the case of pyrazoleborates when bromine was employed. In addition, the carbon bearing the trifluoroborate group on the thiophene is activated towards addition of an electrophile.

Although this result was not planned, it is nonetheless a useful transformation. Bromine is a versatile handle for further functionalisation. Moreover, this simple reaction allowed to change the electronic properties of the carbon at *C*5, changing from an organometallic, and therefore electron-rich carbon, to an electron-poor carbon attach to a halide handle.

6. Conclusions

In this chapter, we have described the successful condensation of ynone trifluoroborates with methylthioglycolate. Various aryl and alkyl substituted ynones were well tolerated giving rise to a wide range of 2-methylester-3-substituted thiophenes bearing an additional trifluoroborate moiety at *C*5, in excellent yields.

We have also extended the scope of methanethiol reagents which could be used in this Fiesselmann-type condensation reaction to amide and heteroaromatics. In doing so we have gained valuable insights in the reaction mechanism and we have proposed a rationale for the scope of thiols that can be used in this reaction.

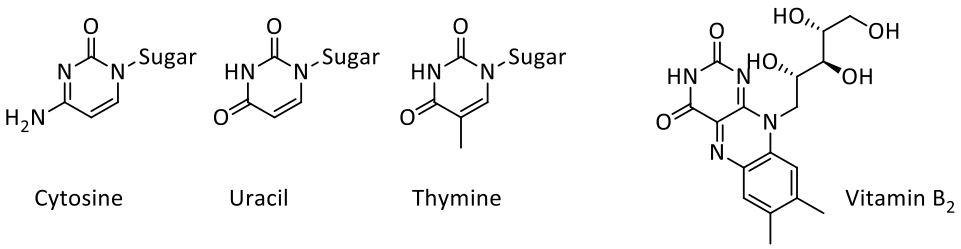
Using the versatility of the boron handle readily installed on our substrates, we have conducted various derivatisation reactions. Our substrates performed well in conventional Suzuki cross-couplings, as well as conjugate addition reactions to some acyclic enones. We have also shown that the bromination of our substrates proceeded under mild conditions to produce the corresponding 5-bromo derivative via bromodeboration.

Chapter 5 – Pyrimidine Trifluoroborates

1. Introduction

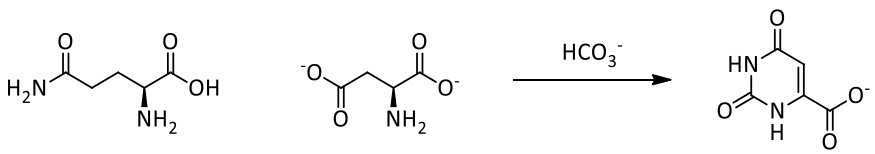
Nitrogen based heterocycles are known to have a very wide range of uses and biological activities. Amongst them, pyrimidines have a privileged place. Indeed, the pyrimidine motif represents the core of several pharmaceuticals but they are also synthesised in all living organisms as they are an essential component of DNA and RNA (scheme 88) as well as being the core of vitamin B_2[99] (scheme 88).

Scheme 88. Pyrimidine in DNA and RNA and vitamin B_2



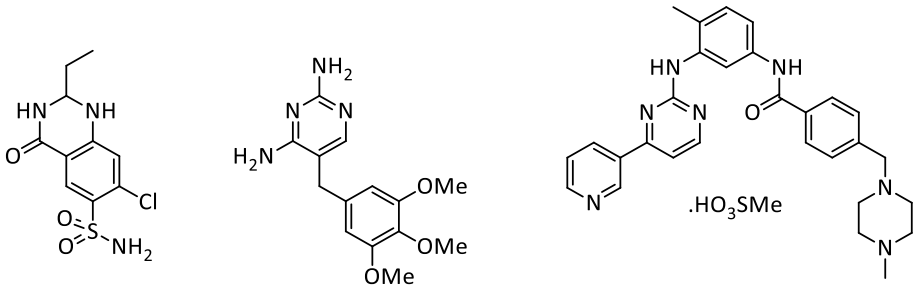
Living organisms synthesise pyrimidine rings from glutamine, aspartate and a bicarbonate source (scheme 89).[100]

Scheme 89. Effective synthesis of pyrimidine core in Nature



As well as being widely present in Nature, there have been many successful pyrimidine-based molecules marketed as potent pharmaceuticals in various areas: quinethazone (*Hydromox*),[101] trimethoprim[102] and Imatinib mesilate (*Gleevec*)[103] have respectively applications in the treatments of hypertension, infection and cancer (scheme 90).

Scheme 90. Pharmaceutically active pyrimidine-based drugs



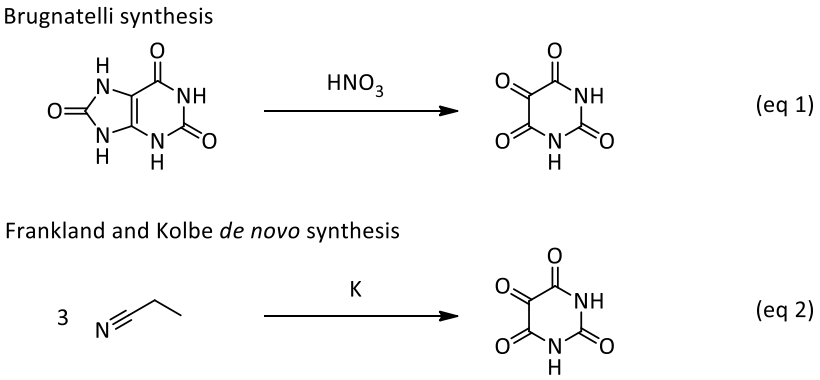
Quinethazone
Hydromox

Trimethoprim

Imatinib mesilate
Gleevec

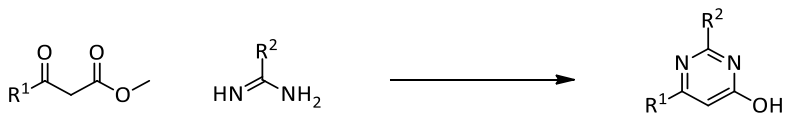
Early in the 19th century, Bruggnatelli[104] synthesised the first pyrimidine derivative: alloxan, from an already preformed fused-pyrimidine ring (scheme 91, eq 1). Forty years later, the first *de novo* synthesis of the pyrimidine core was reported (scheme 91, eq 2). This product was obtained by the reaction of propionitrile and metallic potassium upon heating.[105]

Scheme 91. First synthesis of pyrimidine core by Brugnatelli and Frankland and Kolbe



Since then, many strategies have been explored for the synthesis of pyrimidines. Amongst these, the most common seems to be the condensation reaction of 1,3-dicarbonyl reagents and N-C-N donors. As an example, in the 1880s, Pinner has found that a 1,3-ketoester could react with an amidine to yield pyrimidine derivatives (scheme 92).[106]

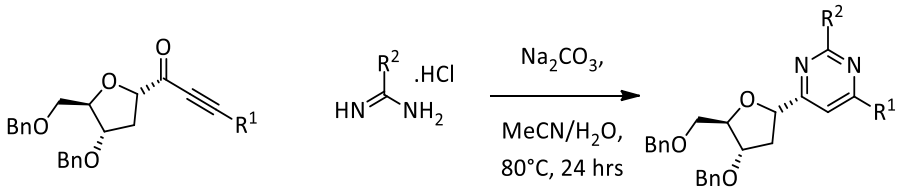
Scheme 92. Pinner pyrimidine synthesis



Since that time, the scope of this reaction has been significantly extended. Regarding the 1,3-dicarbonyl, it has been shown that 1,3-diketones, 1-cyano-3-ketones and 1,3-diesters can all be used. Concerning the N-C-N donor, not only amidines but also guanidines and ureas are well tolerated.

It's only recently that ynone type reagents have found their place in this condensation reaction to form pyrimidines. In 2000, Baldwin *et al.*[107] synthesised a range of 2,4,6-trisubstituted pyrimidines in low to excellent yields by the reacting ynones and amidine salts in the presence of a base, in a mixture of acetonitrile and water (scheme 93).

Scheme 93. Condensation of ynones and amidine salts to yield pyrimidines



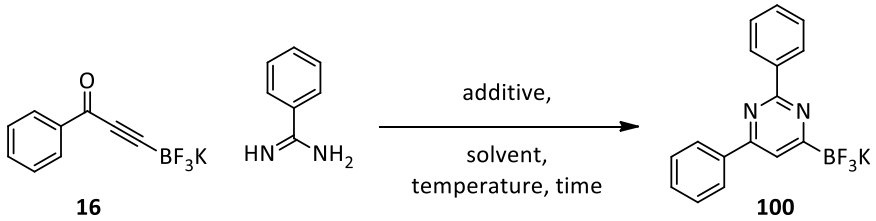
around 20 examples,
25 to 92% yield

In these last decades, ynones have been further investigated as interesting starting materials for the formation of pyrimidine scaffolds in high yields and high regiocontrol. In this chapter, we disclose our efforts to incorporate the boron handle into pyrimidines by the condensation of ynone trifluoroborates with amidines.

2. *Scope of ynone*

There are several literature precedents for the condensation of ynones and amidine type reagents in order to yield various pyrimidines.[108] To the best of our knowledge, those reactions have never been performed with a boron moiety on either substrate. In order to explore the potential of amidine condensation reactions to generate pyrimidine boronic acid derivatives, we explored the reaction of our phenyl substituted ynone trifluoroborate **16** with benzamidine for the optimisation process (table 20).

Table 20. Optimisation of the condensation of phenylynone trifluoroborate and benzamidine



16 **100**

Entry	*Benzamidine (eq)*	*Additive (eq)*	*Solvent, temperature*	*Results*
1	1.2	None	MeCN, rt, 1 hr then reflux, 3 hrs	No product formed[b]
2	1.2	K_2CO_3 (2.4)	MeCN, rt, 1 hr then reflux, o/n	No product formed[b]
3	1.2	Molecular sieves 4Å[a]	Toluene, reflux, o/n	Complete conversion. Product not isolated
4	1.2	$MgSO_4$[a]	Toluene, reflux, o/n	Complete conversion. 54% isolated yield
5	1.2	None	Toluene, reflux, o/n	Complete conversion. 67% isolated yield

[a]200% w/w with respect to benzamidine. [b]LC-MS analysis.

Our first set of conditions were derived from literature,[109] indeed the use of acetonitrile as a solvent was often described. Fortunately, acetonitrile was also a suitable solvent in our case as it efficiently dissolves trifluoroborate salts. The range of temperature used in similar condensations was quite wide: from rt to reflux. Therefore, for our first try, we decided to conduct the reaction in acetonitrile at rt (entry 1). Following the reaction by LC-MS, we could not observe the formation of any product. Heating the reaction at reflux over several hours also failed to generate the product.

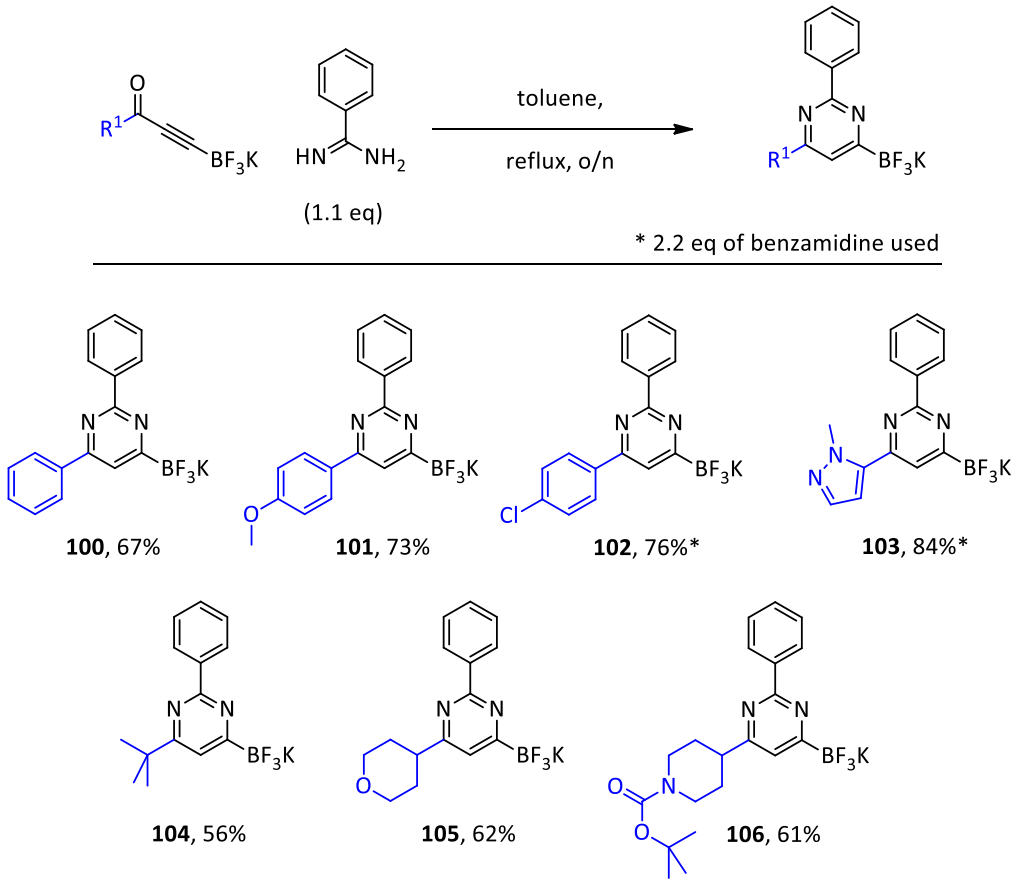
Reported examples of the use of benzamidine as the free base are scarce in the literature, therefore in most reactions a base was added in order to free base the amidine *in situ*. We hypothesised that perhaps, the base had a dual role in these reactions: free-basing

the amidine and perhaps activating the substrates for the reaction. We therefore tested the addition of a base in the reaction mixture to see if it had beneficial impact on the reaction outcome (entry 2). Unfortunately, we saw that at rt as well as at reflux, the base did not encourage the desired condensation reaction as we recovered starting material after prolonged heating.

Our next attempts focused on removing water in order to encourage condensation. In this regard, we thought of using toluene as a solvent instead of acetonitrile so as to have the possibility of removing the water via an azeotrope, we also decided to test dehydrating agents (entries 3 and 4). Indeed, we could observe for the first time the formation of the desired product in both cases. While the use of molecular sieves (entry 3) didn't yield clean product, when using magnesium sulfate as a drying agent (entry 4), we could isolate pure material in an encouraging 54% yield. As a final test, we wanted to assess whether it was the removal of water, the change of solvent or the change in temperature of the reaction that allowed the synthesis of our new pyrimidine substrate, so we carried out the reaction in toluene at reflux without any additive (entry 5). As previously observed for the thiophene synthesis (see chapter 4), the additive was not necessary for the reaction to proceed to completion after overnight stirring at reflux. To our delight, removal of the additive allowed us to isolate clean material in an excellent yield.

Having now optimised conditions for the condensation of phenylynone trifluoroborate **16** with benzamidine, we went on to test the scope of ynones that could be tolerated in this reaction (scheme 94).

Scheme 94. Scope of ynone trifluoroborates



As evidenced by the above yields, the scope of ynone trifluoroborates compatible with this chemistry was broad. Electron-neutral, -poor and -rich aryl ynones were well tolerated giving the highly substituted pyrimidines in excellent yields. However, it should be noted that in the case the electron-poor aryl and the pyrazole substituted ynones, 2.2 equivalents of benzamidine had to be added to the reaction mixture in order for the condensation to reach completion within one day (compounds **102** and **103**). Our range of alkyl ynones also performed very well, once again, the isolated yields were slightly lower than for the aromatic ynones because of some differences in behaviour during the precipitation process. As mentioned previously, alkyl substituted substrates seemed to show a higher propensity for solvation, meaning they tended to oil out instead of precipitating out upon treatment with acetone and ether.

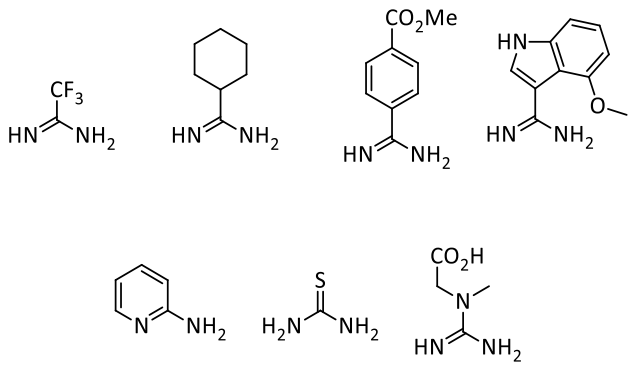
We could now access a wide range of 2-phenyl substituted pyrimidine-6-trifluoroborates and we became interested in exploring the scope of amidine-type reagents we could use in this condensation reaction.

3. Scope of amidines

When we started this project, we came to realise that the number pyrimidines substituted with a boron group at *C*6 are very small (approximately 50 examples of various boronic acid and ester derivatives). We were therefore very interested in exploring the synthesis of such substrates in order to broaden the scope of existing products and facilitate the access to these interesting scaffolds.

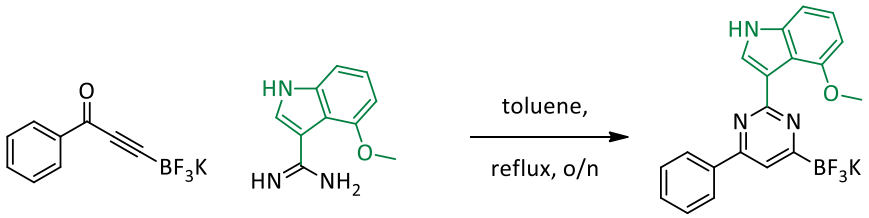
We chose a wide range of potential amidine-type reagent in order to attempt the synthesis of our pyrimidine-6-trifluoroborates (scheme 95).

Scheme 95. Amidine reagents



Unfortunately, it appeared that the conditions we had found to be optimal for the condensation of benzamidine were not universal. Indeed, amongst the substrates shown in scheme 95, only the indole substituted amidine gave complete conversion to the pyrimidine product, which was isolated in modest yield (scheme 96).

Scheme 96. Synthesis of 2-indole-pyrimidine-6-trifluoroborate

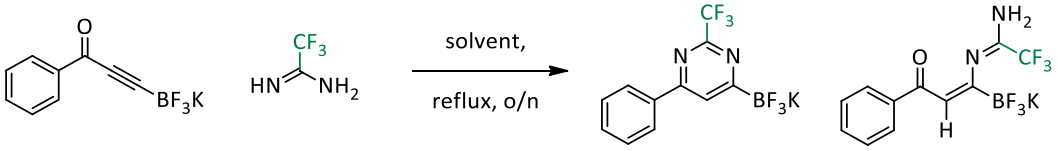


16 (1.1 eq) **107**, 50%

The remaining substrates failed to show any conversion to the desired product in the condensation reaction (according to ^{19}F and ^{1}H NMR spectroscopy of crude reaction mixtures). Furthermore, while the reactions of benzamidine and the indole-substituted substrates were quite clean, in the other cases degradation of the ynone starting material became apparent after one day. Specifically, under prolonged heating, the ynone started to protodeborate in these cases.

Our hypothesis was that, the energy required for the addition/cyclocondensation to proceed was highly dependent on the type of amidine reagent used. Therefore, heating the reaction higher might lead to the formation of the desired product. We chose the trifluoromethylated amidine in order to perform a short optimisation study (table 21).

Table 21. Optimisation of the condensation of CF_3-amidine and phenylynone



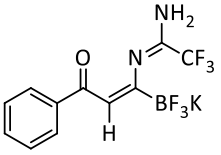
16 **108** **109**

Entry	*Amidine (eq)*	*Solvent*	*Mass of isolated solid (mg)*	*Results*
1	2.4	Toluene (110 °C)	85.5	Complex mixture
2	5	Toluene (110 °C)	127.0	Mixture **108**:**109** in a 1:1 ratio[a]
3	2.4	1,2-DCB (180 °C)	4.2	3% isolated yield of **108**
4	5	1,2-DCB (180 °C)	94.9	Mixture **108**:**109** in a 1:0.4 ratio[a]

[a]Ratio estimated by ^{1}H NMR spectroscopy.

We first attempted to increase the amount of amidine introduced to 2.4 and 5 equivalents (entries 1 and 2). From each reaction we could isolate a solid product from our reaction mixture by dissolving the crude material in acetone and precipitating with ether. Unfortunately, in both cases, the solids were mixtures of 2 products: the desired product **108** and a by-product. Heating the mixture to higher temperatures in 1,2-dichlorobenzene (entry 3) allowed us, for the first time, to isolate clean product (characterised by ^{1}H NMR and HRMS) albeit in very low yield. In these cases (entries 3 and 4), we directly added ether to the reaction mixture, as 1,2-dichlorobenzene has a very high boiling point and is difficult to remove.

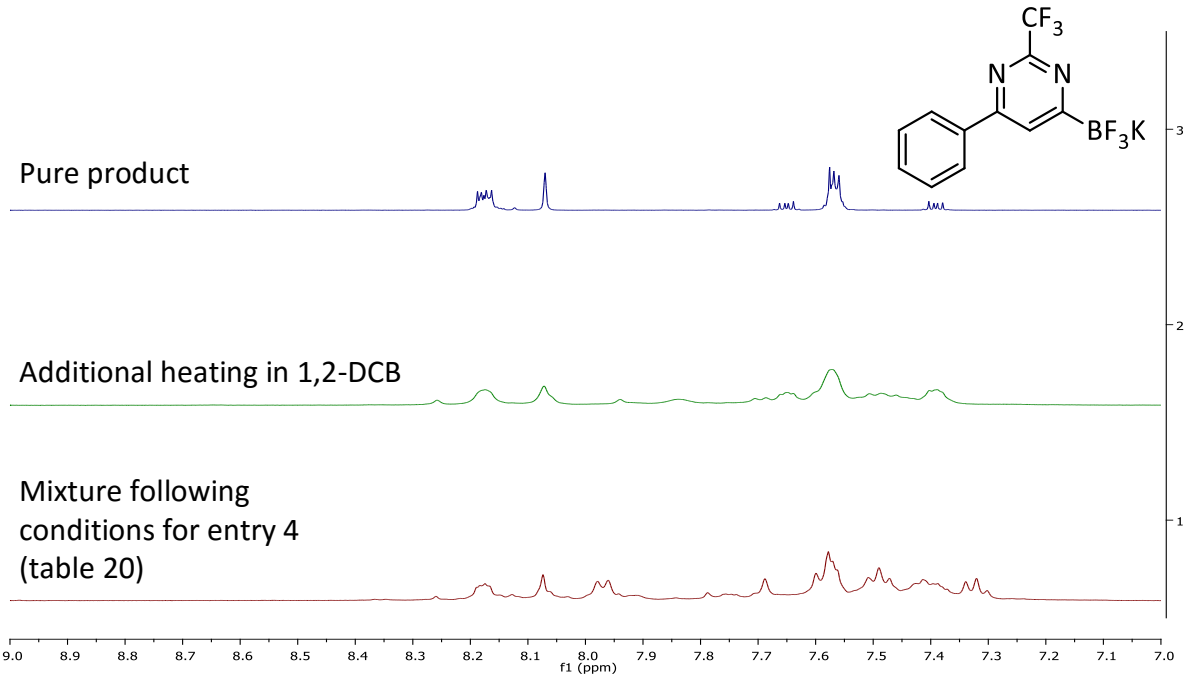
We have tentatively identified the second product generated in these reactions as the 1,4-amidine adduct **109** (figure 6). Isolating this material and resubjecting it to refluxing 1,2-dichlorobenzene resulted in formation of the expected pyrimidine (scheme 97).



109

Figure 6. By-product 109

Scheme 97. ^{1}H NMR spectra showing the evolution of the reaction when heated in 1,2-dichlorobenzene

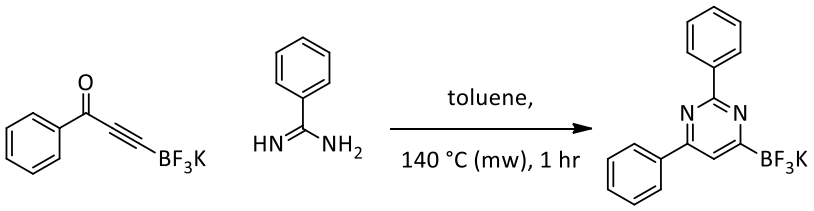


These studies highlighted the limitations of the use of 1,2-dichlorobenzene. The inability to easily remove this solvent made it very difficult to analyse crude reaction mixtures. Also, the use of such a large excess of trifluoromethylamidine made the analysis of conversion by ^{19}F NMR spectroscopy quite problematic.

Literature reports showed that simple ynones tend to undergo such condensations at 80 °C (reflux in acetonitrile), a lower temperature than that required for our ynone trifluoroborates. Therefore, our next investigations focused on the potential of microwave irradiation to promote these reactions.

We first determined optimum conditions to perform the microwave promoted reaction, using benzamidine as a model substrate (scheme 98).

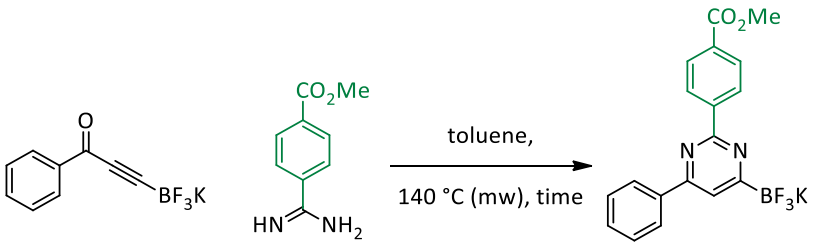
Scheme 98. Microwave promoted condensation of benzamidine and phenylynone



16 (1.2 eq) **100**, 71%

After a short optimisation, we found that the reaction required heating at 140 °C (sealed vessel) to be complete within 1 hour. Moreover, the isolation of product **100** was straightforward leading to a slightly higher yield of product as compared to conventional heating. Notably, we also observed that protodeboration occurred significantly faster under microwave irradiation than under conventional heating. Having now established optimised conditions for this condensation reaction, we set out to test the reactivity of the *para*-methylester-phenylamidine (table 22).

Table 22. Microwave assisted condensation of electron-poor aryl amidine and phenylynone



16 **110**

Entry	*Amidine (eq)*	*Time*	*Results*[a]
1	1.2	o/n[b]	< 10% conversion
2	1.2	1 hr	50% conversion
3	2.4	1 hr	50% conversion
4	2.4	2 hrs	Full conversion. 15% isolated yield

[a]Conversion estimated by ^{19}F NMR spectroscopy. [b]Conventional heating in toluene at reflux o/n.

As stated previously, using the conventional heating method proved inefficient in carrying out the desired condensation (entry 1). Performing the reaction under the microwave conditions which proved highly effective for benzamidine (entry 2) gave an encouraging result

of a 1/1 ratio between ynone and desired product **110**. Whereas increasing the equivalents of amidine introduced (entry 3) seemed to have little effect on the conversion, increasing the reaction time to two hours (entry 4) allowed to reach full conversion. However, the isolated yield was quite low due to a large amount of protodeboration which occurred under these conditions. It should however be noted that the above reactions were carried out on 50 mg scale. As the product was isolated through precipitation and filtered, there was scope to increase the yields through repeating the conditions on a larger scale.

As previously mentioned, under microwave irradiation, it seemed that protodeboration occurred very rapidly compared to conventional heating conditions. However, the studies were stopped at this stage. Therefore, there are still some optimisation to be performed in order to find the adequate set of conditions which would yield complete conversion of the ynone starting material whilst reducing the protodeboration.

4. Conclusions

We have shown that our ynone trifluoroborates could react with benzamidine in the absence of any additive in toluene at reflux to yield a wide scope of 2,4,6-trisubstituted pyrimidines. Notably, pyrimidines bearing a boron handle at *C*6 are rare in literature. And so, we have designed a novel, rapid and efficient synthesis of highly substituted pyrimidine scaffolds bearing a trifluoroborate handle readily installed on the ring. We have shown that all our ynones were well tolerated in this reaction allowing a wide variation at *C*4: from aryl (electron-neutral, -poor and -rich) to heteroaryl (pyrazole) and various alkyl substituents.

There is however the potential for optimisation regarding the scope of amidine-type reagents which could be introduced as N-C-N donors. We have had encouraging results with an indole substituent and it seems that microwave irradiation is the way to go forward in these investigations. Unfortunately, we could not carry this project to its end but considering the valuable potential of such scaffolds, the project will be continued in the next few years in order to solve the remaining issues and also to show the interest of the resulting trifluoroborated compounds for further functionalisation.

Chapter 6 - Library production

1. *Introduction to Medicinal Chemistry*[110] *– ADME assays*

In the drug discovery process, a potential drug candidate is evaluated according to several different parameters. The first is of course the potency against the designated target. However, for a drug to reach the market it must also have a reasonable safety profile. Concerns in the pharmaceuticals sector over the large number of potent candidate molecules that ultimately did not make it as a marketed drug due to poor safety profiles prompted chemists and biologists to focus more on ADME assays.[111]

ADME stands for Absorption, Distribution, Metabolism and Excretion, which relate to the journey of an active molecule (lead compound) in the body. Those aspects are invaluable parameters to monitor when developing a medicine.

If we take the example of an orally administered drug, first, its solubility in water has to be high enough that a large proportion of the administered dose can circulate in the digestive system. Once inside the gastro-intestinal track (GIT), the molecule has already had to withstand the highly acidic conditions in the stomach. It now has to cross the membrane of the GIT in order to enter the blood stream, this process is called ***Absorption***. The cells of the GIT are tightly packed, therefore, the molecule has to have the right balance of hydrophilicity and lipophilicity (measured by the log(D)) in order to enter and then exit the membrane of the GIT into the blood stream. A popular assay used to measure this permeability is the Caco-2 (human colon adenocarcinoma cells) model. The cells are grown into a layer which is then introduced into the assay. The advantage of this method is that it uses a human cell line and it expresses several transport systems that give an accurate depiction of both passive (no transport system) and active mechanism for the transportation of the molecule across the membrane.

After having entered the blood stream through the GIT membrane, the molecule is ***Distributed*** throughout the blood supply within a minute. In order to have a measurable effect on the body, most drugs have to get into the tissue where they can interact with the targeted receptor on the cell membranes. Thankfully the walls of capillaries which supply the tissues with the necessary nutrients are not as thick as the GIT. Indeed, there are pores between the cells (90-150 Å in diameter) which are large enough to let most drug-sized molecules through, meaning that those molecules don't have to cross the membrane.

As soon as a drug enters the body, it is treated as a foreign entity and therefore mechanisms are put in action in order to remove this foreign object from the body: ***Excretion***. There are a variety of enzymes involved in this process, most of them situated in the liver, called cytochromes. The purpose of such enzymes is to render the foreign molecule more polar, as this increases the chances of the drug being excreted after passing through the kidneys, this process is called ***Metabolism***. One particularly prominent family of enzymes in this regard are the cytochromes P450 (or CYP450). Once the drug has been transformed it can either retain or lose its activity but it can also become toxic, which is why it is now mandatory to identify the structure of these modified molecules (metabolites) before a drug can be marketed. Knowing this, it is important to assess the proportion of drug that remains intact after passing through the liver, and this is measured via a metabolic lability assay by dosing the drug candidate in presence of CYP450. Finally, CYP450 are non-specific enzymes, meaning they metabolise many kinds of molecules, a property that is vital to the normal operations in the body. Therefore, if the drug inhibits completely this family of cytochromes then metabolism will be severally diminished. In this case, administration of another otherwise safe drug can cause its accumulation in the body and reach toxic levels. For these reasons, measuring the interaction between the drug and CYP450 is very valuable. This is measured by the CYP inhibition assay, which gives a good picture of potential drug-drug interaction problems.

The assays described in this introduction are critical to the drug discovery effort and it is those that have been conducted on the substrates isolated from the libraries production carried out at Sanofi Deutschland in order to assess their potential drugability.

In the following chapter, we will discuss the synthesis of several small libraries (around 20 compounds) of molecules and the analysis of their ADME properties. The first, **permeability**, was measured through the Caco-2 assay. The **metabolic lability** was an estimation of the degradation of each compound in the presence of human cytochromes, providing results in the form of a percentage of degradation over a fixed period of time (same for all measurements). Log(D) was measured in a buffered solution at pH 6.4 - 8.4 and it was used as a representation of the ratio of **hydrophilicity *versus* lipophilicity** for each compound tested. The **inhibition of cytochromes** (CYP3A4 isoform) was also measured to give an estimation of the potential of the compound to disrupt enzymatic function in the human body. Results are the concentration (µM) of compound necessary to inhibit 50% of the metabolism of a probe compound (Midazolam) in the presence of cytochromes. Finally, the **solubility** of each compound was measured in a water solution, buffered at pH 6.4 – 8.4. It should be noted that these assays were carried out by the ADME department of Sanofi Deutschland, who sent the results to us for interpretation.

Each of the abovementioned parameters will be discussed according to a set range of standards used in Sanofi Deutschland to analyse results. Regarding permeability (Caco-2 value), values above $20x10^{-7}$ cm/s are preferred. Notably, an *in vitro* value above $200x10^{-7}$ cm/s can indicate that the compound is able to cross the blood-brain barrier *in vivo*. A metabolic lability below 10% is ideal, however, in a more general fashion, results above 40% should be deprioritised as it means that the amount of available active principal in the body is severely decreased. Regarding the CYP inhibition assay, results below 30.0 µM should be discarded as the compound then has a high potential of giving adverse effects. Finally, the more soluble a compound is the better, however, it should be noted that compounds with a solubility below 20 mg/mL can be problematic for the amount of compound in the blood stream is then very low. Most of the compound would be excreted very rapidly.

2. Pyrazole scaffolds

We had listed earlier (see chapter 1) the many advantages of organotrifluoroborates, amongst those, their easy synthesis and isolation caught our attention. Furthermore, trifluoroborates are air and moisture stable which makes their handling easier than boronic acids and esters. In the case of our pyrazoles, we have shown earlier in chapter 3 that they could be synthesised in four steps from commercially available aldehydes in good yields. We also showed that not only methylhydrazine, but other homologues could be reacted to give the desired pyrazole-5-trifluoroborates with high selectivity. One substrate **38A** in particular caught our interest.

Indeed, we could synthesise this compound (figure 7) in excellent yield (98%) and excellent regioselectivity (> 92:8) and, as it had an alcohol group, we anticipated that we could further functionalise this intermediate in several ways. Finally, thanks to the significant difference in solubility of both isomers in acetone, the isolation of this single isomer was very easy.

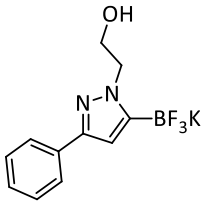
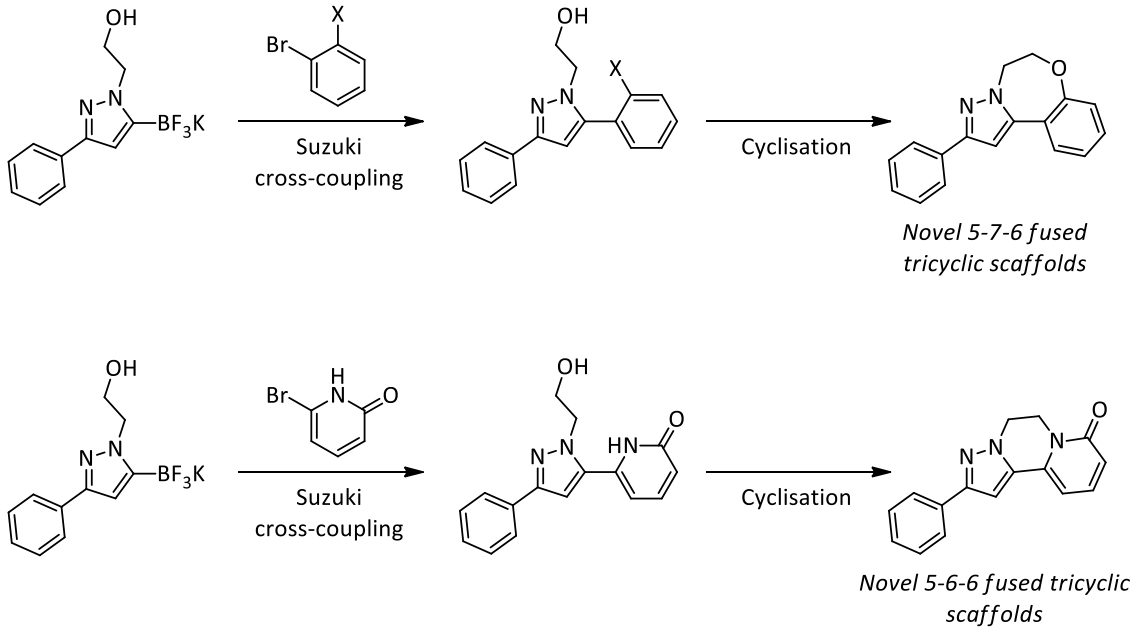


Figure 7. Starting material for all pyrazole libraries

We chose to use the reliable Suzuki-Miyaura cross-coupling reaction in order to functionalise our substrates using an automated reaction system available at Sanofi Deutschland. We envisioned that, with an appropriate coupling partner, we could use this method to synthesise new tricyclic compounds. More specifically, a suitably positioned functional group would allow for cyclisation into a family of novel tricyclic heterocycles (scheme 99).

Scheme 99. Planned syntheses of novel fused tricyclic scaffolds

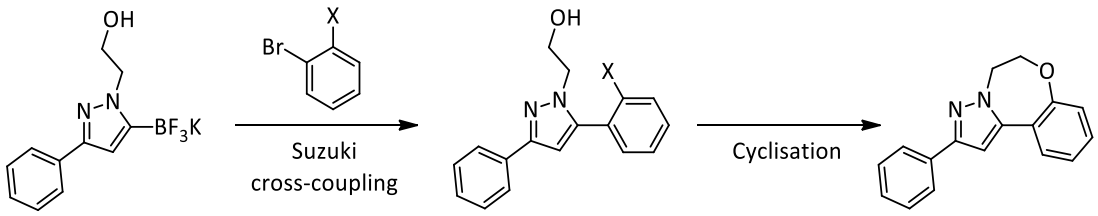


We next report the optimisation and synthesis of four libraries of pyrazole-based compounds, and the analysis of the preliminary ADME data obtained.

2.1. Novel 5-7-6 fused tricycles

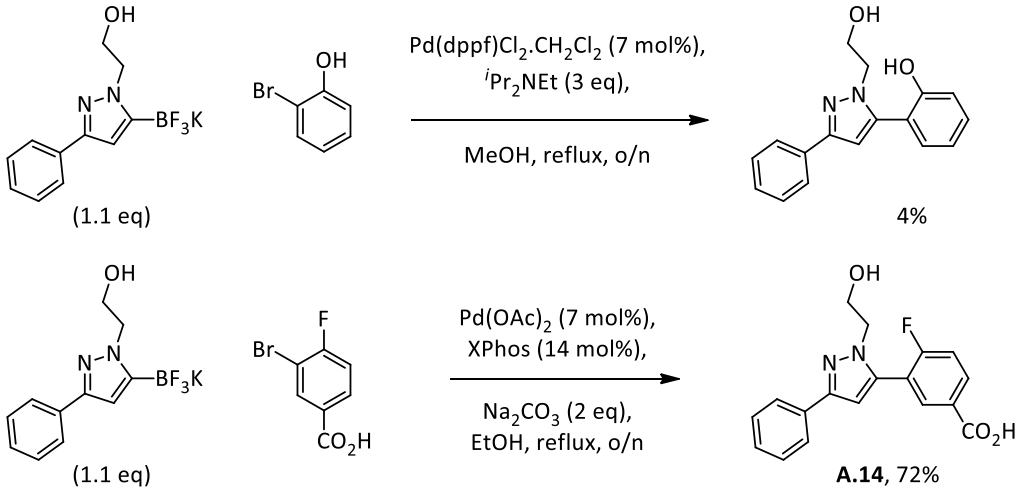
We envisioned that this first library would be generated via a two-step process leading to a 5-7-6 fused system containing the pyrazole core (scheme 100).

Scheme 100. Synthesis of a novel 5-7-6 fused tricyclic system



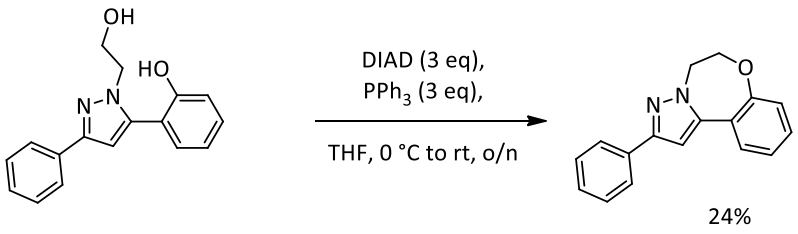
Before submitting any reaction sequence to this automated library production, it is necessary to ensure that the process is synthetically viable. Therefore, we started by testing the type of aryl halides that were tolerated in the Suzuki cross-coupling step (scheme 101).

Scheme 101. Scope of functionality tolerated in the cross-coupling step



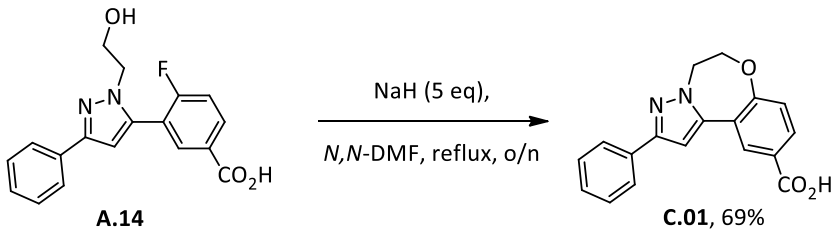
After a short optimisation for each substrate, we found that both the alcohol and the fluoride groups that we required were compatible with formation of the desired coupled product. An excellent yield was observed in the case of the biaryl fluoride product **A.14**, however, a very low yield was observed for the corresponding phenol. Nonetheless, we had enough material to react these intermediates in the subsequent cyclisation to the desired tricyclic systems (schemes 102 and 103).

Scheme 102. Mitsunobu reaction



In the case of the biaryl phenol, the Mitsunobu reaction took place but gave the desired tricyclic scaffold in quite low yield.

Scheme 103. Cyclisation via S_NAr

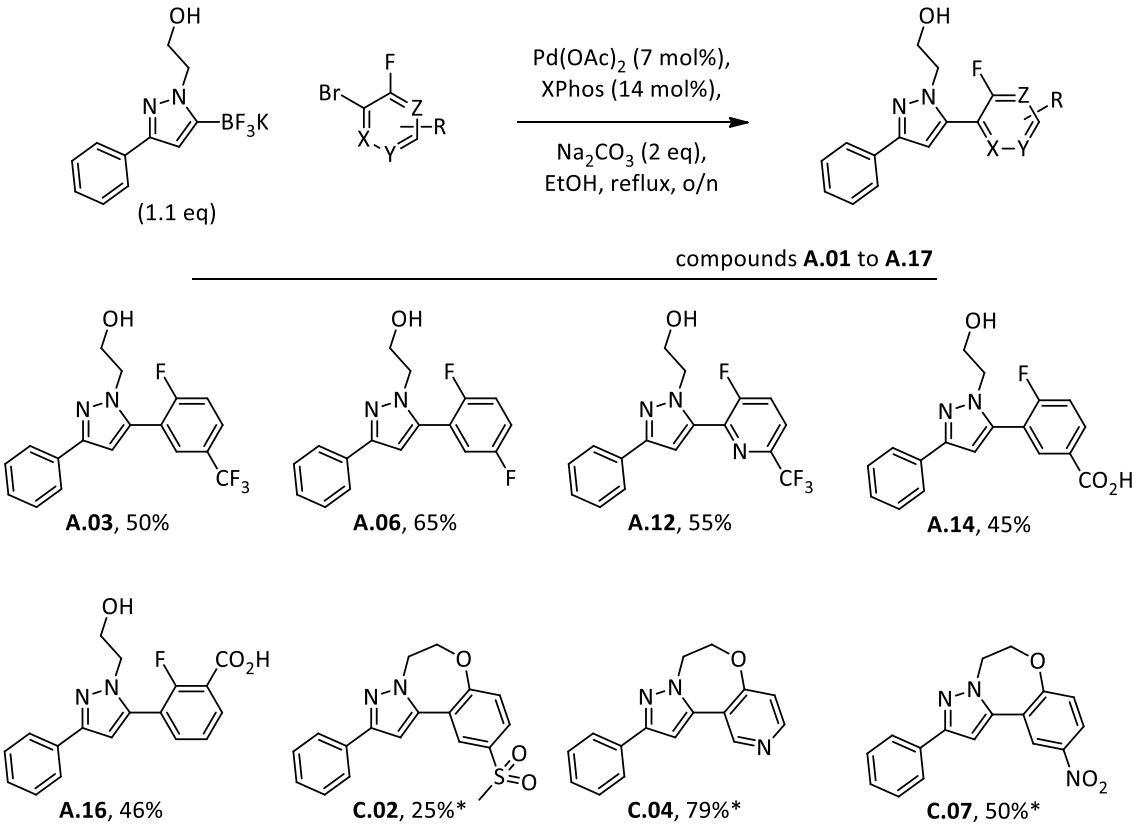


A.14 **C.01**, 69%

We next studied the cyclisation reaction of the biaryl fluoride **A.14**. In a similar manner to the Mitsunobu conditions, we were able to isolate the desired product **C.01**, although the reaction proceeded in much higher yield using an aromatic nucleophilic substitution process.

As Mitsunobu conditions could prove challenging regarding substrate tolerance during the library production, we chose the second approach in order to build our library of compounds. Furthermore, we could find many potential coupling partners which offered the opportunity to synthesise of a diverse range of compounds. We decided to isolate the Suzuki intermediates in order to have them tested as well (library **A**).

Library A. Suzuki cross-coupling

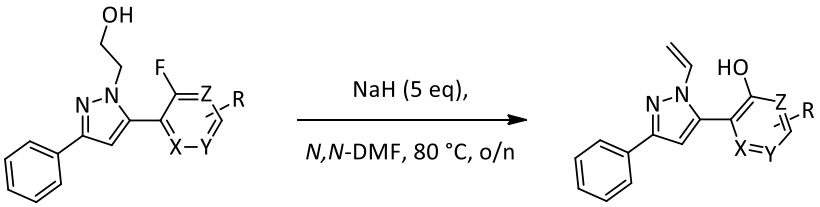


* In these cases, the cyclisation product was isolated after the Suzuki cross-coupling

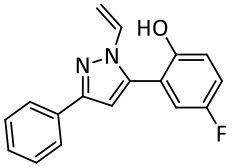
It should be noted that prior to sending the method to the automated library department, the above compounds were synthesised by hand in order to validate the procedure as well as provide full characterisation of said compounds.

When the automated library production department undertook the synthesis of the tricycle library by the S_NAr strategy we were disappointed to find that out of the 17 Suzuki products submitted to our optimised conditions, products having the expected molecular weight (LC-MS analyses) were only observed in 6 cases (library **B**).

Library B. Cyclisation/elimination



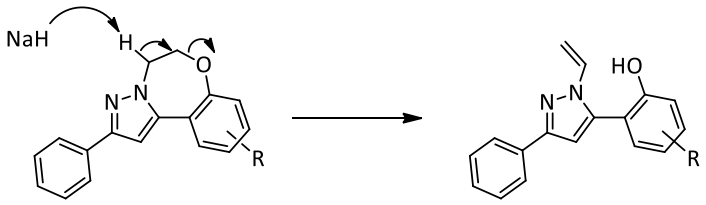
compounds **B.01** to **B.06**



B.06, 22%

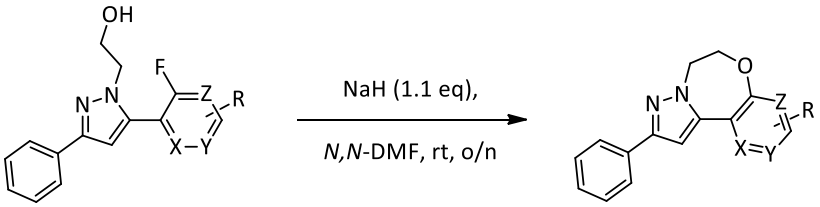
To our surprise however, when analysing those results, we concluded that the desired product had not actually been synthesised. Indeed, we observed that such an excess of base was causing the formation of a by-product (having the same molecular weight as the desired product) during the cyclisation step. When carrying out the synthesis of **B.06** by hand, we could isolate and fully characterise the product as a *N*-vinylpyrazole. We believe this product results from a second deprotonation on the cyclised product and the elimination of phenoxide (scheme 104).

Scheme 104. Formation of the cyclisation by-product

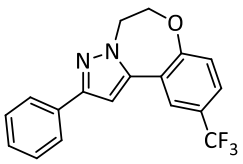


As the above conditions (library **B**) failed to give the desired cyclised products, we decided to lower the amount of base and the temperature of the reaction. In the event, the targeted 5-7-6 tricyclic products could be accessed using of 1.1 equivalent of base at room temperature (library **C**).

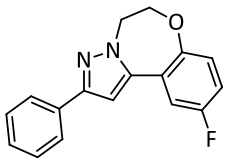
Library C. Cyclisation



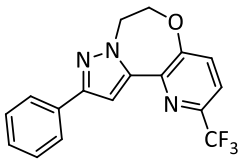
compounds **C.01** to **C.08**



C.03, 81%



C.05, 57%

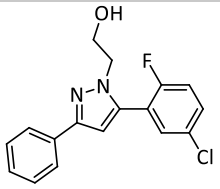
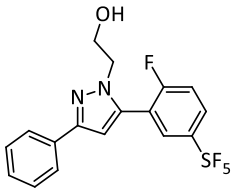
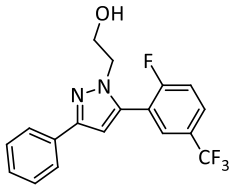
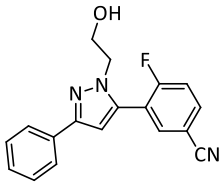
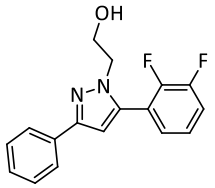
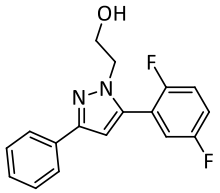
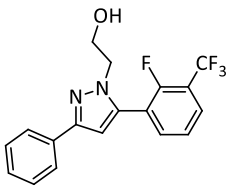


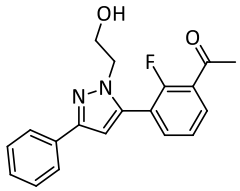
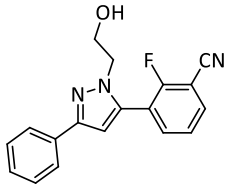
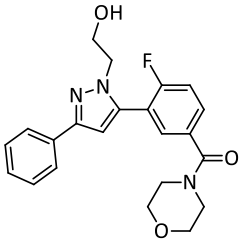
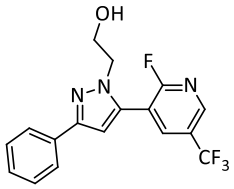
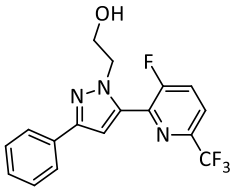
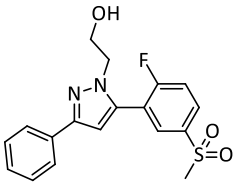
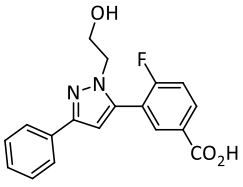
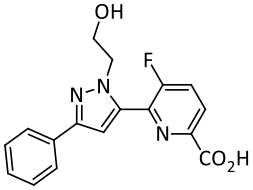
C.06, 71%

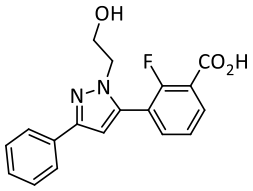
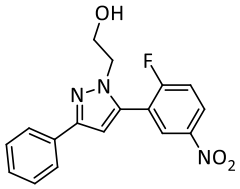
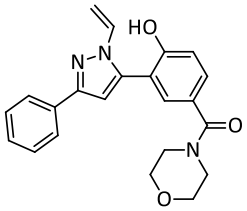
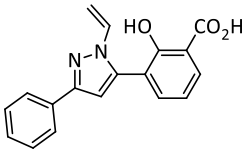
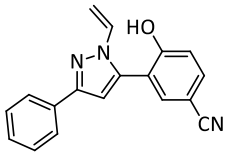
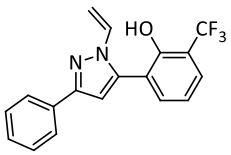
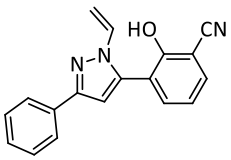
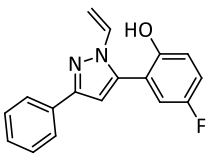
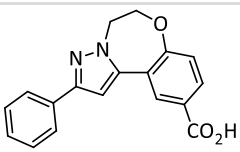
It should be noted that compounds **C.03**, **C.05** and **C.06** were synthesised by hand in order to validate the procedure as well as provide full characterisation of said compounds.

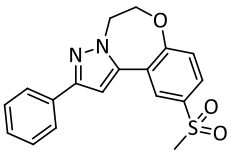
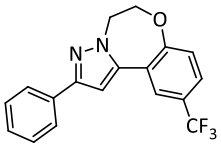
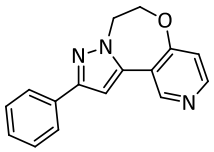
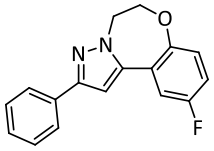
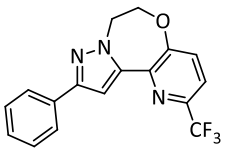
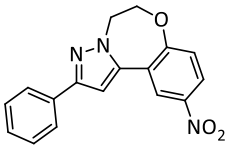
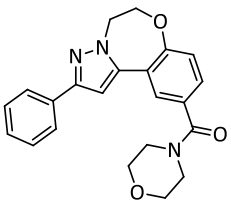
The early ADME data collected for all compounds made from the above three libraries have been combined in the following table (table 23).

Table 23. ADME results for the Suzuki/S_N^{Ar} library

Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**A.01**	316.8	163.4	82	3.17	> 30.0	< 3
	**A.02**	408.4	130.6	74	4.23	> 30.0	< 2
	**A.03**	350.3	169.4	87	3.44	> 30.0	< 3
	**A.04**	307.3	219.5	90	2.28	> 30.0	184
	**A.05**	300.3	146.6	90	2.71	> 30.0	50
	**A.06**	300.3	149.5	81	2.68	> 30.0	28
	**A.07**	350.3	121.9	98	3.41	> 30.0	< 3

	**A.08**	324.4	71.6	86	2.24	> 30.0	257
	**A.09**	307.3	199.7	91	2.31	> 30.0	125
	**A.10**	395.4	138.1	12	1.44	> 30.0	> 1264
	**A.11**	351.3	115.0	45	3.15	> 30.0	< 3
	**A.12**	351.3	157.4	69	3.59	> 30.0	4
	**A.13**	360.4	140.5	34	1.70	> 30.0	> 1387
	**A.14**	326.3	5.3	0	0.24	> 30.0	1532
	**A.15**	327.3	0.3	0	0.28	> 30.0	1528

	**A.16**	326.3	NoVal	4	-0.10	> 30.0	1532
	**A.17**	327.3	186.6	97	2.57	20.08	87
	**B.01**	375.4	98.9	48	1.85	> 30.0	133
	**B.02**	306.3	1.4	8	0.72	> 30.0	1632
	**B.03**	287.3	131.1	97	3.40	> 30.0	< 4
	**B.04**	330.3	58.5	100	4.71	> 30.0	< 3
	**B.05**	287.3	68.2	99	2.61	> 30.0	> 1740
	**B.06**	280.3	NoVal	NoVal	3.52	> 30.0	4
	**C.01**	306.3	63.9	20	-0.04	> 30.0	1632

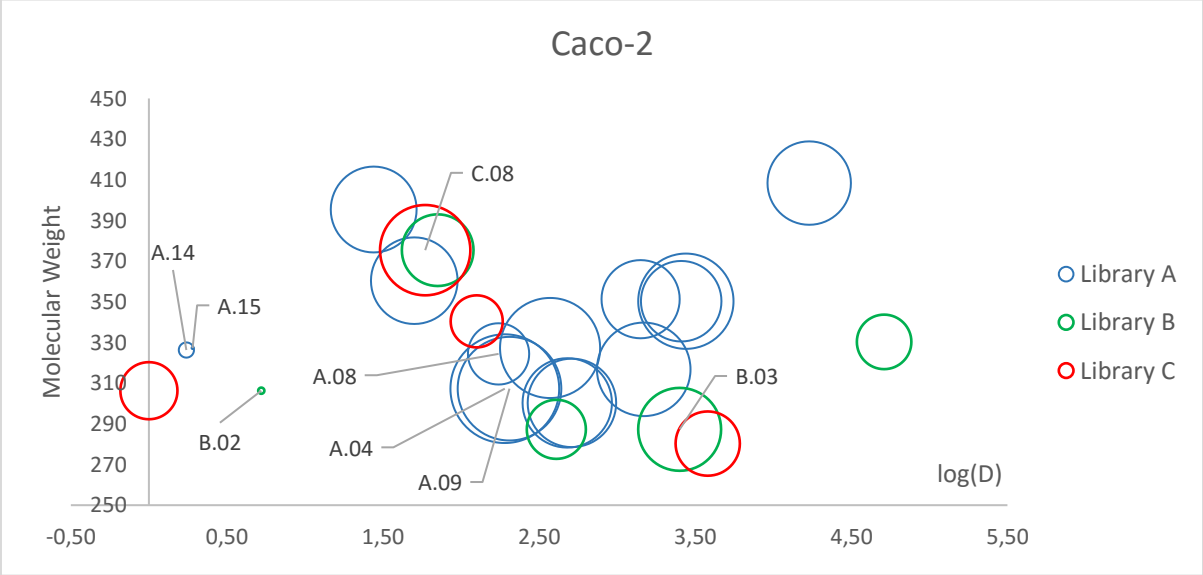
	**C.02**	340.4	53.6	-9	2.10	> 30.0	3
	**C.03**	330.3	NoVal	45	4.39	> 30.0	3
	**C.04**	283.3	NoVal	NoVal	NoVal	14.6	87
	**C.05**	280.3	80.2	65	3.58	> 30.0	4
	**C.06**	331.3	NoVal	46	4.08	> 30.0	3
	**C.07**	307.3	NoVal	68	3.44	> 30.0	3
	**C.08-E.01**	375.4	154.7	38	1.77	> 30.0	26

[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

Through the Suzuki partners chosen, we were able to access a wide range of compounds having a molecular weight within the Lipinski rules and a log(D) spanning from 0 to 5.

Regarding the permeability (Caco-2, figure 8), the results obtained were generally very good except **A.14**, **A.15** and **B.02**, which had values too low to be of use. Interestingly, they were also amongst the molecules with the lowest log(D) values.

Figure 8. Plot of log(D) and molecular weight. Size depending on the values of permeability



As an observation, the elimination and cyclisation products (libraries **B** and **C**) had lower permeability values than the Suzuki adducts (library **A**). Indeed, only three of the Suzuki adducts had values below $100x10^{-7}$ cm/s (**A.08**, **A.14** and **A.15**). Whereas, only one compound from the library **B** (**B.03** in green) and one from the cyclisation library **C** (**C.08** in red) had a value higher than $100x10^{-7}$ cm/s. Notably, **A.04** and **A.09** from the above table had Caco-2 values around or above $200x10^{-7}$ cm/s, meaning that they might be able to cross the blood-brain barrier and therefore could potentially be used to treat diseases located in the brain.

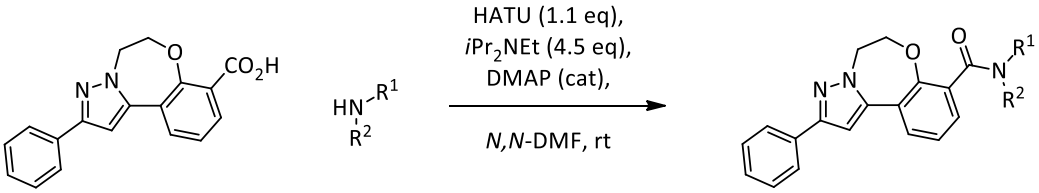
When analysing the metabolic lability values, it could be noted that the values were generally high. Indeed, only 9 compounds showed good potential (values below 40%) when it came to this parameter (**A.10**, **A.13**, **A.14**, **A.15**, **A.16**, **B.02**, **C.01**, **C.02** and **C.08**). It was interesting to note that most compounds with low metabolic lability belonged to the library **A**, resulting from the Suzuki-coupling.

Regarding solubility, these pyrazole scaffolds seemed quite insoluble in water as only approximately half of the candidates have values above 20 mg/mL. Furthermore, it should be noted that all compounds with a high log(D) (above 3) suffer from very low solubility.

Finally, it is interesting to note that all but two compounds synthesised (**A.17** and **C.04**) have detrimental CYP Inhibition (value below 30.0 µM), making this library promising in this regard.

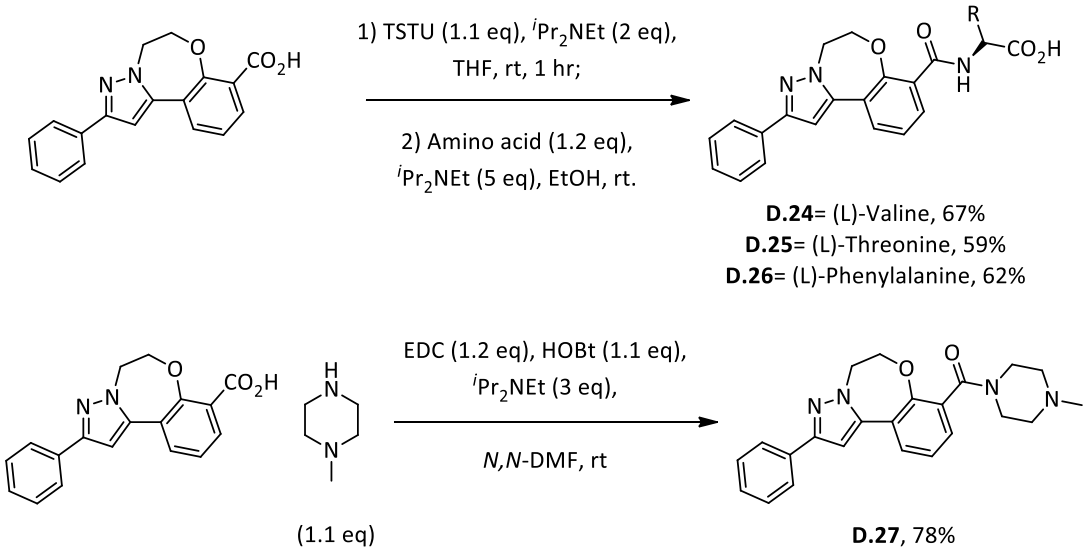
Compound **C.08** should be highlighted for it represents a good compromise between all the parameters that must be taken into account: high permeability ($155x10^{-7}$ cm/s), average metabolic lability (35%) and limited CYP Inhibition albeit a low solubility. We were also interested to see that a carboxylic acid substituent was tolerated on the phenyl ring in both *ortho*- and *para*-positions during both the cross-coupling and the cyclisation steps therefore yielding interesting compounds for further derivatisation. This prompted us to extend the library scope by preparing carboxylic acid substituted tricyclic compounds that would allow the generation of two new libraries via amide coupling reactions (libraries **D** and **E**).

Library D. Amide coupling in *ortho*-position



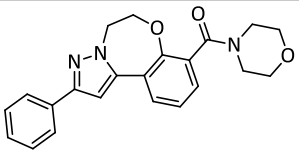
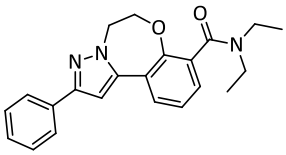
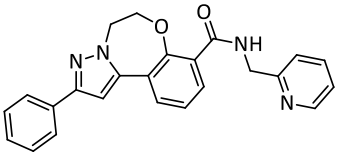
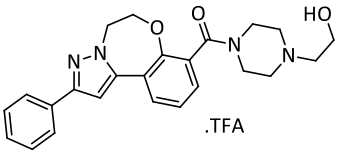
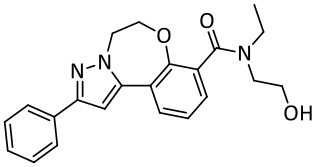
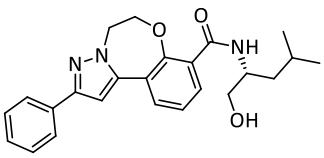
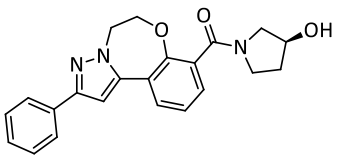
It should be noted that, whereas, compounds **D.01** to **D.23** were only made via the automated method (by the dedicated department), compounds **D.24** to **D.27** were synthesised by hand using different procedures (scheme 105).

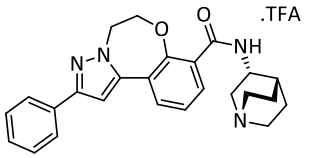
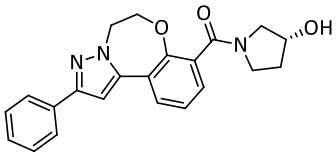
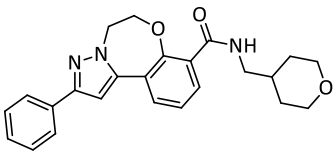
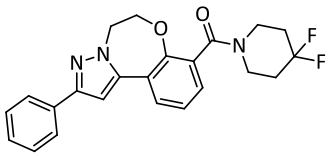
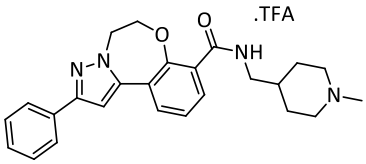
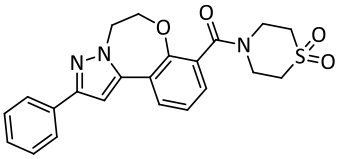
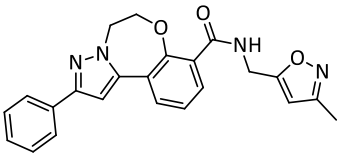
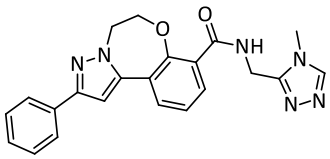
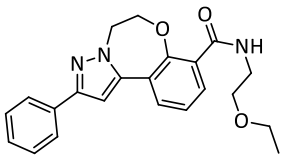
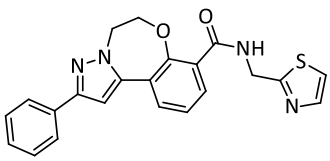
Scheme 105. Synthesis of D.24 to D.27 by hand for full characterisation

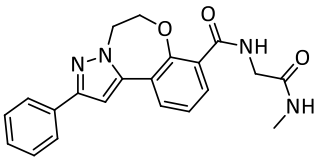
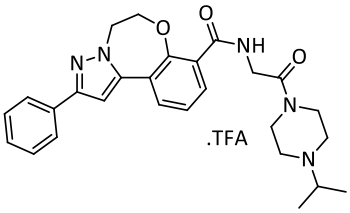
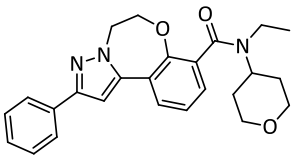
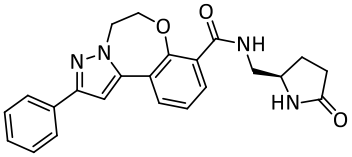
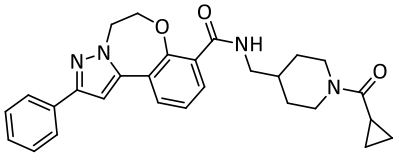
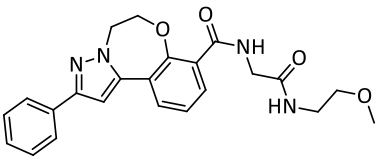
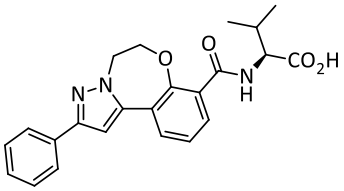
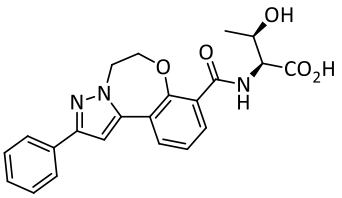


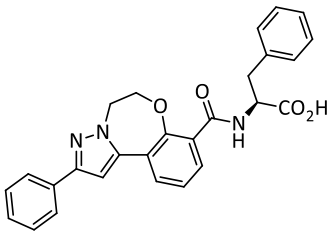
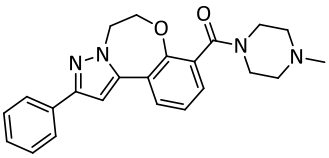
It should be noted that all 23 planned compounds could be synthesised via the automated method. The ADME results for this library are shown in table 24.

Table 24. ADME results for the amide coupling in *ortho*-position library

Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**D.01**	375.4	205.2	13	1.80	> 30.0	230
	**D.02**	361.5	189.1	31	2.69	> 30.0	29
	**D.03**	396.5	149.3	43	2.24	> 30.0	< 3
	**D.04**	532.5	80.9	22	1.11	> 30.0	> 939
	**D.05**	377.5	141.8	30	1.71	> 30.0	> 1325
	**D.06**	405.5	NoVal	93	2.64	> 30.0	< 3
	**D.07**	375.4	NoVal	6	1.25	> 30.0	> 1332

	**D.08**	528.5	14.2	8	1.07	> 30.0	> 946
	**D.09**	375.4	79.9	7	1.26	> 30.0	> 1332
	**D.10**	403.5	178.3	83	2.09	> 30.0	3
	**D.11**	409.4	186.3	24	2.96	> 30.0	3
	**D.12**	530.6	21.6	4	1.02	> 30.0	> 942
	**D.13**	423.5	90.2	7	1.74	> 30.0	83
	**D.14**	400.4	172.4	31	2.4	27.6	< 3
	**D.15**	400.4	57.2	6	1.17	> 30.0	80
	**D.16**	377.5	186.5	91	2.42	> 30.0	54
	**D.17**	402.5	184.8	63	2.23	5.8	< 3

	**D.18**	376.4	136.8	13	1.36	> 30.0	4
	**D.19**	587.6	82.7	70	1.96	> 30.0	11
	**D.20**	417.5	210.7	90	2.32	> 30.0	> 1198
	**D.21**	402.5	36.0	14	1.26	> 30.0	227
	**D.22**	470.6	182.4	91	2.23	> 30.0	< 2
	**D.23**	420.5	131.1	18	1.53	> 30.0	4
	**D.24**	419.5	0.9	-2	1.00	> 30.0	1233
	**D.25**	421.5	0.0	1	0.54	> 30.0	1227

 **D.26**	453.5	0.1	-6	1.43	> 30.0	1103
 **D.27**	388.5	120.3	57	1.54	> 30.0	1287

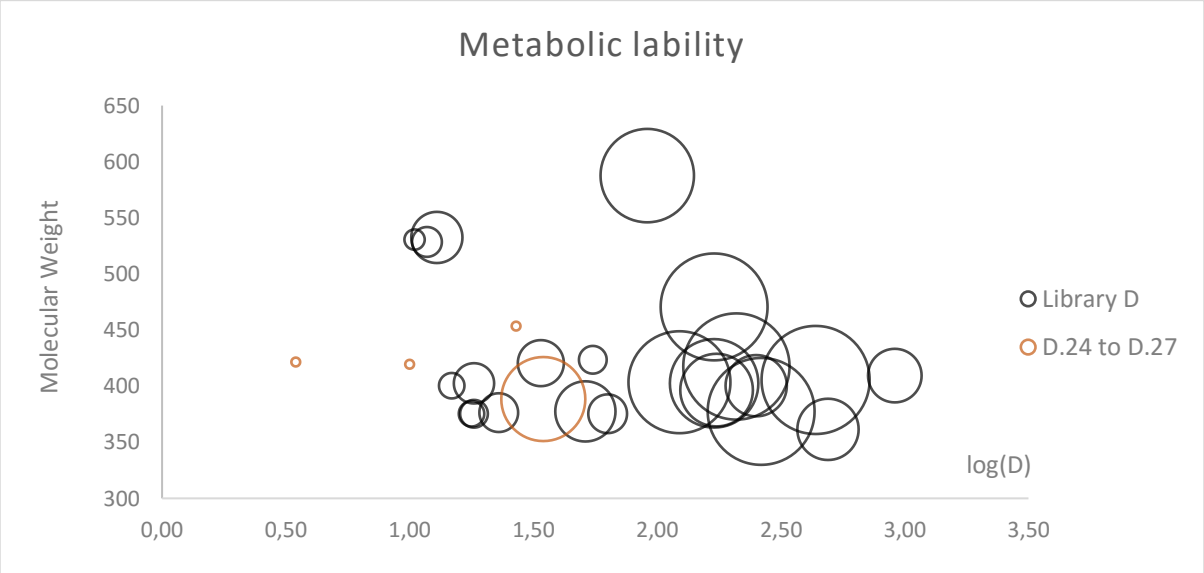
[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

Interestingly, this library of compounds showed a much broader range of values for both Caco-2 and metabolic lability albeit a narrower log(D) range. Indeed, we had observed in libraries **A**, **B** and **C** that a log(D) value higher than 3 resulted in a low solubility, thankfully when synthesising this library, we could effectively target low log(D) values as desired.

The synthesised molecules have very interesting permeability properties as only 4 compounds showed values below $20x10^{-7}$ cm/s (**D.09**, **D.24**, **D.25** and **D.26**). Notably, the latter compounds were formed using amino-acids as coupling partners, the presence of this carboxylic acid group would therefore shift the balance towards hydrophilicity, which could explain the observed adverse impact on the compounds' ability to cross membranes. Furthermore, we observed that over half of these substrates had Caco-2 values above $100x10^{-7}$ cm/s and seven of them showed data consistent with the potential for crossing the blood-brain barrier (**D.01**, **D.02**, **D.11**, **D.16**, **D.17**, **D.20** and **D.22**).

Additionally, the metabolic lability values of the library **D** were considerably improved compared to the previous library as only a third of the compounds listed in table 24 had values higher than 40%. And as evident from figure 9, most compounds had a metabolic lability value of 20% or less indicating that only small amounts of compounds are metabolised in the human body.

Figure 9. Plot of log(D) and molecular weight. Size depending on the values of metabolic lability



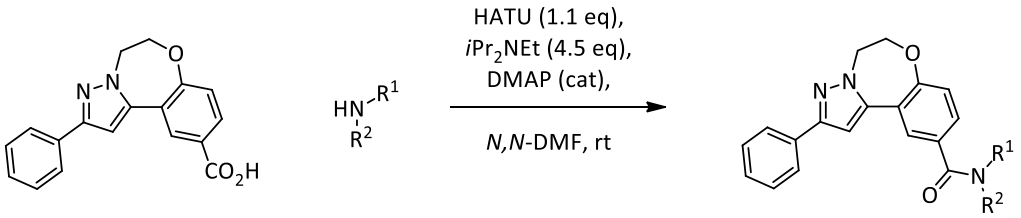
Notably, the use of amino acid coupling partners resulted in compounds with the lowest metabolic lability value in this series. Such an observation correlates with our previous statement: those molecules are very hydrophilic and polar, therefore, might already be polar enough to be efficiently excreted from the body without the intervention of the cytochrome enzymes.

Whereas Caco-2 and metabolic lability were spread throughout a wide range, solubility in library **D** was generally either very high or very low. Furthermore, as observed in the previous libraries (**A**, **B** and **C**), CYP inhibition showed high values throughout this series (only **D.14** and **D.17** should be discarded).

As a conclusion, we could highlight several compounds with interesting properties: **D.01**, **D.04**, **D.05**, **D.09**, **D.13** and **D.15**. It should be noted that amongst said compounds, **D.13** and **D.15** have lower solubility values.

As discussed previously, we could install a carboxylic acid handle in both *ortho*- and *para*-positions. We were therefore curious to assess the influence of the substitution pattern on the properties of our new tricyclic compounds, which is why, using the same coupling partners as for library **D**, we carried out the automated synthesis of a new library of compounds using the *para*-carboxylic acid substrate as the reagent (library **E**).

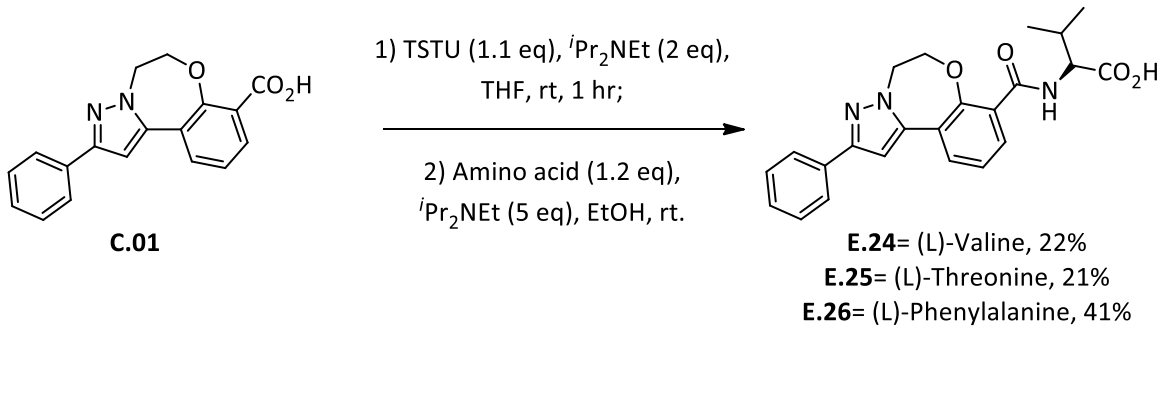
Library E. Amide coupling in *para*-position



C.01 (1.33 eq) compounds **E.01** to **E.23**

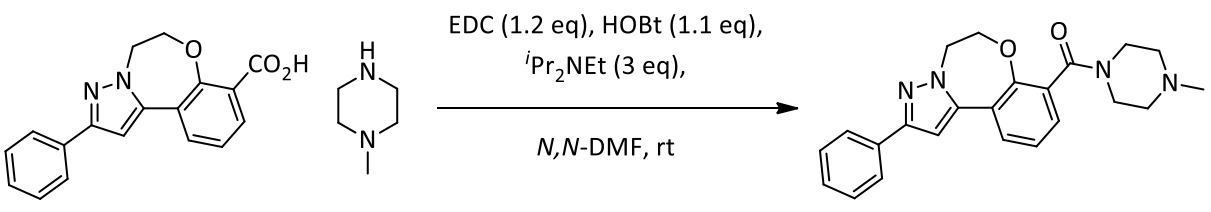
It should be noted that, whereas, compounds **E.01** to **E.23** were only made via the automated method (by the dedicated department), compounds **E.24** to **E.27** were synthesised by hand using different procedures (scheme 106).

Scheme 106. Synthesis of E.24 to E.27 by hand for full characterisation



C.01

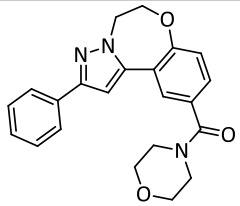
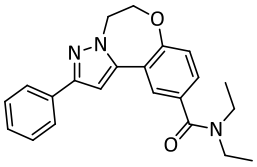
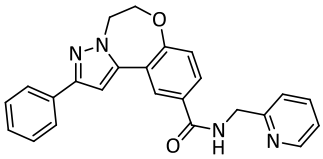
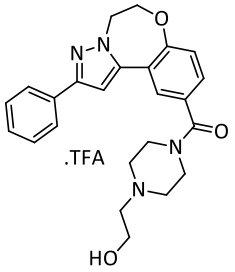
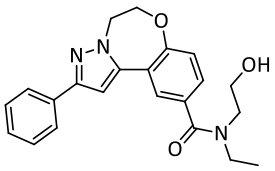
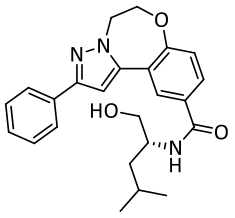
E.24= (L)-Valine, 22%
E.25= (L)-Threonine, 21%
E.26= (L)-Phenylalanine, 41%

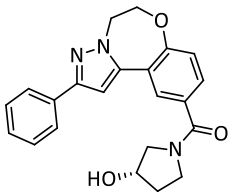
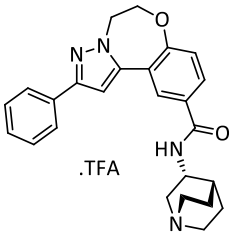
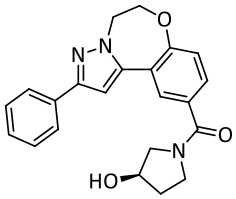
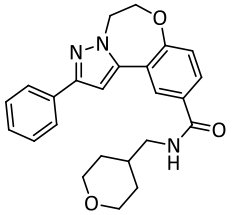
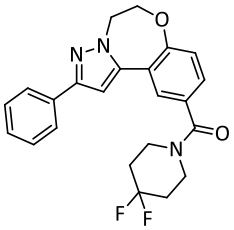
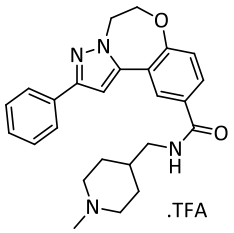
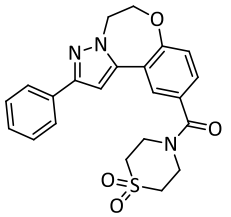


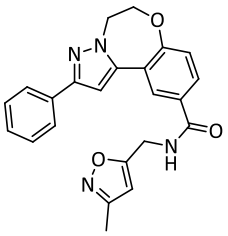
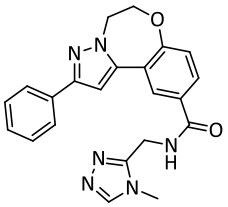
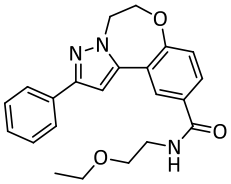
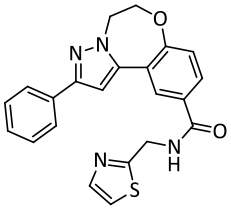
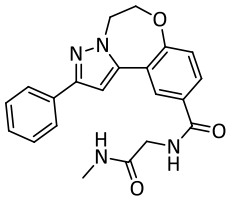
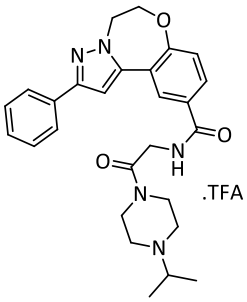
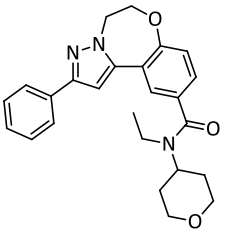
C.01 (1.1 eq) **E.27**, 69%

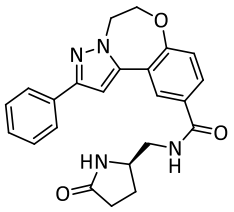
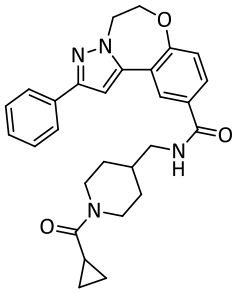
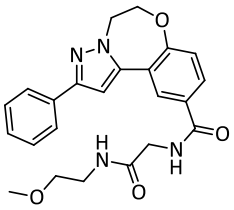
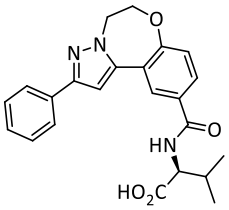
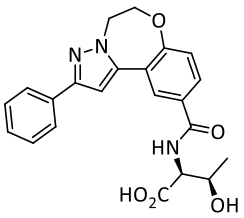
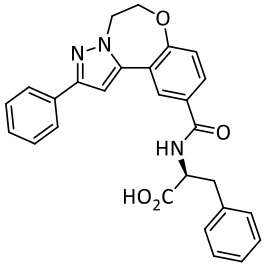
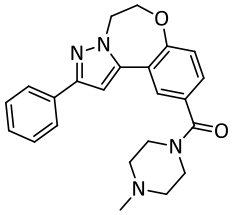
It should be noted that all 23 planned compounds could be synthesised via the automated method. The ADME results are shown in table 25.

Table 25. ADME results for the amide coupling in *para* position library

Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**C.08-E.01**	375.4	154.7	38	1.77	> 30.0	26
	**E.02**	361.5	191.3	80	2.75	> 30.0	4
	**E.03**	396.5	165.0	45	1.96	> 30.0	3
	**E.04**	532.5	80.3	21	0.99	> 30.0	1195
	**E.05**	377.5	28.0	66	1.34	> 30.0	1325
	**E.06**	405.5	64.0	53	2.55	> 30.0	< 3

	**E.07**	375.4	113.3	18	1.04	> 30.0	90
	**E.08**	528.54	2.04	2	0.89	> 30.0	NoVal
	**E.09**	375.4	111.7	16	1.04	> 30.0	114
	**E.10**	403.5	114.6	52	1.99	23.21	< 3
	**E.11**	409.4	158.2	62	2.99	17.27	< 3
	**E.12**	530.6	6.6	9	0.83	> 30.0	> 942
	**E.13**	423.5	113.3	20	1.63	> 30.0	4

	**E.14**	400.4	134.7	39	2.21	> 30.0	< 3
	**E.15**	400.4	6.9	11	0.95	> 30.0	4
	**E.16**	377.5	202.0	59	2.17	23.0	< 3
	**E.17**	402.5	173.0	60	2.02	3.75	< 3
	**E.18**	376.4	62.7	10	1.01	> 30.0	29
	**E.19**	587.6	42.5	53	1.60	> 30.0	379
	**E.20**	417.5	232.6	96	2.31	4.9	37

	**E.21**	402.5	8.0	16	1.14	> 30.0	11
	**E.22**	470.6	148.7	45	2.13	8.02	< 2
	**E.23**	420.5	66.1	10	1.21	> 30.0	158
	**E.24**	419.5	1.0	12	1.61	> 30.0	> 1233
	**E.25**	421.5	0.0	3	1.13	> 30.0	> 1227
	**E.26**	453.5	0.0	-1	1.14	> 30.0	101
	**E.27**	388.5	123.0	37	1.45	> 30.0	1287

[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

As in library **D**, this library also showed a wide range of Caco-2 and metabolic lability values for a similar range of log(D). Regarding the Caco-2 values, similar observations as in the previous library could be made. Namely, more than half of the compounds have high permeability (higher than $100x10^{-7}$ cm/s).

However, whereas only four compounds from the library **D** had very low permeability values (below $20x10^{-7}$ cm/s), in this case there are seven (**E.08**, **E.12**, **E.15**, **E.21**, **E.24**, **E.25** and **E.26**). As observed previously, the amino-acid coupled products (**E.24**, **E.25** and **E.26**) showed very low permeability properties due to the presence of a highly hydrophilic carboxylic acid group. Additionally, the number of molecules having high Caco-2 values (above $180x10^{-7}$ cm/s) was reduced. However, six amine coupling partners gave similarly high Caco-2 values in both libraries: **D.01** and **E.01**, **D.02** and **E.02**, **D.11** and **E.11**, **D.14** and **E.14**, **D.16** and **E.16** finally **D.20** and **E.20**.

Regarding metabolic lability, it would seem that *para*-substitution pattern was generally detrimental. Indeed, only six compounds showed lower metabolic lability values (**E.06**, **E.10**, **E.16**, **E.19**, **E.22** and **E.27**) whereas most of them increased. As a result, around half of the compounds from table 25 have metabolic lability above 40%. As a general trend, it seemed that molecules with a high log(D) (value higher than 2) had also a high metabolic lability values.

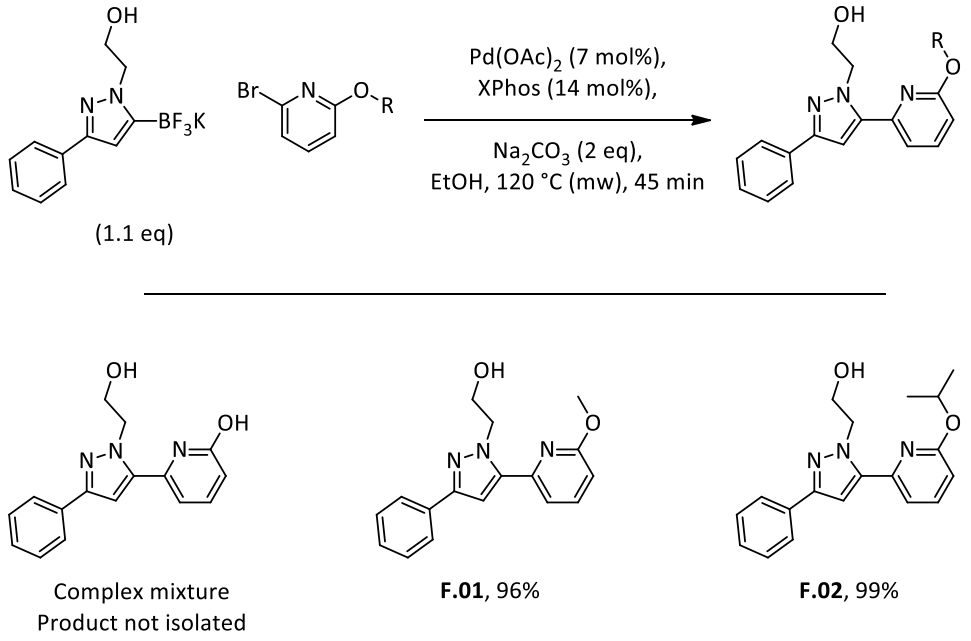
The most significant change in library **E** was the increase in the number of compounds with detrimental CYP inhibition values. No discernible trend could be drawn regarding the impact of the substitution. Indeed, comparing **D.14** to **E.14** we could observe a beneficial effect of the *para*-substituent on the CYP inhibition, whereas **D.17** and **E.17** gave similarly bad results. Finally, **E.10**, **E.11**, **E.16**, **E.20** and **E.22** gave lower values than in the related members of library **D**, showing in these cases the negative impact of having the substituent in *para*-position.

If focusing on the lower log(D) values (values lower than 2), some interesting compounds could be observed. Namely, **E.04**, **E.07**, **E.09**, **E.23** and **E.27** showed good permeability properties, low metabolic lability, good solubility and limited CYP inhibition properties.

2.2. Novel 5-6-6 fused tricycles

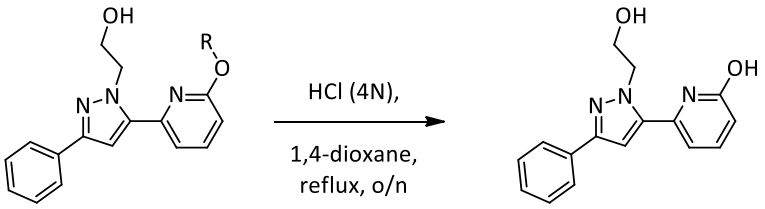
Finally, we became interested in the potential of our molecules to make another type of tricyclic system: 5-6-6 fused core. We had envisioned that the use of derivatives such as the pyridinol family would allow for the cyclisation of the middle 6-membered ring. However before cyclising the intermediates, we first had to test the suitability of pyridinol as Suzuki coupling partners (scheme 107).

Scheme 107. Suzuki cross-coupling of various pyridinol derivatives



The unprotected pyridinol failed to deliver a clean reaction, fortunately, both methyl- and *iso*propyl-protected partners gave excellent yields for the desired coupled products **F.01** and **F.02**. The next step towards the targeted tricyclic scaffolds therefore required the deprotection of the pyridinol ether moiety. We found that using hydrochloric acid (as a 4 M solution) in 1,4-dioxane as solvent was an efficient means to achieve the hydrolysis of both methyl- and *iso*propyl-groups (scheme 108).

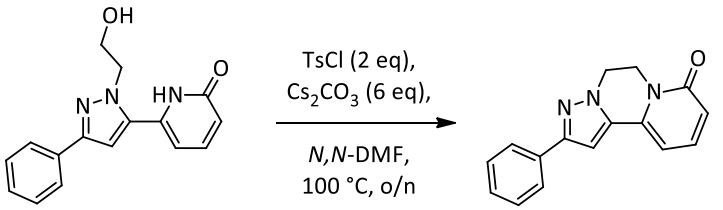
Scheme 108. Deprotection of the pyridinol under acidic conditions



F.13, R=Me, 84%
R= ^{i}Pr, 91%

We next carried out the cyclisation through the exchange of the alcohol moiety for an *O*-tosyl leaving group. The cyclisation was then achieved *in situ* through the use of an excess of base to give the desired 5-6-6 fused tricyclic compounds, as shown in scheme 109.

Scheme 109. Cyclisation into novel 5-6-6 fused tricyclic compounds



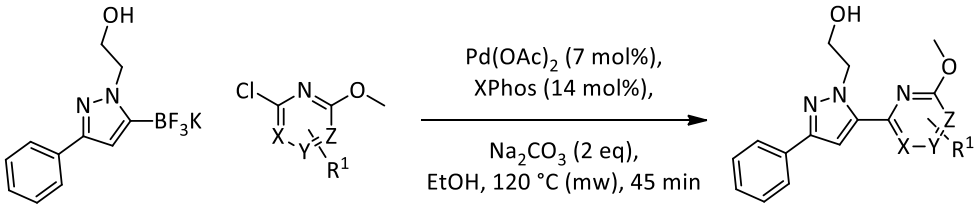
F.24 R =Me, 85%
R = ^{i}Pr, 72%

Both methyl- and *iso*propyl-substituted substrates gave similarly high yields for the desired tricyclic scaffold **F.24** (respectively 69% and 65% over 3 steps). Whereas *iso*propyl protected pyridinol derivatives were challenging to access, we could find twelve methyl-protected pyridinol substrates that could potentially undergo the reaction sequence in order to synthesise a small library of fused tricyclic compounds. Considering the limited number of pyridinol partners we could find, we decided not to use the automated synthesis department and synthesise library **F** by hand.

2.2.1. Chemical aspects of the synthesis

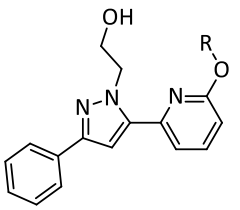
For the chosen substrates, we could successfully carry out the Suzuki cross-coupling under the conditions used previously in this chapter (see section 2.1 – library **A**), therefore showing the wide functional tolerance of these conditions (scheme 110).

Scheme 110. Step 1 - Suzuki-Miyaura cross-coupling

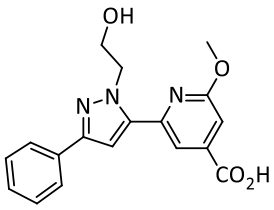


(1.1 eq) * Brominated partners

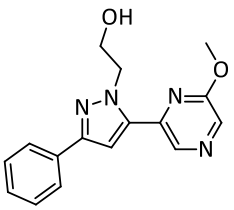
Compounds **F.01** to **F.12**



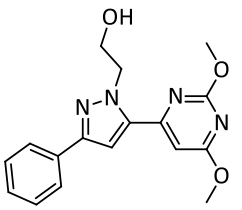
F.01 R=Me, 96%*
F.02 R=^{i}Pr, 99%*



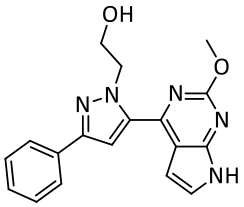
F.03, 69%



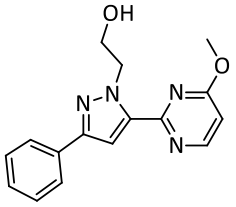
F.04, 66%*



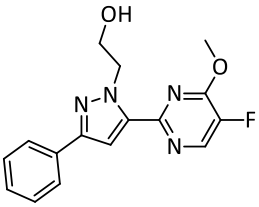
F.05, 66%



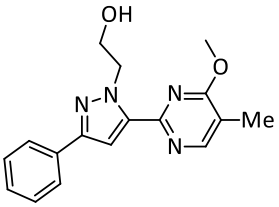
F.06, 49%



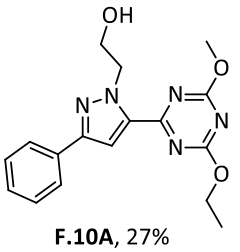
F.07, 57%*



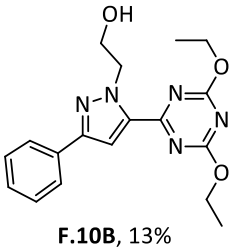
F.08, 56%



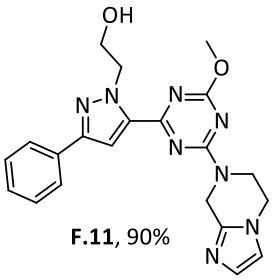
F.09, 60%



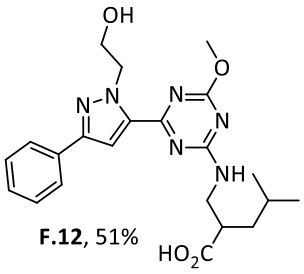
F.10A, 27%



F.10B, 13%



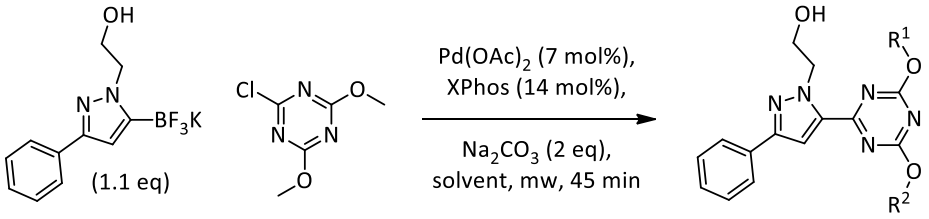
F.11, 90%



F.12, 51%

Interestingly, we found that both brominated and chlorinated coupling partners performed well under the same reaction conditions to give a wide range of products in average to excellent yields. Notably, the triazine substrate gave a mixture of products **F.10A/B** (table 26).

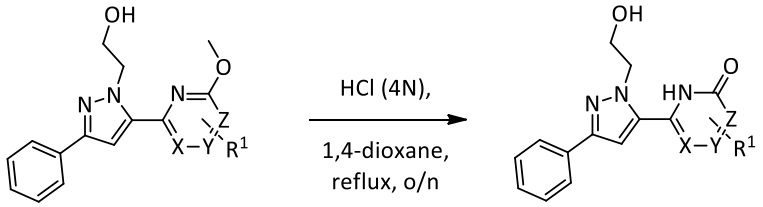
Table 26. Coupling with 2-chloro-4,6-dimethoxy-1,3,5-triazine



Entry	*Solvent*	*Temperature*	*Results*
1	Ethanol	120 °C	Mixture of R^1=R^2=Me (minor – not isolated), **F.10A** R^1=Me, R^2=Et 27% and **F.10B** R^1=R^2=Et, 13%
2	Methanol	80 °C	Only protodeboration observed
3	Water	120 °C	Only protodeboration observed

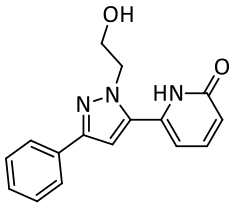
Under typical conditions (entry 1), we observed a complex mixture of products formed during the microwave assisted Suzuki reaction. The LC-MS of the crude material showed the formation of three compounds and protodeboration of starting material **38A**. The compounds were identified (and isolated when possible) as being the expected methylated product (in such small amounts that we could not fully characterise it) and both the mono and the diethylated products **F.10A** and **F.10B**. We believed those products resulted from the mono- and di-transetherification with the solvent. We therefore hypothesised that we could either avoid this exchange by using methanol as the solvent for the reaction (entry 2) or that by using the apparent high reactivity of the triazine moiety, we could form the deprotection product in one step by carrying out the reaction in water (entry 3). To our surprise, none of the two sets of conditions gave the expected product. Instead we only observed protodeboration. As a result, we gathered all three products from the reaction and submitted them to the deprotection step as a mixture (scheme 111).

Scheme 111. Step 2 – Deprotection under acidic conditions

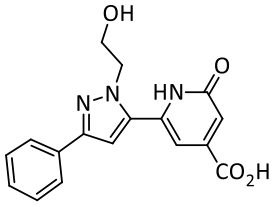


* Water added
(1/3 ratio with 1,4-dioxane)

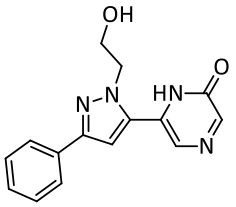
Compounds **F.13** to **F.23**



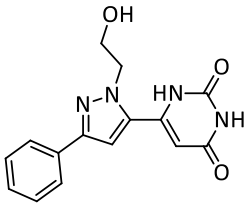
F.13 (from **F.01**), 84%
(from **F.02**), 91%



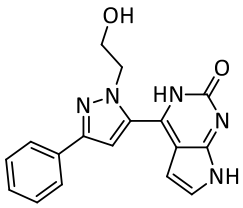
F.14, 70%*



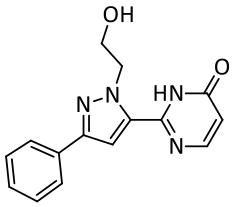
F.15, 31%*



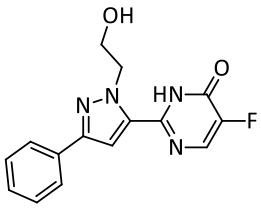
F.16, 90%



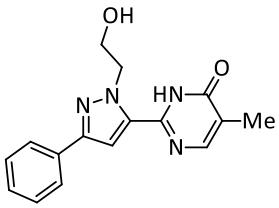
F.17, 70%*



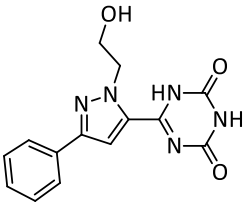
F.18, 70%



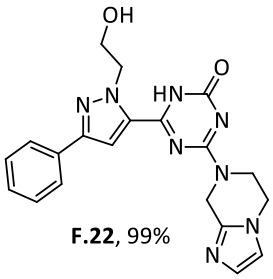
F.19, 74%



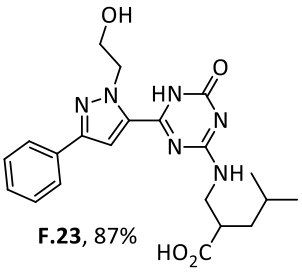
F.20, 79%*



F.21, 60%



F.22, 99%



F.23, 87%

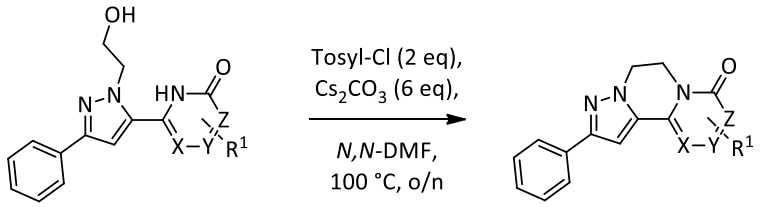
All compounds could be deprotected under acidic conditions giving the pyridinol moiety in average to excellent yields. Compound **F.21** was obtained in high yield from the mixture of substrates as explained above.

It should be noted that four compounds (**F.14**, **F.15**, **F.17** and **F.20**) couldn't be accessed under standard conditions. In those cases, we could recover entirely the starting material after heating overnight. However, adding water in a 1/3 ratio (compared to the volume of HCl solution added) promoted the hydrolysis reaction of these substrates,

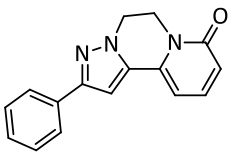
presumably by trapping methylchloride as methanol and regenerating HCl. This change of conditions also considerably reduced the reaction time from overnight to 7 hours for those substrates.

We now had access to a wide range of pyridinol substituted pyrazoles and the final step required to reach our target compounds was the cyclisation under basic conditions (scheme 112).

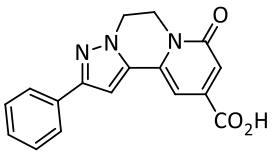
Scheme 112. Step 3 – Cyclisation towards the novel 5-6-6 tricyclic scaffolds



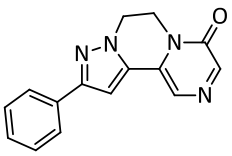
Compounds **F.24** to **F.30**



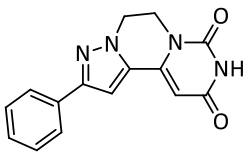
F.24 (from **F.01**), 85%
(from **F.02**), 72%



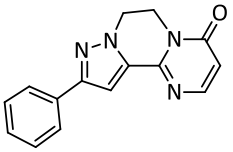
F.25, 45%



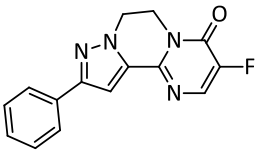
F.26, 29%



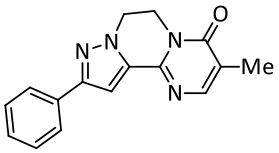
F.27, 78%



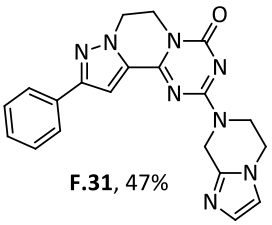
F.28A, 42%



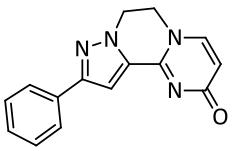
F.29A, 34%



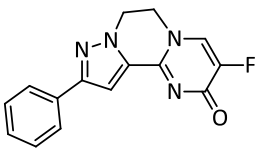
F.30A, 57%



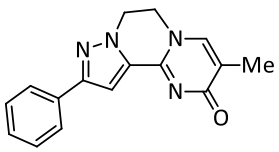
F.31, 47%



F.28B, 14%



F.29B, 10%



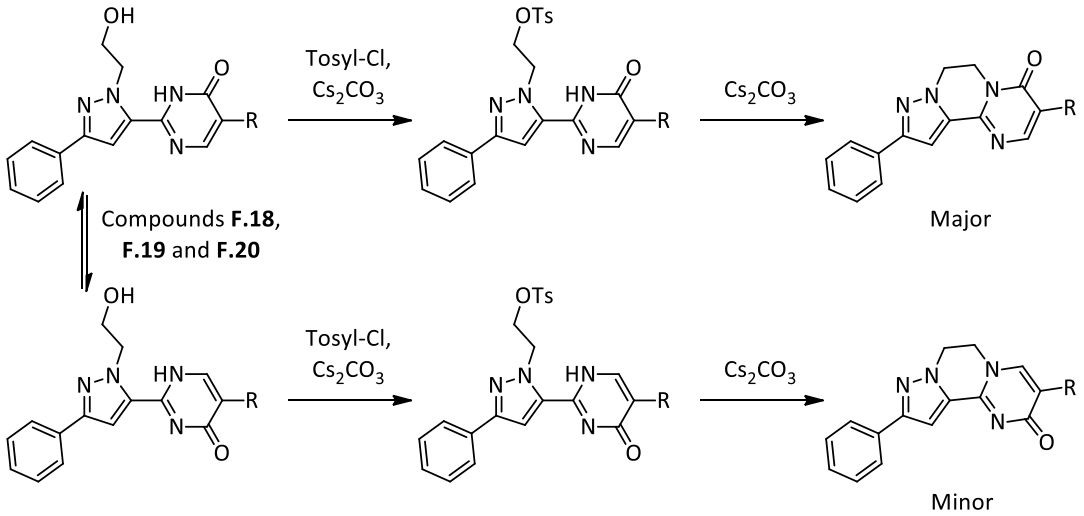
F.30B, 20%

Several pyridinol compounds failed to undergo the cyclisation. Namely, the triazine type reagents **F.21** and **F.23** seemed to degrade under the reaction conditions, giving complex mixtures from which not tricyclic product could be isolated. Furthermore, **F.17** unfortunately

also behaved similarly. Nonetheless, we could isolate several of desired compounds in low to excellent yields.

It was interesting to note that both possible products from the cyclisation of the pyrimidine type substrates could be isolated. However, the major isomer was always the product of addition at the amide-type nitrogen (scheme 113).

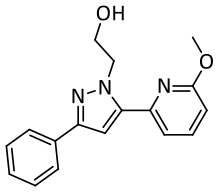
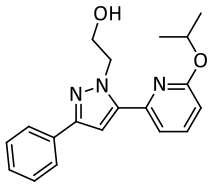
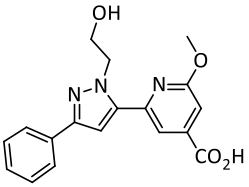
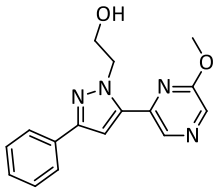
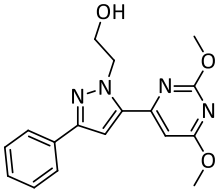
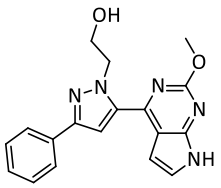
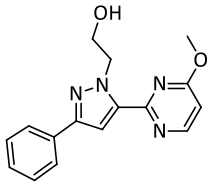
Scheme 113. Cyclisation of the pyrimidine type substrates

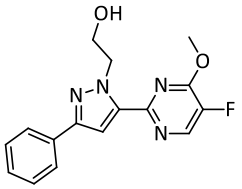
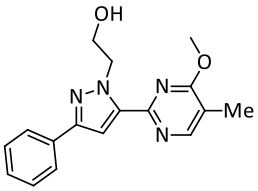
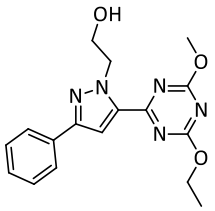
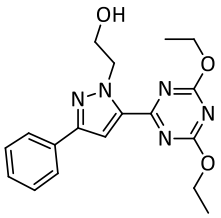
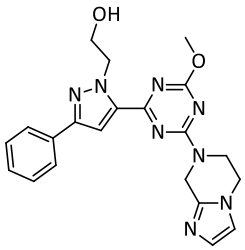
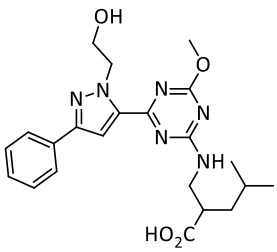
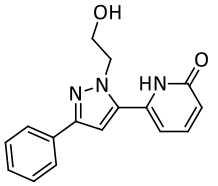
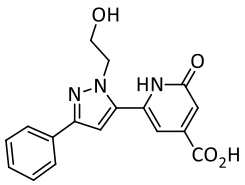


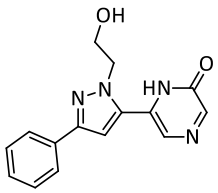
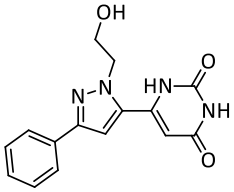
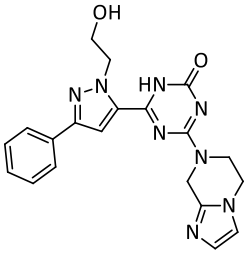
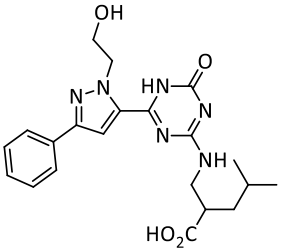
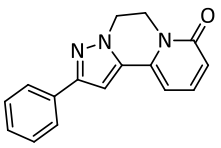
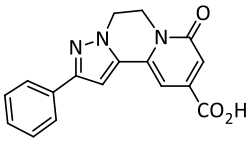
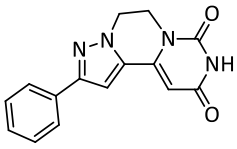
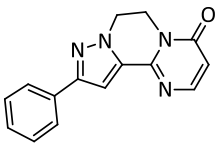
2.2.2. ADME measurements

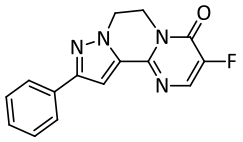
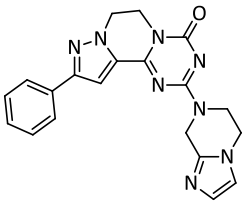
Whenever possible, we submitted compounds from library **F** for the measurement of their early ADME properties. Results obtained are summarised in the following table 27.

Table 27. ADME results for the pyridinol library

Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**F.01**	295.4	148.3	91	2.47	> 30.0	135
	**F.02**	323.4	160.4	97	3.38	> 30.0	< 2
	**F.03**	339.4	1.0	4	-0.03	> 30.0	> 1473
	**F.04**	296.3	132.7	53	1.64	> 30.0	9.8
	**F.05**	326.4	131.8	91	2.35	> 30.0	18
	**F.06**	335.4	106.7	64	1.58	> 30.0	< 3
	**F.07**	296.3	179.3	58	1.85	> 30.0	47

	**F.08**	314.3	157.0	64	2.30	> 30.0	4
	**F.09**	310.4	154.6	91	2.38	> 30.0	< 3
	**F.10A**	341.4	185.2	50	2.40	3.2	6
	**F.10B**	355.4	208.2	51	2.90	29.5	< 3
	**F.11**	418.5	126.2	51	1.63	11.1	< 2
	**F.12**	440.5	1.3	21	0.97	9.4	> 1135
	**F.13**	281.3	86.0	55	0.60	> 30.0	> 1777
	**F.14**	325.3	0.1	2	0.30	> 30.0	288

	**F.15**	282.3	63.7	36	- 0.26	> 30.0	> 1771
	**F.16**	298.3	4.2	8	0.03	> 30.0	329
	**F.22**	404.4	0.1	8	0.21	> 30.0	< 3
	**F.23**	426.5	0.2	2	1.31	> 30.0	> 1772
	**F.24**	263.3	187.7	76	1.11	> 30.0	278
	**F.25**	307.3	3.5	5	1.31	> 30.0	> 1172
	**F.27**	280.3	173.9	58	0.54	> 30.0	26
	**F.28A**	264.3	284.2	94	0.79	> 30.0	86

 **F.29A**	282.3	NoVal	60	2.17	> 30.0	9
 **F.31**	386.4	25.3	23	0.99	14.5	69

[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

Generally, products resulting from the Suzuki cross-coupling (**F.01** to **F.12**) were very efficiently metabolised (metabolic lability above 40%) and additionally not very soluble (below 20 mg/mL), two detrimental factors for this data set. The high metabolism of these compounds could be explained by the presence of the methoxy group, which is usually rapidly metabolised into an alcohol group in the body. And indeed, when comparing metabolic lability values with the products from the deprotection step (**F.13** to **F.23**), a clear improvement could be observed. All measured values were lower for the product of the deprotection with respect to the Suzuki product.

For this second data set (**F.13** to **F.23**), the products were generally more soluble than their protected derivatives, except for **F.22** for which both derivatives were insoluble. Despite the improvements in terms of metabolic lability and solubility, we could unfortunately observe a dramatic decrease in permeability (Caco-2 values). Only **F.13** and **F.15** had acceptable values.

Finally, the cyclisation into the desired tricyclic compounds (**F.24** to **F.31**) caused an increase in the metabolic lability values, only **F.25** and **F.31** showed promising properties (below 20%). Thankfully, the permeability of the cyclised compounds had greatly improved compared with the previous data set (**F.13** to **F.23**) whilst the solubility had generally remained high.

As a conclusion, these 5-6-6 fused tricyclic compounds have disappointing properties compared to the previous 5-7-6 fused systems. Indeed, we can find no compound presenting

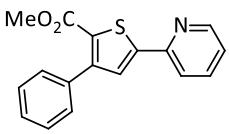
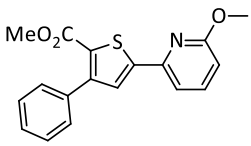
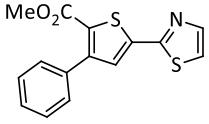
a good compromise betwenn all properties. In the event, the pyrimidine type substrates **F.27**, **F.28A**, **F.29A** showed high metablic lability as well as generally low solubility. Compound **F.25** could potentially be of interest, however improvements would have to be made regarding permeability.

3. Thiophene scaffolds

Despite being a structural alert in potential drug candidates, the thiophene core does not inherently lead to bad drug candidates (see chapter 4) and this encouraged us to test the potential of our substrates to function as starting materials for the synthesis of compound libraries.

As a first round of compounds we decided to measure the properties of several Suzuki products synthesised above (scheme 82). The results are summarised in table 28.

Table 28. ADME measurements of Suzuki cross-coupling products

Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**86**	295.4	72.9	100	3.41	> 30.0	< 3
	**87**	325.4	96.3	100	4.87	> 30.0	< 3
	**90**	301.4	25.1	100	3.45	12.0	< 3

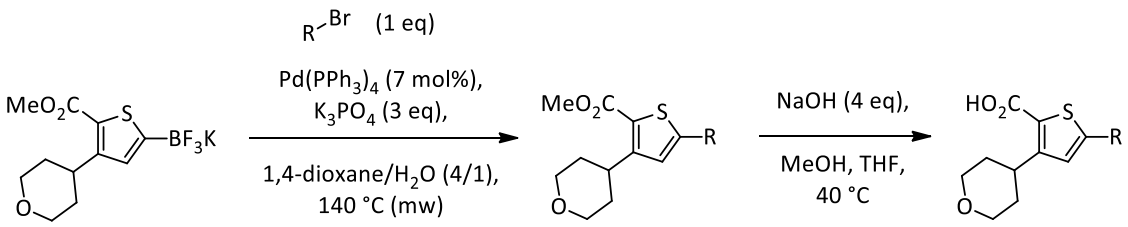
[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

Despite reasonably high permeability properties, all three compounds selected showed a very high sensitivity towards metabolism. Indeed, all have values of 100%. We believe the reason for such high values is the presence of the ester moiety on the thiophene which is very prone to saponification into the acid derivative by the cytochromes. Furthermore, the solubility in water of all above compounds is very low, another possible downside that could be attributed to the ester group on the molecule instead of the acid.

We had decided to use our 3-alkyl substituted thiophene analogues as starting material for the automated synthesis of two thiophene libraries in two steps, the latter, in both cases, being the saponification of the ester functionality. It should be noted that all compounds (**G.01** to **G.11** and **H.01** to **H.13**) were synthesised by the automated synthesis department in Sanofi Deutschland, none was synthesised by hand. The twenty-four resulting compounds were submitted to early ADME bioassays in order to assess their potential as drug candidates and the results of theses tests are discussed below.

Using our 6-pyran thiophene substrate **72**, we designed a library of Suzuki-Miyaura cross-coupling reactions followed by a saponification.

Library G – Suzuki cross-coupling / Saponification

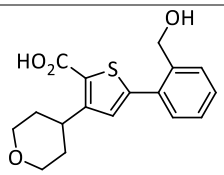
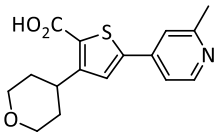
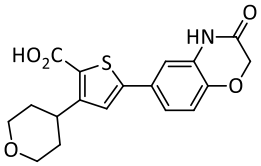
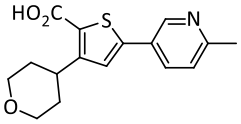
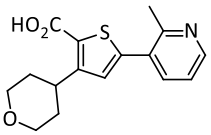
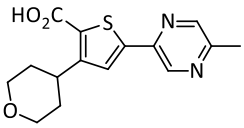
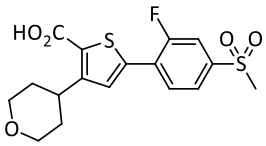
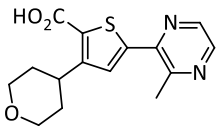
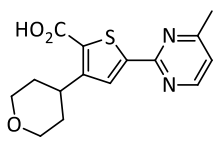


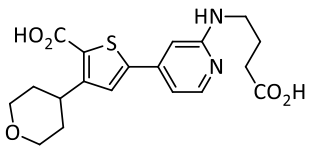
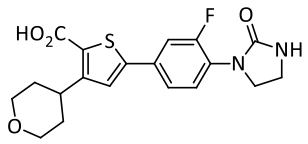
72 (1.1 eq)

Compounds **G.01** to **G.11**

Results of the early ADME assays are shown in table 29.

Table 29. ADME results for library G

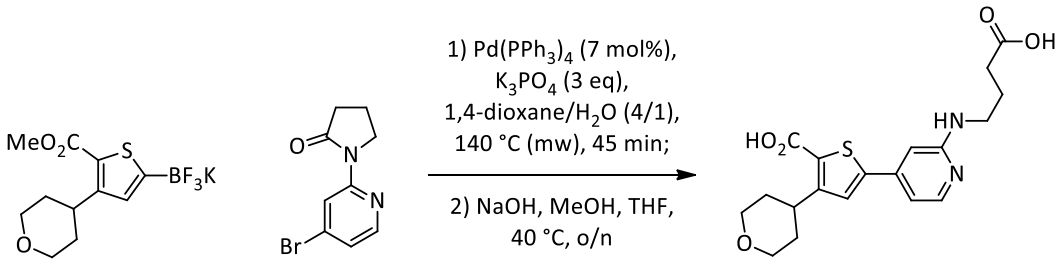
Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**G.01**	318.4	0.4	18	0.56	> 30.0	> 1570
	**G.02**	303.4	5.3	20	0.28	> 30.0	> 1648
	**G.03**	399.3	23.8	24	0.78	> 30.0	> 1648
	**G.04**	303.4	NoVal	10	0.70	> 30.0	> 13391
	**G.05**	303.4	37.0	20	0.48	> 30.0	> 1648
	**G.06**	304.4	34.8	30	0.24	> 30.0	1282
	**G.07**	384.5	1.6	19	0.66	> 30.0	> 1301
	**G.08**	304.4	0.9	11	0.16	> 30.0	1430
	**G.09**	304.4	6.9	21	0.33	> 30.0	> 1643

	**G.10***	390.5	1.7	16	0.53	> 30.0	911
	**G.11**	390.4	0.2	10	-0.34	> 30.0	> 1403

[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

The library yielded 11 compounds out of the 24 planned and a broad selection of analogues were produced. It should be noted however that compound **G.10** was an unexpected product that arose from the hydrolysis of the corresponding lactam under basic conditions (from either the Suzuki or the saponification reactions), see scheme 114.

Scheme 114. Synthesis of compound G.10



72 (1.1 eq) **G.10**

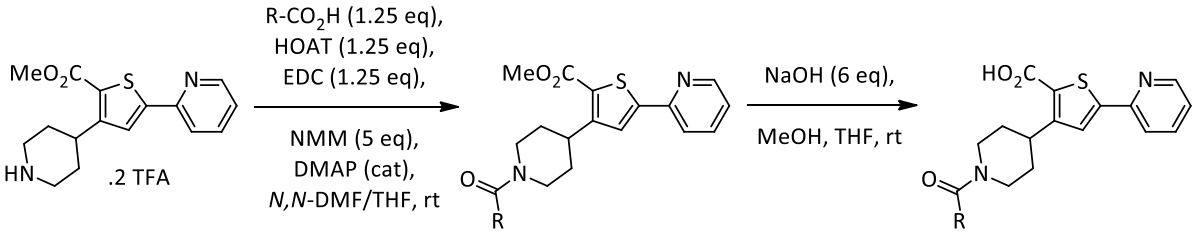
Regarding the ADME values, both the molecular weight and the log(D) of the measured compounds of this series were tightly grouped, respectively between 300 and 400 Da and 0.16 and 0.78 with the exception of **G.11** which had a negative log(D). The high solubility of the thiophene core was also reflected here. Indeed, upon looking at the values of the last column of table 29, all compounds had a solubility around 1000 mg/mL or higher.

Interestingly, whereas the metabolic lability was very low for all the above compounds (compound **G.06** showed the highest at only 30%), we could observe some variations in the Caco-2 values. Unfortunately, the intrinsic lipophilicity of the thiophene core had the expected adverse effect on the permeability properties of the compounds from library **G**, as most compounds had very low values (below $7x10^{-7}$cm/sec). Only three compounds had values that

were satisfactory: **G.03**, **G.05** and **G.06**. However, compound **G.05** stands out as it has the highest Caco-2 value and a metabolic lability below 20%. It should be noted that all compounds in this series have beneficial CYP inhibition properties (all values above 30.0 µM).

As a second library, we envisaged the use of the piperidine substituted thiophene **73** so as to investigate the influence of the modifications on this part of the molecule via an amide coupling, followed by a saponification of the ester group.

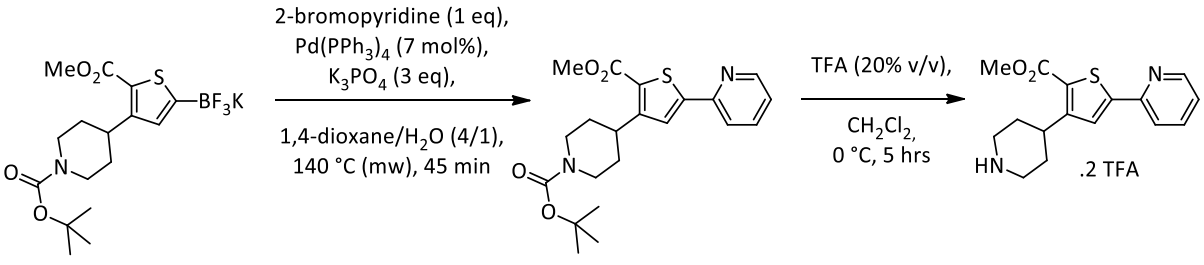
Library H – Amide coupling/Saponification



112 Compounds **H.01** to **H.13**

As installing a pyridine ring at the *C*5 position of the thiophene ring seemed to give promising results (**G.05** – in table 29), we decided to install such handle via Suzuki cross-coupling of thiophene **73**. We then deprotected the Boc group on the amine via classical treatment with trifluoroacetic acid to yield compound **112** in good yield as the bis-trifluoroacetic acid salt (scheme 115).

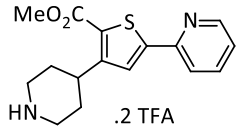
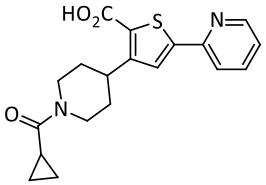
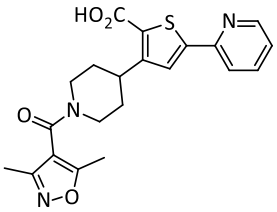
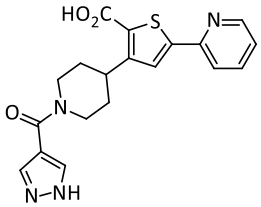
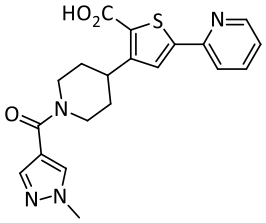
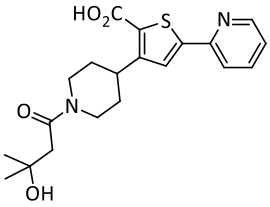
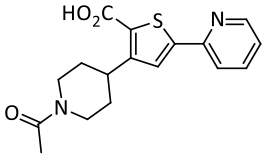
Scheme 115. Synthesis of the starting material 112

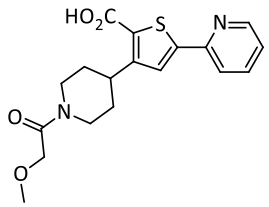
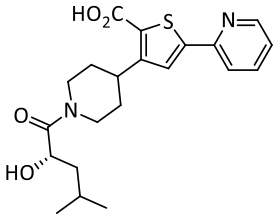
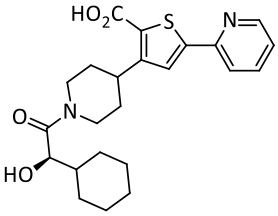
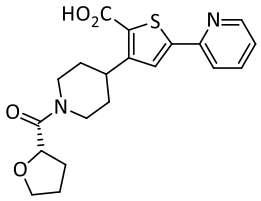
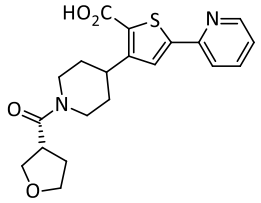
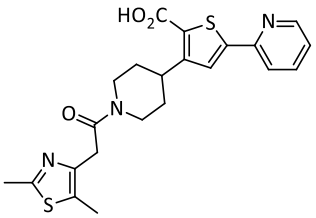
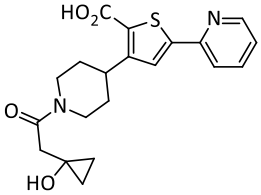


73 (1.1 eq) **111**, 49% **112**, 100%

Using the trifluoroacetic acid salt of **112**, the following set of compounds was synthesised and the bioassays were performed to yield the results listed in table 30.

Table 30. Library H – Amide coupling/Saponification

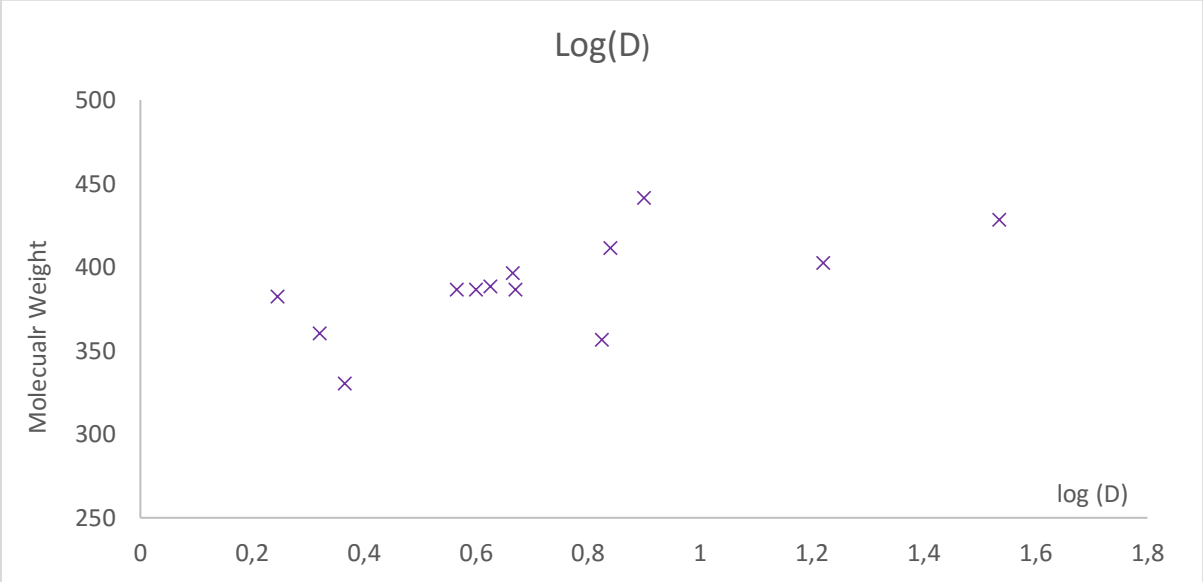
Compounds	Compound ID	Molecular Weight	Caco-2[a]	Metabolic Lability[b]	LogD[c]	CYP Inhibition[d]	Solubility[e]
	**112**	302.4	50.1	77	0.32	> 30.0	> 1653
	**H.01**	356.4	8.5	4	0.83	> 30.0	> 1403
	**H.02**	411.5	1.9	1	0.84	> 30.0	> 1215
	**H.03**	382.4	0.4	4	0.25	> 30.0	> 1261
	**H.04**	396.5	2.9	3	0.67	> 30.0	> 1261
	**H.05**	388.4	1.7	4	0.63	> 30.0	> 1287
	**H.06**	330.4	2.5	4	0.37	> 30.0	1182

	**H.07**	360.4	1.8	6	0.32	> 30.0	> 1387
	**H.08**	402.5	9.3	9	1.22	> 30.0	1191
	**H.09**	428.6	12.5	64	1.54	> 30.0	> 1167
	**H.10**	386.5	2.5	21	0.60	> 30.0	990
	**H.11**	386.5	1.5	7	0.57	> 30.0	> 1132
	**H.12**	441.6	1.1	6	0.90	> 30.0	> 1132
	**H.13**	386.5	2.3	12	0.67	> 30.0	> 1294

[a]Caco-2; Mean; PTotal (A2B) (10^{-7}cm/sec); [b]Metabolic Lability in Human; Mean; TotalMetab% (%), no CYP Inhibitor; [c]LogD(pH 6.4-8.4), Mean; [d]CYP Inhibition, IC50 (INH) (uM), Isoform: CYP3A4, Substrate: Midazolam; [e]Solubility (pH 6.4-8.4), Mean.

Library **H** yielded 13 compounds out of the 20 planned. From the above results, a similar observation (when comparing with library **G**) could be made concerning the solubility: all the thiophene derivatives synthesised were very soluble in water with values around or above 1000 mg/mL. The main difference with library **G** was that the log(D) was now spread over a wider range. This spread of properties is usually preferred as it is more conducive to finding trends and predictive models. For example, this set of compounds seemed to be spread along an almost linear trend (figure 10).

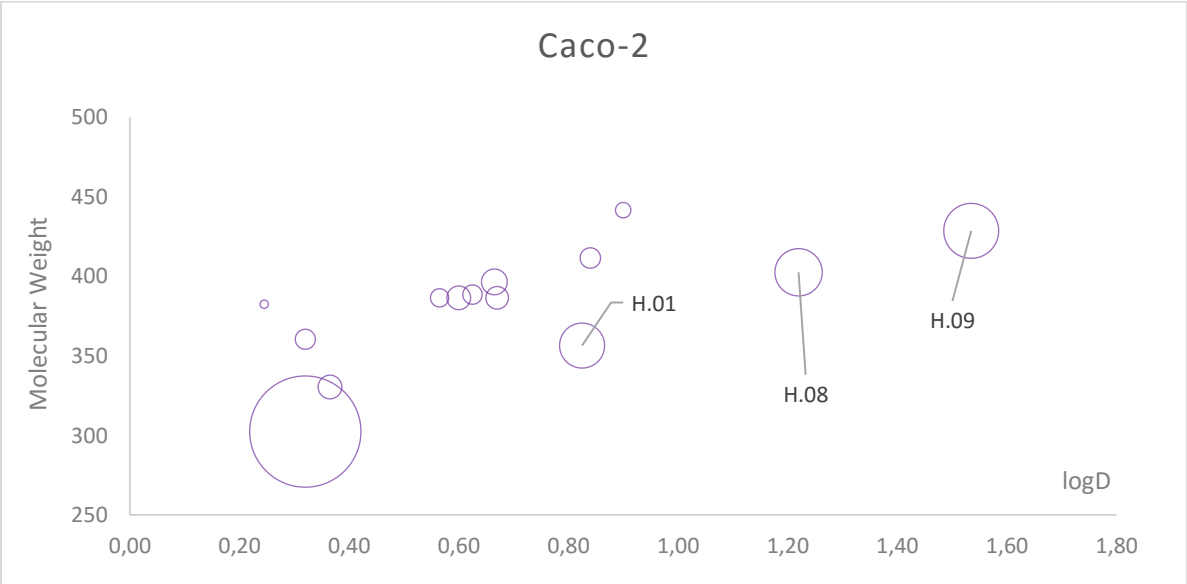
Figure 10. Plot of log(D) and molecular weight



There was also a striking contrast between the two series of data: it appeared that the permeability of the compounds in the latter set (**H.01** to **H.13**) was generally lower than the former (**G.01** to **G.11**). Indeed, unfortunately, a single compound had a value above $10x10^{-7}$ cm/sec: compound **H.09** and its value was still relatively low (below $20x10^{-7}$ cm/sec). Gladly, the same could be said for the metabolic lability which remained very low throughout this series (< 21%), with the exception of compound **H.09** which had a value of 64%. Finally, it should be noted that, as for library **G**, all compounds in this series have beneficial CYP inhibition properties (all values above 30.0 µM).

Compounds highlighted in figure 11 (**H.01**, **H.08** and **H.09**) showed the molecules with the highest permeability values which, as mentioned above, are normally too low to be of interest (below $20x10^{-7}$ cm/s).

Figure 11. Plot of log(D) and molecular weight. Size depending on the values of permeability



It was interesting to note that those molecules were amongst the highest log(D) values. On second observation, **H.09** should then be removed from the list of potentially drug-*like* compounds as it had a high metabolic lability. On the other hand, **H.01** and **H.08** both had very low metabolic lability making them potentially interesting compounds to investigate.

4. Conclusions

In this chapter, we have successfully shown that trifluoroborated pyrazoles and thiophenes were suitable materials to be used in automated parallel synthesis. We could synthesise several dozen compounds which were then tested in various bioassays in Sanofi Deutschland.

Through the efficient and regioselective synthesis of *N*-ethanol-pyrazole-5-trifluoroborate **38A** and the carefull design of the Suzuki partners, we could access a range of new tricyclic compounds. The resulting compounds were synthesised in good yield, either by an automated process or by hand and their early ADME properties were measured.

Also, 3-alkyl substituted thiophene-5-trifluoroborates **72** and **73** were used as starting material for the elaboration of two additional libraries of compounds which were tested using the same bioassays as for the pyrazole scaffolds.

There was a striking contrast between the two heteroaromatic compounds. Whereas pyrazoles were generally more polar, thiophene scaffolds usually showed a very high solubility. For both heterocyclic cores, interesting compounds could be highlighted for their promising set of properties.

Nonetheless, future work could explore derivatisation at other positions or the introduction of different functional groups in order to address some of the limitations observed.

Chapter 7 – Experimental procedures and data

1. General information

All reactions were conducted in flame-dried glassware under ambient conditions unless otherwise stated.

Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer and Nicolet Nexus 470 FTIR spectrometer, νmax in cm-1. Samples were recorded neat. Bands are characterised as broad (br), strong (s), medium (m), or weak (w).

^{1}H NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz, 500 MHz or 600MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: 7.26 ppm, DMSO: 2.50 ppm or acetone: 2.05 ppm) unless otherwise stated. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), assignments). ***^{13}C NMR spectra*** were recorded on a Bruker AVIII HD 400 (100.6 MHz, 125.8 MHz or 150.9 MHz), Bruker AVI 400 (100.6 MHz), Bruker AMX-400 (100.6 MHz) or DPX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CHCl_3$: 77.16 ppm, DMSO: 39.52 ppm or acetone: 29.84 ppm) unless otherwise stated. ***^{19}F NMR spectra*** were recorded on a Bruker AVIII HD 400 (235.1 MHz) or Bruker AMX-400 (235.1 MHz). ***^{11}B NMR spectra*** were recorded on a Bruker AVIII HD 400 (235.1 MHz).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+) or a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode.

Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254) which were developed using standard visualizing agents: UV light or potassium permanganate. Flash chromatography was

performed on silica-gel (BDH Silica Gel 60 43-60). Melting points, performed on recrystallized solids, were recorded on a Gallenkamp melting point apparatus 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).

Microwave experiments were conducted on Emrys Optimizer apparatus.

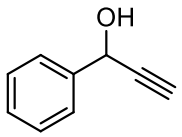
2. *Experiment procedures and data*

2.1. Ynone synthesis

2.1.1. General procedure A - Addition of Grignard reagent

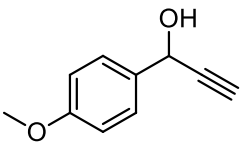
To a solution of ethynylmagnesium bromide (1.25 eq - 0.5 M solution in THF) in anhydrous THF (0.5 M) under nitrogen, aldehyde (1.00 eq) was added dropwise at -78 °C. The mixture was allowed to warm to rt. Upon completion, the reaction was quenched with saturated NH_4Cl, extracted with ethyl acetate and the organic extracts dried over $MgSO_4$. The solvent was removed under vacuum and the residue purified by flash chromatography on silica gel to yield the title compound.

1-Phenylprop-2-yn-1-ol, 1



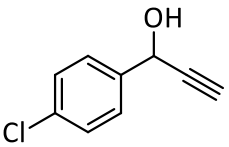
Following general procedure A, using benzaldehyde (2.0 mL, 20.0 mmol) and ethynylmagnesium bromide (60.0 mL, 30.0 mmol) in THF (50 mL), the crude product was obtained after 1 hr. Chromatographic purification using petrol/EtOAc 90/10 followed by a distillation under reduced pressure afforded the title compound[112] as a colorless oil (2.24 g, 87% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.60 – 7.54 (m, 2H), 7.45 – 7.34 (m, 3H), 5.46 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.07 (d, *J* = 6.0 Hz, 1H), 2.69 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 140.1, 128.7, 128.5, 126.7, 83.7, 74.9, 64.3.

1-(p-Methoxyphenyl)-prop-2-yn-1-ol, 2



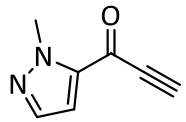
Following general procedure A using *p*-anisaldehyde (1.2 mL, 10.0 mmol) and ethynylmagnesium bromide (25.0 mL, 12.5 mmol) in THF (20 mL), the crude product was obtained after 2 hrs. Chromatographic purification using Petrol/EtOAc from 90/10 to 70/30 afforded the title compound[113] as an orange solid (1.60 g, 100% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.50 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.45 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.84 (s, 3H), 2.69 (d, *J* = 2.0 Hz, 1H), 2.20 (d, *J* = 6.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 159.7, 132.5, 128.1, 114.0, 83.8, 74.6, 63.0, 55.4.

1-(p-Chlorophenyl)-prop-2-yn-1-ol, 3



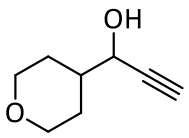
Following general procedure A, using *p*-chloro-benzaldehyde (1.41 g, 10.0 mmol) and ethynylmagnesium bromide (25.0 mL, 12.5 mmol) in THF (50 mL), the crude product was obtained after 2 hrs. Chromatographic purification using petrol/EtOAc 70/30 afforded the title compound[114] as a yellow oil (1.58 g, 95% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.46 – 7.41 (m, 2H), 7.36 – 7.30 (m, 2H), 5.39 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.60 (d, *J* = 6.0 Hz, 1H), 2.68 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 138.5, 134.2, 128.8, 128.1, 83.2, 75.2, 63.5.

1-(1-Methyl-1H-pyrazol-5-yl)prop-2-yn-1-ol, 4



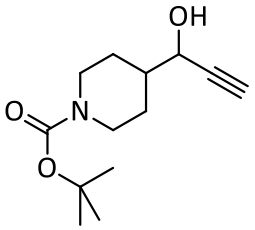
Following general procedure A, using 1-methyl-1*H*-pyrazole-5-carboxaldehyde (1.0 g, 9.1 mmol) and ethynylmagnesium bromide (23.0 mL, 11.4 mmol) in THF (17 mL), the crude product was obtained after 2 hrs. The crude material was triturated in dichloromethane by stirring at rt for 30 min and filtering to yield the title compound as a light brown solid (0.98 g, 79% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.29 (d, *J* = 2.0 Hz, 1H), 6.24 (d, *J* = 2.0 Hz, 1H), 5.55 (d, *J* = 2.5 Hz, 1H), 3.82 (s, 3H), 3.56 (d, *J* = 2.5 Hz, 1H), 3.40 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 141.7, 137.0, 104.8, 83.1, 75.6, 54.6, 36.8. **m. pt.** 107 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3392 (w), 3231 (m), 3120 (m), 3036 (m), 2115 (w), 1420 (s). **HRMS** calculated for $C_7H_8N_2O$ (ESI^+): 137.0709. Found: 137.0711.

1-Tetrahydro-2H-pyran-4-yl)prop-2-yn-1-ol, 5



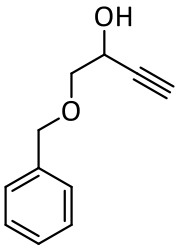
Following general procedure A, using 4-formyltetrahydropyran (0.66 g, 5.8 mmol) and ethynylmagnesium bromide (15 mL, 7.2 mmol) in THF (11 mL), the crude product was obtained after 2 hrs. Chromatographic purification using petrol/EtOAc 60/40 afforded the title compound as a yellow oil (0.40 g, 49% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 4.18 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.04-3.94 (m, 3H), 3.42 – 3.35 (m, 2H), 2.50 (d, *J* = 2.0 Hz, 1H), 1.88 – 1.78 (m, 3H), 1.56 – 1.45 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 83.2, 74.2, 67.6, 66.3, 41.4, 28.6, 28.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3319 (s), 3258 (s), 2954 (m), 2946 (m), 2858 (s), 2109 (s), 1080 (s), 1037 (s), 1023 (s). **HRMS** calculated for $C_8H_{12}O_2$ (ESI^+): 140.0837. Found: 140.0836.

tert-Butyl 4-(1-hydroxyprop-2-yn-1-yl)piperidine-1-carboxylate, 6



Following general procedure A, using 4-formylcyclohexanecarboxylic acid *tert*-butyl ester (3.03 g, 14.1 mmol) and ethynylmagnesium bromide (42.0 mL, 21.1 mmol) in THF (28 mL), the crude product was obtained after 2 hrs. Chromatographic purification using petrol/EtOAc 70/30 afforded the title compound[115] as a yellow oil (2.43 g, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 4.21 – 4.13 (m, 3H), 2.69 (tt, *J* = 13.0, 3.0 Hz, 2H), 2.49 (d, *J* = 2.0 Hz, 1H), 1.99 (br, 1H), 1.86 – 1.77 (m, 2H), 1.77 – 1.68 (m, 1H), 1.46 (s, 9H), 1.40-1.23 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 154.9, 83.2, 79.5, 74.3, 66.1, 43.6, 42.4, 28.5, 27.7, 27.2.

1-Benzyloxybut-3-yn-2-ol, 7



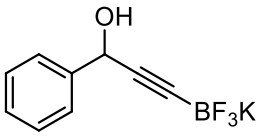
Following general procedure A, using benzyloxyacetaldehyde (5.0 g, 33 mmol) and ethynylmagnesium bromide (83.0 mL, 41.6 mmol) in THF (61 mL), the crude product was obtained after 2 hrs. Chromatographic purification using petrol/EtOAc 60/40 afforded the title compound[116] as a yellow oil (5.42 g, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.39 – 7.28 (m, 5H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.56 (ddd, J = 7.0, 3.5, 2.0 Hz, 1H), 3.66 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.59 (dd, *J* = 10.0, 7.0 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 2.39 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 137.5, 128.6, 128.0, 127.9, 81.7, 73.8, 73.5, 73.4, 61.6.

2.1.2. General procedure B - Borylation of terminal alkynes

To a solution of terminal alkyne (1 eq) in anhydrous THF under nitrogen, ^{n}BuLi (~2.5 M in hexanes, 2.2 eq) was added dropwise at -78 °C. After stirring the resulting mixture at -78 °C for 1 h, *iso*-propoxy-pinacolborane (3 eq) was added dropwise and the mixture was allowed to warm to -20 °C over 1 hr. To this mixture was added slowly a saturated solution of aqueous hydrogen potassium difluoride (12 eq) and the mixture allowed to warm to rt over 1 hr. The solvent was then removed under vacuum to yield a solid. The residue was stirred in acetone for 30 min and filtered. The solvent was removed under vacuum and the residue redissolved in minimum of acetone, Et_2O was added and a solid precipitated to yield the desired compound.

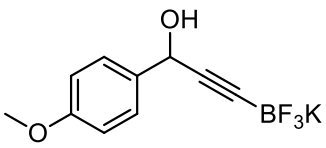
Note that for the following trifluoroborate compounds, ^{13}C NMR spectra are missing a signal for the carbon atom directly attached to the boron due to broadening arising from the quadrupolar relaxation effect.

Potassium trifluoro(3-hydroxy-3-phenylprop-1-yn-1-yl)borate, 8



Following general procedure B using **1** (0.83 g, 6.3 mmol), ^{n}BuLi (7.0 mL, 14 mmol), B(O^{i}Pr)Pin (3.6 mL, 19 mmol) in THF (22 mL) and KHF_2 (5.85 g, 75 mmol) dissolved in water (40 mL) yielded the title compound[57] as a colorless solid (1.42 g, 95% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.45 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.60 (d, *J* = 5.5 Hz, 1H), 5.17 (d, *J* = 5.5 Hz, 1H). . **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 144.1, 128.3, 127.4, 127.0, 91.0, 63.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -131.6. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.8. **m. pt.** 176 °C (Lit: 232-235 °C).

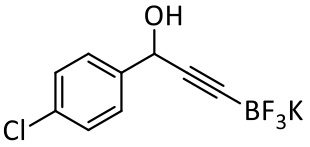
Potassium trifluoro(3-hydroxy-3-(4-methoxyphenyl)prop-1-yn-1-yl)borate, 9



Following general procedure B using **2** (0.19 g, 1.2 mmol), ^{n}BuLi (1.4 mL, 3 mmol), B(O^{i}Pr)Pin (0.8 mL, 4 mmol) in THF (4 mL) and KHF_2 (1.13 g, 14 mmol) dissolved in water (4 mL) yielded the title compound[57] as a yellowish solid (215 mg, 68% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.35 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.45 (d, *J* = 5.5 Hz, 1H), 5.10 (d, *J* = 5.5 Hz, 1H), 3.74

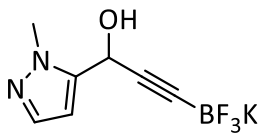
(s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 158.8, 136.3, 129.1, 128.2, 113.7, 63.2, 55.5. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** 131.5. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.6. **m. pt.** > 300 °C (Lit: 283-284 °C).

Potassium trifluoro(3-hydroxy-3-(4-chlorophenyl)prop-1-yn-1-yl)borate, 10



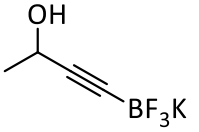
Following general procedure B using **3** (0.99 g, 6.0 mmol), ^{n}BuLi (6.8 mL, 13 mmol), B(O^{i}Pr)Pin (3.5 mL, 18 mmol) in THF (25 mL) and KHF_2 (5.43 g, 71.0 mmol) dissolved in water (20 mL) yielded the title compound as a colorless solid (1.13 g, 70% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.46 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.72 (d, *J* = 5.0 Hz, 1H), 5.18 (d, *J* = 5.0 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 142.7, 131.4, 128.3, 127.8, 89.9, 62.4. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -131.6. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 5.0. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3537 (w), 2929 (w), 1001 (s), 933 (s). **HRMS** calculated for $C_9H_6{}^{11}BOF_3{}^{35}Cl$ (ESI^-): 233.0152. Found: 233.0163.

Potassium 1-(1-methyl-1H-pyrazol-5-yl)-3-(trifluoroboranyl)prop-2-yn-1-ol, 11



Following general procedure B using **4** (0.80 g, 5.8 mmol), ^{n}BuLi (5.5 mL, 13 mmol), B(O^{i}Pr)Pin (3.6 mL, 18 mmol) in THF (23 mL) and KHF_2 (5.57 g, 70.1 mmol) dissolved in water (18 mL) yielded the title compound as a brown solid (0.52 g, 37% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.25 (d, *J* = 2.0 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 5.78 (s, 1H), 5.33 (s, 1H), 3.82 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 143.7, 137.1, 104.9, 74.0, 55.9, 37.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -131.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 5.2. **m. pt.** 111 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3598 (m), 3316 (w), 2219 (w), 1645 (w), 1630 (w). **HRMS** calculated for $C_7H_7{}^{10}BOF_3N_2Na$ (ESI^+): 225.0538. Found: 225.0535.

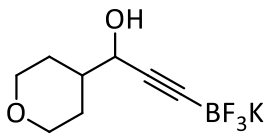
Potassium trifluoro(3-hydroxy-but-1-yn-1-yl)borate, 12



Following general procedure B using commercial 3-butyn-2-ol (0.80 mL, 10 mmol), ^{n}BuLi (12.5 mL, 22 mmol), B(O^{i}Pr)Pin (6.5 mL, 30 mmol) in THF (40 mL) and KHF_2 (9.29 g, 119 mmol) dissolved in water (35 mL) yielded the title compound[57] as a colorless solid (0.77 g, 44% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 4.86

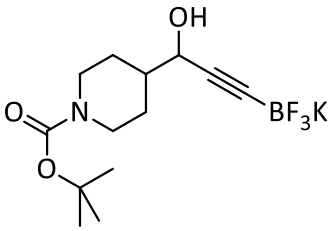
(d, J = 5.0 Hz, 1H), 4.21 – 4.12 (m, 1H), 1.19 (d, J = 6.5 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 74.0, 57.2, 25.8, 25.4. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -131.5. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.6. **m. pt.** 139 °C (Lit: 225 °C decomp.).

Potassium 1-(tetrahydro-2H-pyran-4-yl)-3-(trifluoroboranyl)prop-2-yn-1-ol, 13



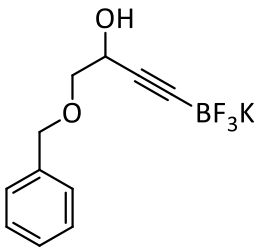
Following general procedure B using **5** (0.78 g, 6.0 mmol), ^{n}BuLi (5.0 mL, 12 mmol), B(O^{i}Pr)Pin (3.5 mL, 17 mmol) in THF (22 mL) and KHF_2 (5.29 g, 67.0 mmol) dissolved in water (18 mL) yielded the title compound as a colorless solid (0.52 g, 38% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 4.86 (d, *J* = 5.5 Hz, 1H), 3.90 – 3.77 (m, 3H), 3.28 – 3.16 (m, 2H), 1.67 – 1.56 (m, 2H), 1.57 – 1.44 (m, 1H), 1.31 – 1.20 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 66.9, 65.3, 41.6, 28.7, 28.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -131.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 5.1. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3496 (s), 2957 (m), 2917 (m), 2872 (m), 2854 (m), 1238 (s), 1082 (s), 1024 (s). **HRMS** calculated for $C_8H_{11}{}^{11}BO_2F_3$ (ESI$^-$): 207.0810. Found: 207.0817.

Potassium tert-butyl 4-(1-hydroxy-3-(trifluoroboranyl)prop-2-yn-1-yl)piperidine-1-carboxylate, 14



Following general procedure B using **6** (2.78 g, 12.0 mmol), ^{n}BuLi (12 mL, 26 mmol), B(O^{i}Pr)Pin (7.5 mL, 35 mmol) in THF (48 mL) and KHF_2 (10.93 g, 139.0 mmol) dissolved in water (40 mL) yielded the title compound as a colorless solid (2.91 g, 73% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 4.89 (d, *J* = 5.0 Hz, 1H), 4.02-3.90 (m, 2H), 3.88 - 3.82 (m, 1H), 2.62 (br, 2H), 1.69 (app. d, *J* = 12.0 Hz, 2H), 1.49 – 1.39 (m, 10H), 1.17-1.03 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 153.9, 78.4, 64.9, 42.4, 28.1, 27.6, 27.4, 24.9. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -131.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 5.0. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3402 (br, w), 2975(w), 2931 (w), 2860 (w), 2214 (w), 1690 (m), 1667 (m), 1479 (m), 1425 (m). **HRMS** calculated for $C_{13}H_{20}{}^{11}BO_3F_3N$ (ESI$^-$): 306.1494. Found: 306.1504.

Potassium 1-(benzyloxy)-4-(trifluoroboranyl)but-3-yn-2-ol, 15

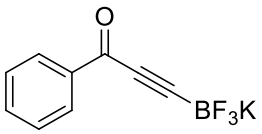


Following general procedure B using **7** (5.38 g, 31.0 mmol), ^{n}BuLi (30 mL, 67 mmol), B(O^{i}Pr)Pin (19 mL, 92 mmol) in THF (125 mL) and KHF_2 (28.61 g, 366.0 mmol) dissolved in water (102 mL) yielded the title compound as a colorless solid (8.12 g, 94% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.36 – 7.24 (m, 5H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.52 (s, 2H), 4.26 – 4.19 (m, 1H), 3.43 – 3.33 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 139.0, 128.6, 128.0, 127.8, 89.9, 75.4, 72.5, 61.3, 25.5. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -131.8. **^{11}B NMR (128 MHz, DMSO-d$_6$*), ppm:*** 5.1. **m. pt.** 86 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3512 (w), 3376 (w), 3034 (w), 2869 (w), 2217 (w), 1097 (s), 1064 (s). **HRMS** calculated for $C_{11}H_{11}{}^{11}BO_2F_3$ (ESI^-): 243.0810. Found: 243.0819.

2.1.3. General procedure C - Oxidation to ynone trifluoroborates

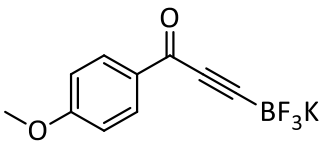
To a suspension of manganese(IV) oxide (5 eq) in acetone (0.3 M), was added trifluoroborate (1 eq) portionwise at rt. The reaction was monitored by ^{19}F NMR spectroscopy. Upon completion, the mixture was filtered through Celite. All volatiles were evaporated from the filtrate under vacuum. Then the residue was redissolved in minimum of acetone and upon addition of Et_2O a solid precipitated. The solid was filtered and washed with Et_2O and dried to yield the title compound.

Potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate, 16



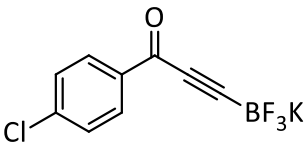
Following general procedure C using **8** (1.65 g, 7 mmol) and manganese(IV) oxide (3.08 g, 35 mmol) in acetone (18 mL) yielded the title compound[57] as a colorless solid (1.32 g, 80% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.07 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 178.6, 137.2, 134.3, 129.4, 129.2. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -133.1. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.8. **m. pt.** 168-169 °C (Lit: 143-145 °C).

Potassium trifluoro(3-oxo-3-(4-methoxyphenyl)prop-1-yn-1-yl)borate, 17



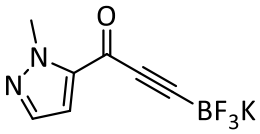
Following general procedure C using **9** (0.56 g, 2.1 mmol) and manganese(IV) oxide (0.90 g, 10 mmol) in acetone (5 mL) yielded the title compound[57] as a yellowish solid (0.37 g, 68% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.03 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 177.3, 164.2, 131.7, 130.6, 114.5, 56.1. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -133.0. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.6. **m. pt.** > 300 °C (Lit: 133-135 °C).

Potassium trifluoro(3-oxo-3-(4-chlorophenyl)prop-1-yn-1-yl)borate, 18



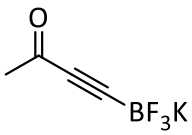
Following general procedure C using **10** (1.9 g, 7.0 mmol) and manganese(IV) oxide (3.01 g, 34.9 mmol) in acetone (22 mL) yielded the title compound as a pale yellow solid (1.44 g, 76% yield). **^{1}H NMR (500 MHz, DMSO-d$_6$), ppm:** 8.05 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 176.9, 138.8, 135.5, 130.7, 129.0, 87.9. **^{19}F NMR (377 MHz, Acetone-d$_6$), ppm:** -136.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.8. **m. pt.** > 300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2946 (w), 1661 (s), 1222 (s), 984 (s). **HRMS** calculated for $C_9H_4{}^{11}BOF_3{}^{35}Cl$ (ESI^-): 231.0152. Found: 231.0163.

Potassium 1-(1-methyl-1H-pyrazol-5-yl)-3-(trifluoroboranyl)prop-2-yn-1-one, 19



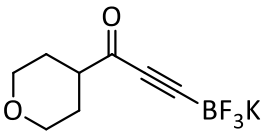
Following general procedure C using **11** (0.41 g, 1.7 mmol) and manganese(IV) oxide (0.75 g, 8.5 mmol) in acetone (5.5 mL) yielded the title compound as a light brown solid (0.12 g, 30% yield**). ^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.53 (d, *J* = 2.0 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 4.05 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 167.7, 139.6, 137.7, 114.2, 89.0, 39.6. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -133.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.9. **m. pt.** 252 °C (deg). **FTIR (neat, cm^{-1}), ν_{max}:** 3142 (s), 2962 (s), 2191 (m), 3392 (w), 3231 (m), 3120 (m), 3036 (m), 2115 (w), 1420 (s). **HRMS** calculated for $C_7H_5{}^{11}BOF_3N_2$ (ESI^-): 201.0453. Found: 201.0462.

Potassium trifluoro(3-oxobut-1-yn-1-yl)borate, 20



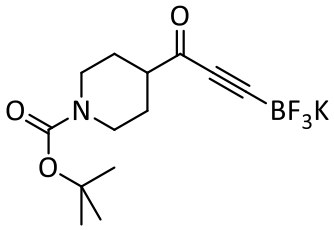
Following general procedure C using **12** (1.25 g, 7.1 mmol) and manganese(IV) oxide (3.14 g, 36 mmol) in acetone (23 mL) yielded the title compound[57] as a colorless solid (0.74 g, 60% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 2.20 (s, 1H). ***^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:*** 185.7, 90.9, 33.2. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -133.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.9. **m. pt.** 169-170 °C (Lit: 142-144 °C).

Potassium 1-(tetrahydro-2H-pyran-4-yl)-3-(trifluoroboranyl)prop-2-yn-1-one, 21



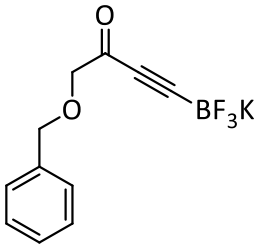
Following general procedure C using **13** (0.56 g, 2.3 mmol) and manganese(IV) oxide (1.03 g, 11.4 mmol) in acetone (7 mL) yielded the title compound as a colorless solid (0.19 g, 34% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 3.84 – 3.79 (m, 2H), 3.35 (td, *J* = 11.5, 2.0 z, 2H), 2.58 – 2.50 (m 1H), 1.81 – 1.74 (m, 2H), 1.55 – 1.44 (m, 2H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 190.0, 88.6, 66.1, 48.1, 27.9. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -133.2. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.9. **m. pt.** 158 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2960 (w), 2851 (w) 2183 (w), 1649 (m), 1110, (s), 1008 (s). **HRMS** calculated for $C_8H_9{}^{11}BO_2F_3$ (ESI^-): 205.0653. Found: 205.0659.

Potassium tert-butyl 4-(3-(trifluoroboranyl)propioloyl)piperidine-1-carboxylate, 22



Following general procedure C using **14** (0.17 g, 0.50 mmol) and manganese(IV) oxide (0.21 g, 2.5 mmol) in acetone (1.5 mL) yielded the title compound as a colorless solid (0.07 g, 42% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 3.89 – 3.84 (m, 2H), 2.89 – 2.71 (m, 2H), 2.49 (m 1H), 1.86 – 1.80 (m, 2H), 1.41-1.28 (m, 11H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 190.0, 153.8, 88.9, 78.6, 49.0, 40.1, 28.1, 27.2. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -133.2. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.9. **m. pt.** 169 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2932 (w), 2187 (w), 1679 (m), 1658 (m). **HRMS** calculated for $C_{13}H_{18}{}^{11}BO_3F_3N$ (ESI^-): 304.1337. Found: 304.1351.

Potassium 1-(benzyloxy)-4-(trifluoroboranyl)but-3-yn-2-one, 23

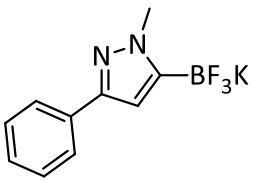


Following general procedure C using **15** (3.30 g, 11.7 mmol) and manganese(IV) oxide (5.12 g, 58.5 mmol) in acetone (35 mL) yielded the title compound as an orange solid (0.37 g, 11% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.37 – 7.26 (m, 5H), 4.52 (s, 2H), 4.23 (s, 2H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 185.4, 137.8, 128.2, 127.8, 127.6, 87.7, 75.8, 72.1**. ^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -133.5. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** -1.1. **m. pt.** 116-117 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3032 (w), 2868 (w), 2182 (w), 1676 (s), 1455-1380 (s), 1087 (s). **HRMS** calculated for $C_{11}H_9{}^{11}BO_2F_3$ (ESI^-): 241.0653. Found: 241.0658.

2.2. Synthesis of pyrazole trifluoroborates

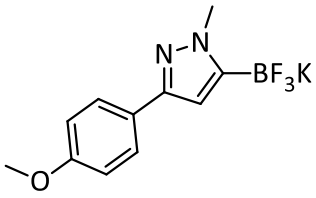
General procedure D - To a solution of ynone (1 eq) in ethanol (0.14 M) at 0 °C, the hydrazine reagent (1.2 or 2.4 eq) was added dropwise under nitrogen. The flask was covered with foil (when using *N*-methylhydrazine) and left to stir at rt. The reaction was followed by ^{19}F NMR. Upon completion, the mixture was evaporated to dryness. The residue was redissolved in the minimum of acetone and upon addition of Et_2O a solid precipitated. The solid was filtered and washed with Et_2O and dried to yield the title compound.

Potassium trifluoro(1-methyl-3-phenyl-1H-pyrazol-5-yl)borate, 25



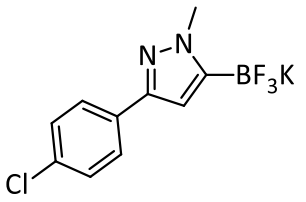
Following general procedure D using **16** (1.41 g, 6.0 mmol) and methylhydrazine (0.4 mL, 7 mmol) in ethanol (40 mL) yielded the title compound[57] as a colorless solid (1.49 g, 94% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.70 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.22 – 7.15 (tt, *J* = 8.0, 1.0 Hz, 1H), 6.29 (s, 1H), 3.78 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 148.0, 135.5, 128.8, 126.6, 125.2, 105.9, 31.2**. ^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -137.0. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** > 300 °C (Lit: 158-160 °C).

Potassium trifluoro(1-methyl-3-(4-methoxyphenyl)-1H-pyrazol-5-yl)borate, 26



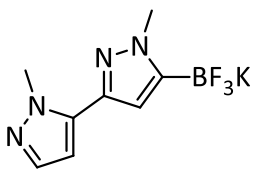
Following general procedure D using **17** (0.50 g, 1.9 mmol) and methylhydrazine (0.1 mL, 2 mmol) in ethanol (13 mL) yielded the title compound[57] as a colorless solid (0.49 g, 89% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.61 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.19 (s, 1H), 3.76 (s, 6H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 158.3, 147.9, 128.3, 126.4, 114.2, 105.3, 55.5, 38.4. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -137.0. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** > 300 °C (Lit: 141-143 °C).

Potassium trifluoro(1-methyl-3-(4-chlorophenyl)-1H-pyrazol-5-yl)borate, 27



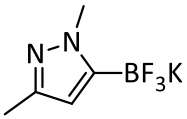
Following general procedure D using **18** (0.50 g, 1.9 mmol) and methylhydrazine (0.1 mL, 2 mmol) in ethanol (12 mL) yielded the title compound as a colorless solid (0.47 g, 84% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.71 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.31 (s, 1H), 3.78 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 146.9, 134.3, 130.9, 128.8, 126.9, 106.1, 38.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -137.1. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** > 300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2950 (w), 1425 (m), 1191 (m), 1168 (s), 935 (s). **HRMS** calculated for $C_{10}H_8{}^{11}B^{35}ClF_3N_2$ (ESI^-): 259.0429. Found: 259.0437.

Potassium 1,2'-dimethyl-5-(trifluoroboranyl)-1H,2'H-3,3'-bipyrazole, 28



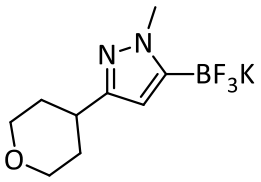
Following general procedure D using **19** (100 mg, 0.373 mmol) and methylhydrazine (60 µL, 0.9 mmol) in ethanol (3 mL) yielded the title compound as a colorless solid (93 mg, 83% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.33 (d, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 6.18 (s, 1H), 4.01 (s, 3H), 3.80 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 139.4, 137.53, 137.47, 108.0, 104.0, 38.3, 38.1. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -137.2. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.7. **m. pt.** >300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3152 (s), 3127 (s), 1386 (s). **HRMS** calculated for $C_8H_9{}^{11}BF_3N_4$ (ESI^-): 229.0878. Found: 229.0888.

Potassium trifluoro(1,3-dimethyl-1H-pyrazol-5-yl)borate, 29



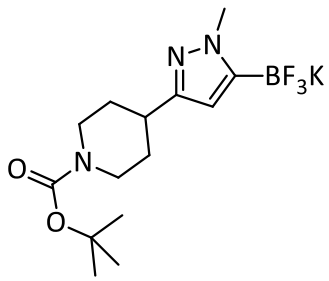
Following general procedure D using **20** (0.50 g, 1.9 mmol) and methylhydrazine (0.1 mL, 2 mmol) in ethanol (12 mL) yielded the title compound[57] as a colorless solid (0.47 g, 84% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 5.62 (s, 1H), 3.63 (s, 3H), 2.02 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 144.3, 108.1, 37.9, 13.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -136.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** 300 °C (Lit: 101-103 °C).

Potassium 1-methyl-3-(tetrahydro-2H-pyran-4-yl)-5-(trifluoroboranyl)-1H-pyrazole, 30



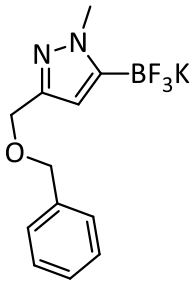
Following general procedure D using **21** (204 mg, 0.750 mmol) and methylhydrazine (110 µL, 1.80 mmol) in ethanol (6 mL) yielded the title compound as a light yellow solid (181 mg, 80% yield, > 90:10). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 5.69 (s, 1H), 3.88 – 3.83 (m, 2H), 3.65 (s, 3H), 3.37 (td, *J* = 11.5, 2.0 Hz, 2H), 2.66 (tt, *J* = 11.5, 4.0 Hz, 1H), 1.75 – 1.69 (m, 2H), 1.55 (qd, *J* = 11.5, 4.0 Hz). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 152.7, 104.8, 67.2, 37.6, 34.0, 33.0. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -136.9. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2937 (w), 2918 (w), 2850 (w), 1444 (w), 1428 (w), 1168 (m), 1126 (m). **HRMS** calculated for $C_9H_{13}{}^{11}BOF_3N_2$ (ESI^-): 233.1079. Found: 233.1086.

Potassium tert-butyl 4-(1-methyl-5-(trifluoroboranyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate, 31



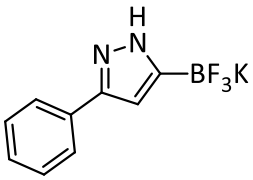
Following general procedure D using **22** (200 mg, 0.539 mmol) and methylhydrazine (55 µL, 1.1 mmol) in ethanol (4 mL) yielded the title compound as a light yellow solid (177 mg, 82% yield, > 90:10). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 5.67 (s, 1H), 3.95 – 3.90 (m, 2H), 3.64 (s, 3H), 2.84 – 2.75 (m, 2H), 2.60 (tt, *J* = 11.5, 4.0 Hz, 1H), 1.80 – 1.75 (m, 2H), 1.40 - 1.32 (m, 11H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 154.0, 152.4, 104.8, 78.4, 37.6, 34.8, 32.0, 28.1, 26.8. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -136.9. ***^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:*** 1.6. **m. pt.** 161 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2934 (w), 1674 (m), 1425 (m), 1366 (m). **HRMS** calculated for $C_{14}H_{22}{}^{11}BO_2F_3N_3$ (ESI^-): 332.1763. Found: 332.1779.

Potassium 3-((benzyloxy)methyl)-1-methyl-5-(trifluoroboranyl)-1H-pyrazole, 32



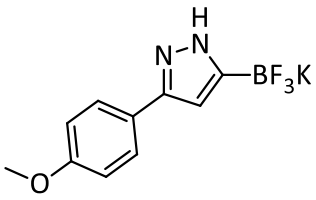
Following general procedure D using **23** (167 mg, 0.596 mmol) and methylhydrazine (80 µL, 1.7 mmol) in ethanol (5 mL) yielded the title compound as an orange oil (110 mg, 70% yield, > 98:2). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.32 – 7.22 (m, 5H), 5.88 (s, 1H), 4.44 (s, 2H), 4.34 (s, 2H), 3.70 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 145.9, 138.8, 128.1, 127.4, 127.2, 107.9, 70.6, 65.6, 37.7. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -137.0. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.7. **FTIR (neat, cm^{-1}), ν_{max}:** 3031 (w), 2933 (w), 2865 (w), 1453 (m), 1164 (m), 1148 (m). **HRMS** calculated for $C_{12}H_{13}{}^{11}BOF_3N_2$ (ESI^-): 269.1079. Found: 269.1086.

Potassium trifluoro(3-phenyl-1H-pyrazol-5-yl)borate, 33



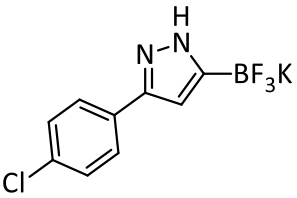
Following general procedure D using **16** (0.51 g, 2.2 mmol) and hydrazine monohydrate (0.20 mL, 3 mmol) in ethanol (15 mL) yielded the title compound[57] as a colorless solid (0.51 g, 93% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.91 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 149.2, 135.9, 128.8, 126.6, 125.4, 104.2. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -136.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.9. **m. pt.** 250 °C (Lit: 180 °C decomp.).

Potassium trifluoro(3-(4-methoxyphenyl)-1H-pyrazol-5-yl)borate, 34



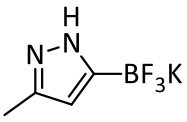
Following general procedure D using **17** (0.50 g, 1.9 mmol) and hydrazine monohydrate (0.10 mL, 2 mmol) in ethanol (13 mL) yielded the title compound[57] as a colorless solid (0.34 g, 64% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.74 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.22 (s, 1H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 158.3, 148.9, 128.8, 126.6, 114.2, 103.7, 55.5. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -136.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.9. **m. pt.** 229-230°C (Lit: 233-234 °C).

Potassium trifluoro(3-(4-chlorophenyl)-1H-pyrazol-5-yl)borate,35



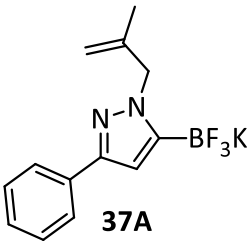
Following general procedure D using **18** (0.51 g, 1.9 mmol) and hydrazine monohydrate (0.20 mL, 2 mmol) in ethanol (13 mL) yielded the title compound as a colorless solid (0.49 g, 92% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.95 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.31 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 148.0, 134.9, 130.9, 128.8, 127.0, 104.3. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -136.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.9. **m. pt.** 250 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3406 (w), 1432 (w), 1197 (m), 961 (s). **HRMS** calculated for $C_9H_6{}^{11}B^{35}ClF_3N_2$ (ESI^-): 245.0272. Found: 245.0279.

Potassium trifluoro(3-methyl-1H-pyrazol-5-yl)borate, 36

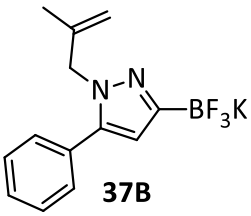


Following general procedure D using **20** (0.50 g, 2.9 mmol) and hydrazine monohydrate (0.20 mL, 3.5 mmol) in ethanol (19 mL) yielded the title compound as a colorless solid (0.22 g, 41% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.22 (s, 1H), 5.63 (s, 1H), 2.07 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 145.1, 106.5, 13.9. ***^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:*** -136.1. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.9. **m. pt.** > 300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3372 (w), 1167 (m), 954 (s). **HRMS** calculated for $C_4H_5{}^{11}BF_3N_2$ (ESI^-): 146.0454. Found: 146.0453.

Potassium 1-(2-methylallyl)-3-phenyl-5-(trifluoroboranyl)-1H-pyrazole, 37A and Potassium 1-(2-methylallyl)-5-phenyl-3-(trifluoroboranyl)-1H-pyrazole, 37B



37A



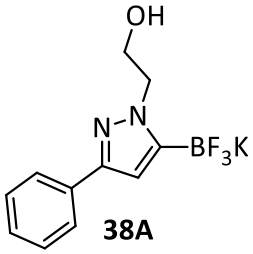
37B

Following general procedure D using **16** (200 mg, 0.847 mmol) and (2-methyl-2-propenyl)hydrazine (182 mg, 2.03 mmol) in ethanol (6 mL) yielded the title compound as a mixture of the 2 regioisomers A/B in a 76:24 ratio (254 mg, 98% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.69 (d, *J* = 7.0 Hz, 1.5H), 7.44 – 7.34 (m, 1.25H), 7.32 (t, *J* = 7.0Hz, 1.5H), 7.18 (t, *J* = 7.0 Hz, 0.75H), 6.30 (s, 0.75H), 6.10 (s, 0.25H), 4.76 (s, 1.5H), 4.67 (s, 2H), 4.58 (s, 0.5H), 1.58 (s, 2.25H), 1.56 (s, 0.75H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 148.8, 143.5, 143.2, 141.8, 135.5, 132.6, 129.0, 128.8, 128.3, 127.8, 126.7, 125.3, 111.6, 111.4, 110.0, 105.7, 56.5, 54.7, 20.4, 20.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -136.2. **^{11}B NMR (128**

MHz, DMSO-d_6), ppm: 1.7. **FTIR (neat, cm^{-1}), ν_{max}:** 2973 (w), 1640 (w), 1604 (w), 1458 (m), 1190 (m), 1136 (s). **HRMS** calculated for $C_{13}H_{13}{}^{11}BF_3N_2$ (ESI^-): 265.1129. Found: 265.1142.

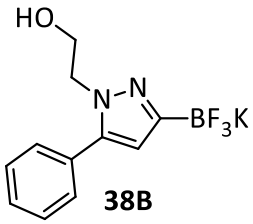
Potassium 2-(3-phenyl-5-(trifluoroboranyl)-1H-pyrazol-1-yl)ethan-1-ol, 38A and Potassium 2-(5-phenyl-3-(trifluoroboranyl)-1H-pyrazol-1-yl)ethan-1-ol, 38B

Following general procedure D using **16** (200 mg, 0.847 mmol) and 2-hydroxyethylhydrazine (186 mg, 2.03 mmol) in ethanol (6 mL) yielded the title compound as a mixture of the 2 regioisomers A/B in a 92:8 ratio (244 mg, 98% yield). Upon trituration in acetone, isomer B remained insoluble and it was filtered off. Isomer A was precipitated by addition of ether.



38A

38A as an orange oil (151 mg, 61% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.69 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.29 (s, 1H), 4.67 (t, *J* = 6.0 Hz, 1H), 4.17 (t, *J* = 7.0 Hz, 2H), 3.73 – 3.69 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 147.9, 134.9, 128.3, 126.2, 124.8, 105.4, 61.1, 52.6. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -136.7. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 2.2. **FTIR (neat, cm^{-1}), ν_{max}:** 3364 (br. w), 2947 (w), 1604 (w), 1430 (m), 1189 (s), 1139 (s). **HRMS** calculated for $C_{11}H_{11}{}^{11}BOF_3N_2$ (ESI^-): 255.0922. Found: 255.0928.

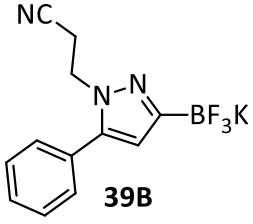


38B

38B as a colorless solid (8 mg, 3% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.48 – 7.41 (m, 4H), 7.38 – 7.33 (m, 1H), 6.03 (s, 1H), 4.96 (t, *J* = 5.0 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.76 – 3.72 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 141.5, 132.0, 128.5, 128.5, 127.3, 109.2, 60.6, 50.3. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -136.3. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 2.2. **m. pt.** 222-223 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3193 (br. w), 2930 (w), 2920 (w), 1460 (m), 1429 (m), 1407 (m), 1140 (s). **HRMS** calculated for $C_{11}H_{11}{}^{11}BOF_3N_2$ (ESI^-): 255.0922. Found: 255.0933.

Potassium 3-(5-phenyl-3-(trifluoroboranyl)-1H-pyrazol-1-yl)propanenitrile, 39B

Following general procedure D using **16** (203 mg, 0.860 mmol) and cyanoethylhydrazine (126 mg, 2.06 mmol) in ethanol (6 mL) yielded the title compound as a mixture of the 2 regioisomers A/B in a 29:71 ratio (218 mg, 84% yield). Trituration in acetone and filtration provided a pure



39B

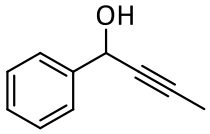
sample of **49B** as a colorless solid. **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.49-7.38 (m, 5H), 6.06 (s, 1H), 4.20 (t, *J* = 6.5 Hz, 2H), 3.03 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 141.7, 131.5, 128.6, 128.5, 127.7, 118.9, 109.8, 43.7, 18.4. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -136.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 2.3. **m. pt.** 199 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3059 (w), 2977 (w), 2247 (w), 1486 (m), 1134 (s). **HRMS** calculated for $C_{12}H_{10}{}^{11}BF_3N_3$ (ESI^-): 264.0925. Found: 264.0951.

2.2.1. Alkylation on *N*-H pyrazole **33**

To a solution of pyrazole **33** (104 mg, 0. 40 mmol) and potassium carbonate (71 mg, 0.48 mmol) in acetonitrile (0.6 mL), at rt under nitrogen, was added dropwise iodomethane (0.05 mL, 0.48 mmol). The mixture turned yellow and was left overnight to stir at rt. The solvent was then removed under vacuum. The crude mixture shows a 77/23 ratio between **25A** and **25B**. Ratio based on the integration of the =C-*H* signals (6.58 ppm for **25A** and 6.07 ppm for **25B)** and N-C*H$_3$* signals (3.93 ppm for **25A** and 3.75 ppm for **25B**).

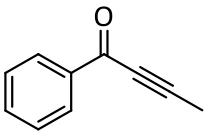
2.2.2. Synthesis of 1-Phenylbut-2-yn-1-one

1-Phenylbut-2-yn-1-ol, 40



To a solution of 1-propynylmagnesium bromide (55 mL, 24.6 mmol - 0.5 M solution in THF) in anhydrous THF (39 mL) under nitrogen, benzaldehyde (2.1 mL, 19.7 mmol) was added dropwise at -78 °C. The mixture was allowed to warm to rt. The reaction was complete in 1 hr and quenched with saturated NH_4Cl, extracted with ethyl acetate and the organic extracts dried over $MgSO_4$. The solvent was removed under vacuum. The title compound[117] was obtained after flash chromatography as a colourless oil (3.02 g, 80% yield). **^{1}H NMR (400 MHz, CDCl$_3$), ppm:** 7.59 – 7.54 (m, 2H), 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 5.50 - 5.42 (m, 1H), 2.25 – 2.11 (m, 1H), 1.94 (d, *J* = 2.0 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$), ppm:** 141.3, 128.7, 128.4, 126.7, 83.3, 79.3, 65.0, 3.9.

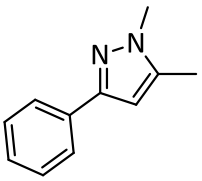
1-Phenylbut-2-yn-1-one, 41



To a suspension of manganese(IV) oxide (5.95 g, 68.4 mmol) in acetone (41 mL), was added the 1-phenylbut-2-yn-1-ol **40** (2.00 g, 13.7 mmol) at rt. The reaction was left to stir o/n. Upon completion, the mixture was filtered through Celite. All volatiles were removed from the filtrate under vacuum. Then the residue was purified by flash chromatography on silica gel to yield the title compound[118] as a colorless oil (1.48 g, 76% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 8.14 – 8.05 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 2.12 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 178.2, 136.8, 134.0, 129.6, 128.5, 92.6, 79.0, 4.3.

2.2.3. Synthesis of 5-methylpyrazoles

1,5-Dimethyl-3-phenyl-1H-pyrazole, 42



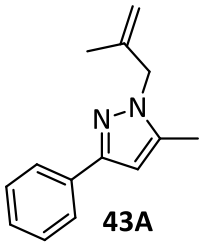
Following general procedure D using 1-phenylbut-2-yn-1-one **41** (213 mg, 1.47 mmol) and *N*-methylhydrazine (0.18 mL, 3.52 mmol) in ethanol (10 mL) yielded the title compound as a colorless oil (184 mg, 72% yield; 96:4). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.80 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.34 (s, 1H), 3.82 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 150.0, 139.8, 133.8, 128.6, 127.4, 125.4, 102.5, 36.2, 11.3.

5-Methyl-1-(2-methylallyl)-3-phenyl-1H-pyrazole, 43A and 3-methyl-1-(2-methylallyl)-5-phenyl-1H-pyrazole, 43B

Following general procedure D using 1-phenylbut-2-yn-1-one **41** (206 mg, 1.43 mmol) and (2-methyl-2-propenyl)hydrazine (286 mg, 3.32 mmol) in ethanol (10 mL) yielded the title compound as a colorless oil (216 mg, 71% yield; 78:22).

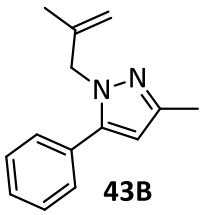
43A: colourless oil (145 mg, 48%). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.82 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.37 (s, 1H), 4.95 – 4.86 (m, 1H), 4.65 (s, 2H),

4.56 (s, 1H), 2.25 (s, 3H), 1.75 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 150.1, 140.8, 140.0, 133.8, 128.5, 127.3, 125.5, 111.8, 102.9, 55.2, 19.9, 11.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3123 (w), 3080 (w), 3062 (w), 2984 (w), 2935 (w), 2914 (w), 1658 (m), 1602 (m), 1568 (s), 1512 (s), 1480 (m). **HRMS** calculated for $C_{14}H_{16}N_2$ (ESI^+): 213.1386. Found: 213.1393.



43A

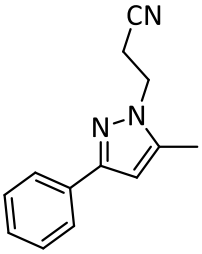
43B: colourless oil (71 mg, 23%). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.41 – 7.34 (m, 5H), 6.10 (s, 1H), 4.91 – 4.88 (m, 1H), 4.57 (s, 2H), 4.54 (s, 1H), 2.32 (s, 3H), 1.65 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 148.2, 144.9, 141.9, 131.1, 128.7, 128.6, 128.5, 112.1, 105.7, 54.9, 20.1, 13.7. **FTIR (neat, cm^{-1}), ν_{max}:** 3080 (w), 2976 (w), 2925 (m), 1655 (m), 1607 (w), 1571 (w), 1497 (s). **HRMS** calculated for $C_{14}H_{16}N_2$ (ESI^+): 213.1386. Found: 213.1392.



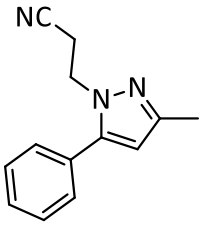
43B

3-(5-Methyl-3-phenyl-1H-pyrazol-1-yl)propanenitrile, 44A and 3-(3-methyl-5-phenyl-1H-pyrazol-1-yl)propanenitrile, 44B

Following general procedure D using 1-phenylbut-2-yn-1-one **41** (202 mg, 1.40 mmol) and cyanoethylhydrazine (300 mg, 3.36 mmol) in ethanol (10 mL) yielded the title compound as a colorless oil (290 mg, 98% yield; 67:33).



44A

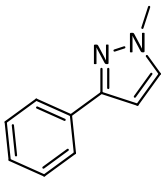


44B

2.2.4. General procedure E - Protodeboration of pyrazole-5-trifluoroborates

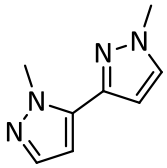
To a solution of pyrazole trifluoroborate (1 eq) in water (0.4 M), Na_2CO_3 (1.2 eq) was added. The mixture was then stirred at reflux for 4 hrs. Upon removal of all volatiles, the title compounds were obtained in pure enough form to analyse directly.

1-Methyl-3-phenyl-1H-pyrazole, 45



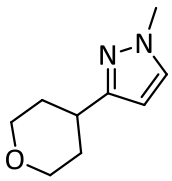
Following general procedure E using potassium trifluoro(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)borate **25** (48 mg, 0.19 mmol) and Na_2CO_3 (26 mg, 0.23 mmol) in water (0.5 mL) yielded the title compound[57] as a colorless oil (24 mg, 84% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.78 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 3H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 149.9, 133.5, 132.3, 128.6, 127.2, 124.9, 102.4, 38.6.

1,2'-Dimethyl-1H,2'H-3,3'-bipyrazole, 46



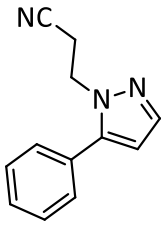
Following general procedure E using potassium 1,2'-dimethyl-5-(trifluoroboranyl)-1*H*,2'*H*-3,3'-bipyrazole **28** (19 mg, 0.07 mmol) and Na_2CO_3 (20 mg, 0.09 mmol) in water (0.5 mL) yielded the title compound as a colorless oil (11 mg, 96% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.79 (d, *J* = 2.5 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.04 (s, 3H), 3.90 (s, 3H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 141.6, 138.1, 137.7, 136.0, 132.0, 104.9, 38.7, 38.5. **FTIR (neat, cm^{-1}), ν_{max}:** 2944 (w), 1509 (m), 1480 (s). **HRMS** calculated for $C_8H_{10}N_4$ (ESI^+): 163.0978. Found: 163.0976.

1-Methyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole, 47



Following general procedure E using potassium 1-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-5-(trifluoroboranyl)-1*H*-pyrazole **30** (21 mg, 0.08 mmol) and Na_2CO_3 (11 mg, 0.09 mmol) in water (0.5 mL) yielded the title compound as a colorless oil (13 mg, 40% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.53 (d, *J* = 2.0 Hz, 1H), 6.05 (d, *J* = 2.0 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.87 – 3.84 (m, 1H), 3.75 (s, 3H), 3.37 - 3.30 (m, 2H), 2.77 (tt, *J* = 11.5, 4.0 Hz, 1H), 1.79 - 1.74 (m, 2H), 1.65 – 1.53 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 155.3, 130.9, 102.0, 67.0, 38.2, 34.0, 32.6. **FTIR (neat, cm^{-1}), ν_{max}:** 2921 (s), 2849 (s), 1520 (s), 1443 (m), 1128 (s), 1087 (s). **HRMS** calculated for $C_9H_{14}N_2O$ (ESI^+): 167.1179. Found: 167.1176.

3-(5-Phenyl-1H-pyrazol-1-yl)propanenitrile, 48

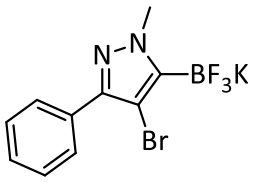


Following general procedure E using potassium 3-(5-phenyl-3-(trifluoroboranyl)-1*H*-pyrazol-1-yl)propanenitrile **39B** (20 mg, 0.07 mmol) and Na_2CO_3 (9 mg, 0.08 mmol) in water (0.5 mL) yielded the title compound as a colorless oil (13 mg, 71% yield). This product was analysed by NMR spectroscopy only: **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.60 (d, *J* = 2.0 Hz, 1H), 7.55 – 7.46 (m, 5H), 6.41 (d, *J* = 2.0 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 3.05 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 143.5, 139.1, 129.8, 128.86, 128.84, 128.7, 118.5, 106.3, 44.4, 18.2.

2.2.5. General procedure F- Halogenation of pyrazole trifluoroborates

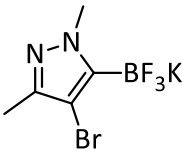
A solution of halogenating agent (1 eq) in MeCN (0.2 M) was added to the pyrazole (1 eq) and the mixture stirred for 1 hr at rt. The solvent was removed *in vacuo* and a small amount of CH_2Cl_2 was added. EtOAc was added dropwise to the suspension with stirring until all material was solubilised. The solution was transferred to a larger vessel before CH_2Cl_2 was added leading to the precipitation of a solid. The solid was isolated by filtration and washed with CH_2Cl_2.

Potassium trifluoro(1-methyl-3-phenyl-4-bromo-1H-pyrazol-5-yl)borate, 50



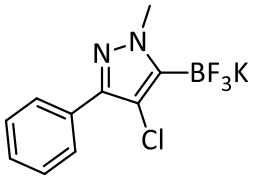
Following general procedure F using **25** (0.1 g, 0.4 mmol), *N*-bromosuccinimide (0.07 g, 0.4 mmol) in acetonitrile (3 mL) yielded the title compound as a colorless solid (0.11 g, 83% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.76 (d, *J* = 7.0 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 145.9, 134.0, 128.5, 127.8, 127.4, 94.2, 30.0. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -135.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 0.9. **m. pt.** 221-222 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2901 (w), 2845 (w), 1440 (m), 1426 (m), 1182 (s), 1144 (m), 986 (s), 936 (s). **HRMS** calculated for $C_{10}H_8{}^{11}B^{79}BrF_3N_2$ (ESI^-): 302.9921. Found: 302.9935.

Potassium trifluoro(1-methyl-3-methyl-4-bromo-1H-pyrazol-5-yl)borate, 51



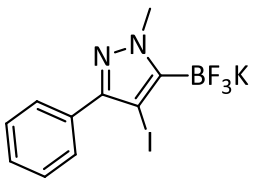
Following general procedure F using **29** (0.10 g, 0.5 mmol), N-bromosuccinimide (0.09 g, 0.5 mmol) in acetonitrile (4 mL) yielded the title compound as a colorless solid (0.07 g, 51% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 3.67 (s, 1H), 1.99 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 143.1, 95.6, 54.9, 11.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -135.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.34. **m. pt.** > 300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 1449 (w), 1168 (m), 931 (s). **HRMS** calculated for $C_5H_6{}^{11}B^{79}BrF_3N_2$ (ESI^-): 240.9765. Found: 240.9766.

Potassium trifluoro(1-methyl-3-phenyl-4-chloro-1H-pyrazol-5-yl)borate, 52



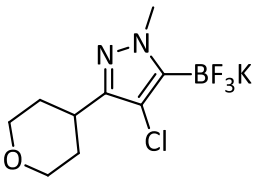
Following general procedure F using **25** (0.1 g, 0.4 mmol), *N*-chlorosuccinimide (0.05 g, 0.4 mmol) in acetonitrile (3 mL) yielded the title compound as a colorless solid (0.09 g, 75% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.78 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 144.1, 133.6, 128.6, 127.4, 127.3, 109.1, 40.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -135.7. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.3. **m. pt.** 209-210 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2950 (w), 2875 (w), 1430 (w), 1197 (m), 1144 (m), 1005 (s), 966 (s), 924 (s). **HRMS** calculated for $C_{10}H_8{}^{10}B^{35}ClF_3N_2$ (ESI^-): 258.0463. Found: 258.0471.

Potassium trifluoro(1-methyl-3-phenyl-4-iodo-1H-pyrazol-5-yl)borate, 53



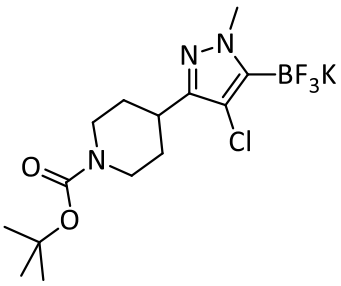
Following general procedure F using **25** (0.1 g, 0.4 mmol), *N*-iodosuccinimide (0.09 g, 0.4 mmol) in acetonitrile (3 mL) yielded the title compound as a colorless solid (0.06 g, 50% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.69 (d, *J* = 7.0 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 3.85 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 149.6, 134.9, 128.6, 128.3, 127.4, 60.9, 40.6. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -134.9. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.2. **m. pt.** 272-273 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2957 (w), 1436 (m), 1424 (m), 1171, (m) 1140 (m), 1028 (m), 974 (s), 935 (s). **HRMS** calculated for $C_{10}H_8{}^{11}BF_3IN_2$ (ESI^-): 349.9819. Found: 349.9822.

Potassium 4-chloro-1-methyl-3-(tetrahydro-2H-pyran-4-yl)-5-(trifluoroboranyl)-1H-pyrazole, 54



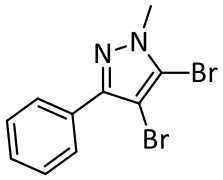
Following general procedure F using **30** (100 mg, 0.37 mmol), *N*-chlorosuccinimide (50 mg, 0.37 mmol) in acetonitrile (3 mL) heated at 45 °C yielded the title compound as a colorless solid (60 mg, 53% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 3.90 – 3.86 (m, 2H), 3.67 (s, 3H), 3.42 – 3.34 (m, 2H), 2.82 – 2.71 (m, 1H), 1.75 – 1.62 (m, 4H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 148.9, 108.8, 67.7, 32.0, 28.6, 26.5.**^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -135.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 0.8. **m. pt.** > 260 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2958 (w), 2919 (m), 2855 (w), 1238 (m), 1060 (s), 953 (s), 930 (s). **HRMS** calculated for $C_9H_{12}{}^{11}B^{35}ClOF_3N_2$ (ESI^-): 267.0689. Found: 267.0680.

Potassium tert-butyl 4-(4-chloro-1-methyl-5-(trifluoroboranyl)-1H-pyrazol-3-yl)piperidine-1-carboxylate, 55



Following general procedure F using **31** (102 mg, 0.27 mmol), *N*-chlorosuccinimide (37 mg, 0.27 mmol) in acetonitrile (2.1 mL) and heated at 45 °C yielded the title compound as a colorless solid (36 mg, 33% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 3.99 – 3.94 (m, 2H), 3.66 (s, 3H), 2.89 – 2.75 (m, 2H), 2.71 (tt, *J* = 11.5, 4.0, 1H), 1.73 – 1.68 (m, 2H), 1.57 – 1.43 (m, 2H), 1.40 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 153.9, 148.2, 108.3, 78.4, 43.3, 32.9, 30.6, 28.1. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -135.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 0.8. **m. pt.** 101 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2977 (w), 2950 (w), 2860 (w), 1664 (s), 1429 (s), 1162 (s), 971 (s), 956 (s). **HRMS** calculated for $C_{14}H_{21}{}^{11}B^{35}ClO_2F_3N_3$ (ESI^-): 366.1373. Found: 366.1389.

4,5-Dibromo-1-methyl-3-phenyl-1H-pyrazole, 49

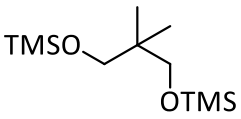


A solution of bromine (21 µL, 0.42 mmol) in acetonitrile (2.1 mL) was added dropwise to potassium trifluoro(1-methyl-3-phenyl-1H-pyrazol-5-yl)borate **25** (100 mg, 0.38 mmol) in 0.5 mL of acetonitrile and the mixture stirred for 1 hr at rt. The solvent was removed under vacuum and CH_2Cl_2 was added. The resulting mixture was filtered through Celite and the filtrate was concentrated under vacuum to yield the title compound as a purple oil (114 mg, 95% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.87 (d, *J* = 7.0 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 1H), 4.00 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 149.0, 131.8, 128.5, 128.4, 127.4, 116.8, 95.0, 39.0. **FTIR (neat, cm^{-1}), ν_{max}:** 3058 (w), 2940 (w), 1604 (w), 1579 (w), 1482 (s), 1448 (s). **HRMS** calculated for $C_{10}H_8{}^{79}Br^{81}BrN_2$ (ESI^-): 316.9107. Found: 316.9105.

The orthogonal cross-coupling method was developped and exemplified Andy Brown, PhD student from the Harrity group. Therefore, procedures and full characterisation of all synthesised compounds can be found in the article published earlier this year.[119]

2.2.6. Ligand exchange from trifluoroborate to boronamide

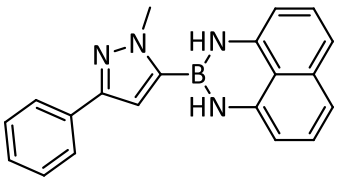
2,2,5,5,8,8-Hexamethyl-3,7-dioxa-2,8-disilanonane, 56



To a solution of commercial 2,2-dimethyl-1,3-propanediol (0.55 g, 5 mmol) in hexamethyldisilazane (1.1 mL, 5 mmol) under nitrogen, a few drops of TMS-Cl were added. The mixture was stirred overnight at rt. Then the reaction was quenched with water (enough to dissolve all solid). The aqueous solution was extracted with Et_2O, dried over $MgSO_4$, filtered and the solvent was removed under vacuum (cold water bath). The crude was purified by flash chromatography on silica gel (Petrol/CH_2Cl_2 90/10). The pure title compound[75] was obtained as a colorless oil (0.68 g, 59% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 3.30 (s, 2H), 0.82 (s, 3H), 0.10 (s, 8H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 67.9, 37.1, 21.3, 0.0.

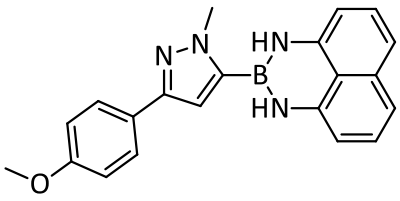
General procedure G - To a solution of pyrazole trifluoroborate (1.0 eq) and 1,8-diaminonaphthalene (1.1 eq) in toluene (0.05 M) under nitrogen, NEt_3 (2.0 eq) was added. After 5 min, TMS-Cl (3.0 eq) was added dropwise then the mixture was heated at reflux overnight. The solvent was removed under vacuum and the crude was purified by flash chromatography on silica gel (Petrol/CH_2Cl_2, slowly from 100/0 to 0/100) to yield the desired compound pure.

Naphthalen(1-methyl-3-phenyl-1H-pyrazol-5-yl)boronamide, 57



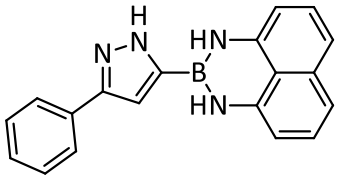
Following general procedure G using **25** (103 mg, 0.4 mmol), 1,8-diaminonaphthalene (68 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.8 mmol) and TMS-Cl (0.2 mL, 1.2 mmol) in toluene (10 mL) yielded the title compound as a pink oil (100 mg, 77% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.82 (d, *J* = 7.0 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (dd, J = 8.5, 7.0 Hz, 1H), 7.18 - 7.09 (m, 5H), 6.82 (s, 1H), 6.42 (dd, *J* = 7.0, 1.0 Hz, 2H), 4.12 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 149.2, 140.4, 136.4, 133.5, 128.8, 127.8, 127.1, 125.8, 118.7, 117.3, 109.7, 106.6, 39.7. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 27.3. **FTIR (neat, cm^{-1}), ν_{max}:** 3403 (w), 3280 (br), 3049 (w), 1596 (s), 1398 (s), 764 (s). **HRMS** calculated for $C_{20}H_{18}{}^{11}BN_4$ (ESI^+): 325.1235. Found: 325.1242.

Naphthalen(1-methyl-3-(4-methoxyphenyl)-1H-pyrazol-5-yl)boronamide, 58



Following general procedure G using **26** (101 mg, 0.3 mmol), 1,8- diaminonaphthalene (62 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.7 mmol) and TMS-Cl (0.1 mL, 1.0 mmol) in toluene (9 mL) yielded the title compound as a yellow oil (51 mg, 42% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.77 (dd, J = 3, 2.5 Hz, 1H), 7.75 (dd, J = 2.5, 3 Hz, 1H), 7.18 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.12 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.98 (dd, J = 3, 2.5 Hz, 1H), 6.96 (dd, J = 2.5, 3 Hz, 1H), 6.75 (s, 1H), 6.43 (dd, *J* = 7.10 1.10Hz, 2H), 5.94 (s, 2H), 4.10 (s, 3H), 3.86 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 159.3, 151.1, 140.3, 136.3, 127.6, 126.9, 126.0, 119.9, 118.5, 114.1, 109.1, 106.5, 55.3, 39.5. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 27.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3411 (w), 3271 (br), 2936 (w), 1602 (s), 1264 (s), 733 (s). **HRMS** calculated for $C_{21}H_{20}{}^{11}BN_4O$ (ESI^+): 355.1730. Found: 355.1743.

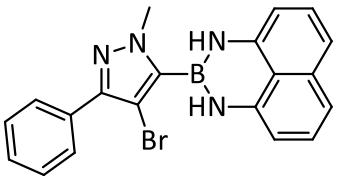
Naphthalen(3-phenyl-1H-pyrazol-5-yl)boronamide, 59



Following general procedure G using **33** (103 mg, 0.4 mmol), 1,8- diaminonaphthalene (72 mg, 0.5 mmol), NEt_3 (0.2 mL, 0.8 mmol) and TMS-Cl (0.2 mL, 1.2 mmol) in toluene (11 mL) yielded the title compound as a colorless oil (96 mg, 75% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 12.83 (s, 1H), 8.26 (s, 2H), 7.83 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.50 (d, *J* = 7.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 151.1, 142.1, 136.5, 134.2, 129.2, 128.2, 127.8, 125.6, 120.1, 117.2, 109.4, 106.1. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 21.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3430 (br), 3323 (w), 1601 (s), 765 (s). **HRMS** calculated for $C_{19}H_{16}{}^{11}BN_4$ (ESI^+): 311.1468. Found: 311.1460.

General procedure H - To a solution of pyrazole trifluoroborate (1.0 eq) in acetonitrile (0.4 M) at 0°C under nitrogen, NBS (1.0 eq) was added as a 0.2 M solution in acetonitrile and left to stir at 0 °C for 1 hr. The solvent was then removed under vacuum and the residue redisolved in toluene (0.05 M). Then 1,8-diaminonaphthalene (1.1 eq), NEt_3 (2.0 eq) were added to the mixture. After 5 min, TMS-Cl (3.0 eq) was added dropwise then the mixture was heated at reflux overnight. The solvent was removed under vacuum and the crude was purified by flash chromatography on silica gel (Petrol/CH_2Cl_2, slowly from 100/0 to 0/100) to yield the desired compound pure.

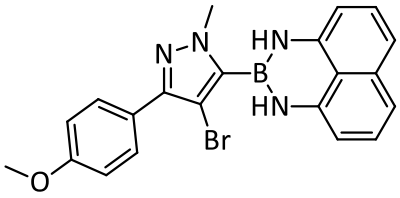
Naphthalen(1-methyl-3-phenyl-4-bromo-1H-pyrazol-5-yl)boronamide, 60



Following general procedure H using **25** (109 mg, 0.4 mmol), NBS (74 mg, 0.4 mmol) in acetonitrile (3 mL) then 1,8-diaminonaphthalene (72 mg, 0.5 mmol), NEt_3 (0.2 mL, 0.8 mmol) and TMS-Cl (0.2 mL, 1.2 mmol) in toluene (10 mL) yielded the title compound as a pink solid (121 mg, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.89 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.13 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.45 (dd, *J* = 7.0, 1.0 Hz, 2H), 6.05 (s, 2H), 4.10 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 148.9, 140.1, 136.3, 131.8, 128.4, 128.2, 127.9, 127.7, 120.1, 118.8,

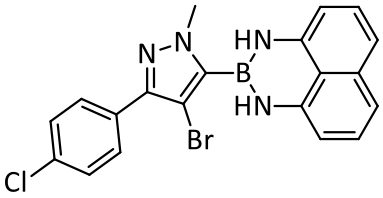
106.6, 98.4, 40.4. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 27.5. **m. pt.** 185-186 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3414 (w), 3361 (w), 1599 (s), 1338 (s), 980 (s), 818 (s). **HRMS** calculated for $C_{20}H_{16}{}^{11}B^{79}BrN_4$ (ESI^+): 403.0724. Found: 403.0716.

Naphthalen(1-methyl-3-(4-methoxyphenyl)-4-bromo-1H-pyrazol-5-yl)boronamide, 61



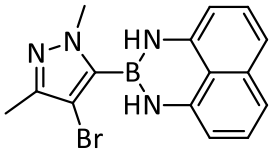
Following general procedure H using **26** (100 mg, 0.3 mmol), NBS (61 mg, 0.3 mmol) in acetonitrile (3 mL) then 1,8-diaminonaphthalene (61 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.7 mmol) and TMS-Cl (0.1 mL, 1.0 mmol) in toluene (9 mL) yielded the title compound as a pink solid (71 mg, 49% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.82 (d, *J* = 9.0 Hz, 2H), 7.18 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.13 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.44 (dd, *J* = 7.0, 1.0 Hz, 2H), 6.04 (s, 2H), 4.09 (s, 3H), 3.88 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 159.6, 148.7, 140.1, 136.3, 129.2, 127.6, 124.4, 120.1, 118.7, 113.8, 106.6, 98.1, 55.3, 40.3. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 27.4. **m. pt.** 189-190 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3419 (w), 3359 (w), 1599 (s), 1249 (s), 1028 (m), 820 (s). **HRMS** calculated for $C_{21}H_{18}{}^{11}B^{79}BrN_4O$ (ESI^+): 433.0830. Found: 433.0824.

Naphthalen(1-methyl-3-(4-chlorophenyl)-4-bromo-1H-pyrazol-5-yl)boronamide, 62



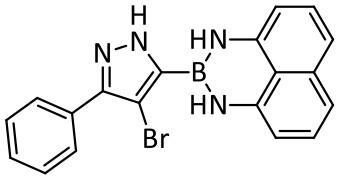
Following general procedure H using **27** (100 mg, 0.3 mmol), NBS (60 mg, 0.3 mmol) in acetonitrile (3 mL) then 1,8- diaminonaphthalene (59 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.7 mmol) and TMS-Cl (0.1 mL, 1.0 mmol) in toluene (9 mL) yielded the title compound as a brown solid (121 mg, 82% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.84 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 7.20 – 7.16 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.14 (dd, *J* = 8.0, 1.0 Hz, 2H), 6.44 (dd, *J* = 7.0, 1.0 Hz, 2H), 6.03 (s, 2H), 4.09 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 147.7, 140.0, 136.3, 134.1, 130.4, 129.1, 128.5, 127.7, 120.1, 118.8, 106.7, 98.3, 40.4. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 26.7. **m. pt.** 175-176 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3416 (s), 3268 (w), 1599 (s), 1338 (m), 818 (m), 762 (s). **HRMS** calculated for $C_{20}H_{16}{}^{11}B^{79}Br^{35}ClN_4$ (ESI^+): 437.0340. Found: 437.0319.

Naphthalen(1,3-dimethyl-4-bromo-1H-pyrazol-5-yl)boronamide, 63



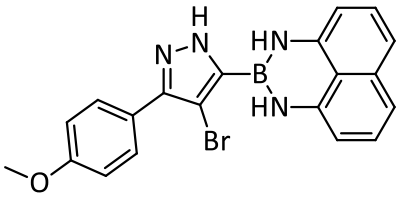
Following general procedure H using **29** (105 mg, 0.5 mmol), NBS (93 mg, 0.5 mmol) in acetonitrile (4 mL) then 1,8- diaminonaphthalene (94 mg, 0.6 mmol), NEt_3 (0.1 mL, 1.0 mmol) and TMS-Cl (0.2 mL, 1.6 mmol) in toluene (14 mL) yielded the title compound as a brown solid (81 mg, 46% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.17 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.11 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.43 (dd, *J* = 7.0, 1.0 Hz, 2H), 6.01 (s, 2H), 4.01 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 147.1, 140.1, 136.3, 127.6, 120.0, 118.7, 106.6, 100.7, 40.1, 11.7. **^{11}B NMR (128 MHz, $CDCl_3$), ppm:** 26.6. **m. pt.** 219-220 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3410 (w), 3302 (w), 1600 (s), 1334 (s), 818 (s). **HRMS** calculated for $C_{15}H_{14}{}^{11}B^{79}BrN_4$ (ESI^+): 341.0568. Found: 341.0567.

Naphthalen(3-phenyl-4-bromo-1H-pyrazol-5-yl)boronamide, 64



Following general procedure H using **33** (105 mg, 0.4 mmol), NBS (75 mg, 0.4 mmol) in acetonitrile (3 mL) then 1,8-diaminonaphthalene (75 mg, 0.5 mmol), NEt_3 (0.1 mL, 0.8 mmol) and TMS-Cl (0.2 mL, 1.3 mmol) in toluene (12 mL) yielded the title compound as a pink solid (163 mg, 72% yield) as an inseparable mixture with succinimide. **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 11.06 (s, 1H), 8.15 (s, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 7.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 152.2, 141.4, 136.0, 128.5, 128.0, 127.7, 127.4, 125.2, 119.9, 117.0, 105.9, 97.1. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 22.3. **FTIR (neat, cm^{-1}), ν_{max}:** 3421 (m), 3342 (m), 3052 (w), 1600 (s), 1505 (s), 1454 (w), 1434 (m), 1343 (m). **HRMS** calculated for $C_{19}H_{14}{}^{11}B^{79}BrN_4$ (ES^+): 389.0568. Found: 389.0563.

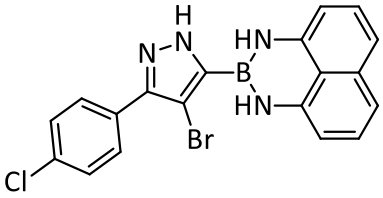
Naphthalen(3-(4-methoxyphenyl)-4-bromo-1H-pyrazol-5-yl)boronamide, 65



Following general procedure H using **34** (101 mg, 0.4 mmol), NBS (65 mg, 0.4 mmol) in acetonitrile (3 mL) then 1,8-diaminonaphthalene (65 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.7 mmol) and TMS-Cl (0.2 mL, 1.1 mmol) in toluene (12 mL) yielded the title compound as a pink solid (89 mg, 59% yield) as an inseparable mixture with succinimide. **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 11.07 (s, 1H), 8.12 (s, 2H), 7.77 (d, *J* = 8.0 Hz,

2H), 7.10 (t, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 159.2, 152.9, 141.5, 136.1, 128.8, 128.5, 127.8, 120.0, 117.1, 114.0, 106.2, 96.9, 55.2. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 21.7. **FTIR (neat, cm^{-1}), ν_{max}:** 3431 (m), 3363 (m), 3053 (w), 2992 (w), 1601 (s), 1578 (s), 1533 (w), 1504 (s), 1028 (s). **HRMS** calculated for $C_{20}H_{16}{}^{11}B^{79}BrN_4O$ (ESI^+): 419.0673. Found: 419.0669.

Naphthalen(3-(4-methoxyphenyl)-4-bromo-1H-pyrazol-5-yl)boronamide, 66



Following general procedure H using **35** (104 mg, 0.4 mmol), NBS (66 mg, 0.4 mmol) in acetonitrile (3 mL) then 1,8-diaminonaphthalene (65 mg, 0.4 mmol), NEt_3 (0.1 mL, 0.7 mmol) and TMS-Cl (0.2 mL, 1.1 mmol) in toluene (10 mL) yielded the title compound as a pink solid (85 mg, 55% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 13.46 (s, 1H), 8.16 (s, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.10 (app t, J = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 146.7, 141.4, 135.9, 132.8, 131.8, 129.0, 128.6, 127.7, 119.9, 117.1, 106.1, 97.0. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 22.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3419 (m), 3334 (m), 3053 (w), 2998 (w), 1598 (s), 1561 (m), 1501 (s), 1436 (m). **HRMS** calculated for $C_{19}H_{13}{}^{11}B^{79}Br^{35}ClN_4$ (ESI^+): 423.0178. Found: 423.0168.

2.2.7. Libraries of 5-7-6 tricyclic compounds (**A**, **B**, **C**, **D** and **E**)

General procedure for library A - For each of the 22 selected substrates, the library production was carried out according to the following procedure:

In a RG24-flask, the aryl bromide partner (0.5 mmol, 1 eq) was put under argon atmosphere. Na_2CO_3 (1.5 mmol, 3 eq) was added, followed by **38A** (0.6 mmol, 1.2 eq) in 3 mL of ethanol. Palladium(II) acetate (0.04 mmol, 0.07 eq) and XPhos ligand (0.07 mmol, 0.14 eq) were added in 2 mL of ethanol. The mixture was then heated at 80 °C until completion of the reaction (LC-MS monitoring). Si-TMT-Scavenger (150 mg) was added and the reaction was stirred at rt for 4 hours, it was then filtered and washed with ethanol (2 mL). The crude was evaporated and redissolved in *N,N*-DMF and purified by prep. HPLC to yield the compounds **A.01** to **A.17**.

General procedure for library B - All compounds from library A were submitted to the following procedure:

In a RG24-flask, compounds **A.01** to **A.17** (0.25 mmol, 1 eq) were dissolved in *N,N*-DMF (1 mL). Potassium *tert*-butoxide (1 mmol, 4 eq) was then added in *N,N*-DMF (1 mL). The mixture was then heated at 80 °C until completion of the reaction (LC-MS monitoring). The crude was then filtered, washed with *N,N*-DMF and purified by prep. HPLC to yield compounds **B.01** to **B.06**.

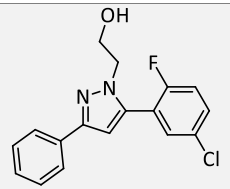
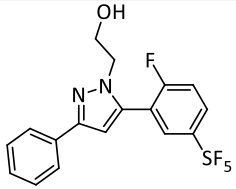
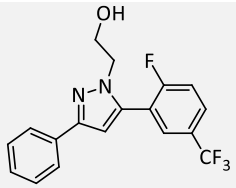
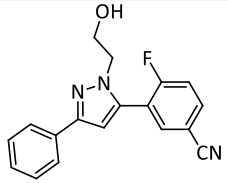
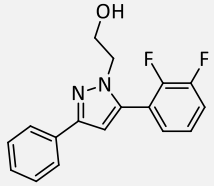
General procedure for library C (by hand)

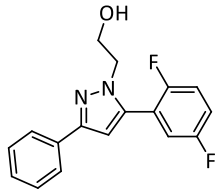
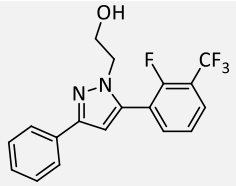
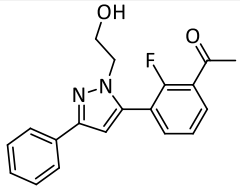
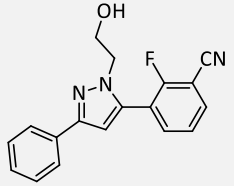
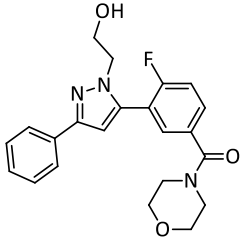
Compounds from library C were synthesised using the modified procedure L (see page 198)

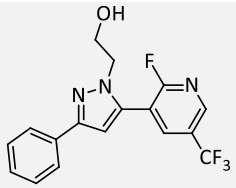
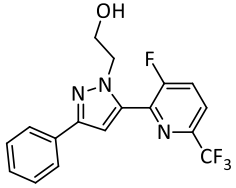
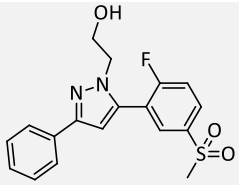
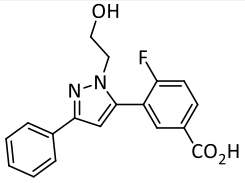
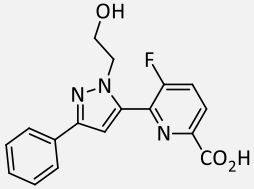
It should be noted that direct cyclisation products **C.02**, **C.04** and **C.07** were observed after reaction of respectively 2-bromo-1-fluoro-4-(methylsulfonyl)benzene, 3-bromo-4-fluoropyridine and 2-bromo-1-fluoro-4-nitrobenzene with **38A** when following procedure for library A.

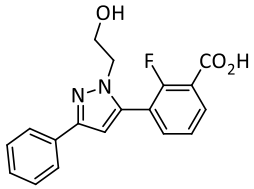
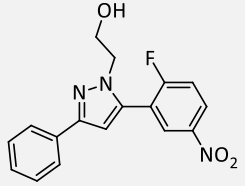
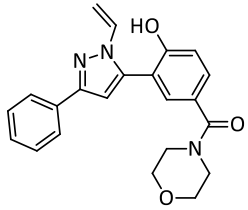
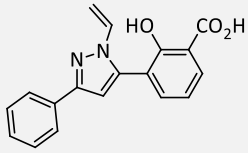
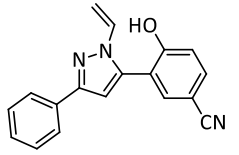
General procedure for the libraries D and E - For each of the 50 selected substrates (25 for each library), the library production was carried out according to the following procedure:

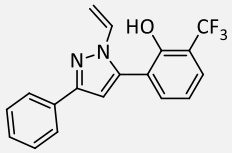
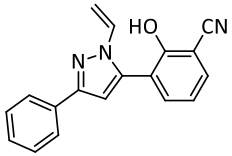
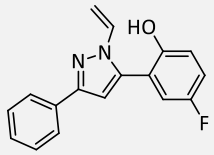
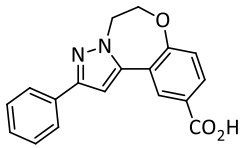
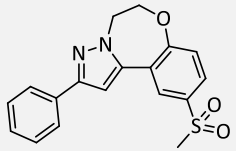
In a RG24-flask, the amine partner (0.2 mmol, 1.33 eq) was put under nitrogen atmosphere. Diisopropylethylamine (0.45 mmol, 3 eq), dimethylaminopyridine (0.01 mmol, 0.07 eq) were added in *N,N*-DMF (1 mL). Finally, the acid partner (2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid or **A.17** – 0.15 mmol, 1 eq) was added. The mixture was stirred at rt for 5 min before addition of (dimethylamino)-*N,N*-dimethyl(3H-[1,2,3]triazolo[4,5-b]pyridine-3-yloxy)methaniminium hexafluorophosphate (0.17 mmol, 1.1 eq) and additional diisopropylethylamine (0.23 mmol, 1.5 eq). The reaction was stirred at rt until completion (LC-MS monitoring). The crude was then directly purified by prep. HPLC to yield compounds **D.01** to **D.23** and **E.01** to **E.23**.

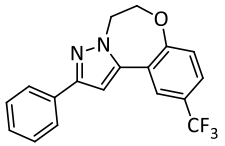
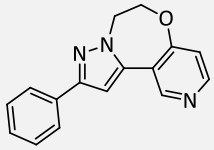
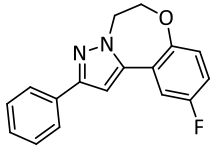
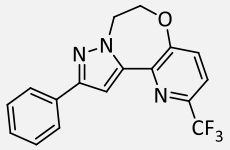
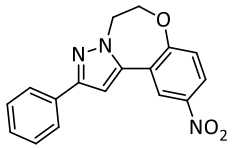
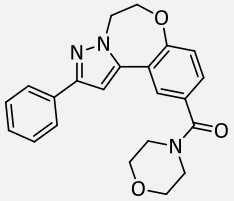
Compound ID	*Compound structure*	*LC-MS purity*	*^{1}H NMR*
A.01		93%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 7.85 – 7.83 (m, 2H), 7.75 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.63 (ddd, *J* = 9.0, 4.5, 3.0 Hz, 1H), 7.47 (t, *J* = 9.0 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.34 – 7.30 (m, 1H), 6.91 (s, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).
A.02		97%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.32 (dd, *J* = 6.0, 3.0 Hz, 1H), 8.14 (ddd, *J* = 9.0, 4.0, 3.0 Hz, 1H), 7.86 – 7.84 (m, 2H), 7.67 (t, *J* = 9.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 6.99 (s, 1H), 4.07 (t, *J* = 5.5 Hz, 2H), 3.78 (t, *J* = 5.5 Hz, 2H).
A.03		91%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.09 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.98 – 7.95 (m, 1H), 7.86 – 7.84 (m, 2H), 7.66 (t, *J* = 9.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 – 7.30 (m, 1H), 6.97 (s, 1H), 4.07 (t, *J* = 5.5 Hz, 2H), 3.77 (t, *J* = 5.5 Hz, 2H).
A.04		90%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.21 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.09 (ddd, *J* = 8.5, 5.0, 2.0 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 6.94 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).
A.05		97%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 7.86 – 7.84 (m, 2H), 7.62 – 7.56 (m, 1H), 7.47 – 7.41 (m, 3H), 7.39 – 7.36 (m, 1H), 7.34 – 7.31 (m, 1H), 6.92 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).

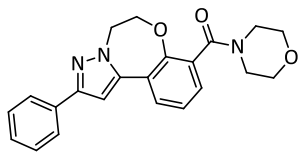
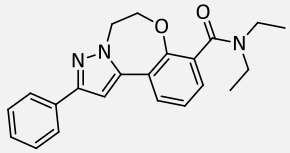
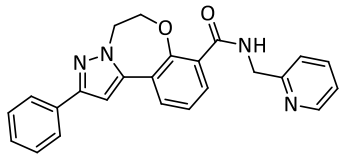
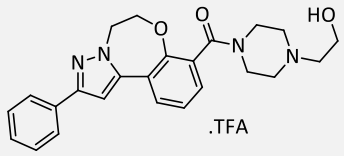
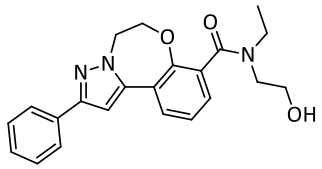
A.06		92%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.85 – 7.83 (m, 2H), 7.56 (ddd, *J* = 9.0, 6.0, 3.0 Hz, 1H), 7.47 (td, *J* = 9.0, 5.0 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.34 – 7.30 (m, 1H), 6.90 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.77 (t, *J* = 6.0 Hz, 2H).
A.07		86%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.98 (t, *J* = 7.5 Hz, 1H), 7.94 (t, *J* = 7.5 Hz, 1H), 7.85 (dt, *J* = 8.0, 1.5 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 6.96 (s, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).
A.08		97%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.93 (td, *J* = 8.0, 2.0 Hz, 1H), 7.86 – 7.82 (m, 3H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 – 7.31 (m, 1H), 6.90 (s, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.63 (d, *J* = 4.0 Hz, 3H).
A.09		87%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.08 (ddd, *J* = 8.0, 6.0, 2.0Hz, 1H), 8.01 (td, *J* = 8.0, 2.0 Hz, 1H), 7.84 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.35 – 7.31 (m, 1H), 6.95 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 2H).
A.10		89%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.85 – 7.83 (m, 2H), 7.68 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.61 (ddd, *J* = 8.5, 5.0, 2.0 Hz, 1H), 7.49 (dd, *J* = 9.5, 8.5 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.34 – 7.30 (m, 1H), 6.90 (s, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.68 – 3.43 (m, 8H).

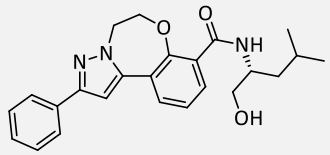
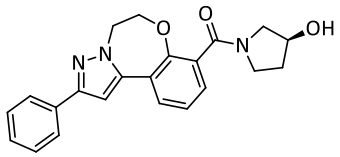
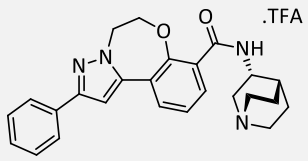
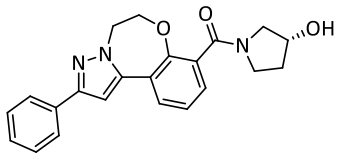
A.11		89%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 9.00 (s, 1H), 8.53 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.88 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.36 – 7.33 (m, 1H), 7.26 (d, *J* = 3.5 Hz, 1H), 4.62 (t, *J* = 6.0 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H).
A.12		96%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.22 (t, *J* = 9.0 Hz, 1H), 8.09 (dd, *J* = 9.0, 3.5 Hz, 1H), 7.88 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.37 – 7.32 (m, 1H), 7.25 (d, *J* = 3.5 Hz, 1H), 4.58 (t, *J* = 6.0 Hz, 2H), 3.73 (t, *J* = 6.0 Hz, 2H).
A.13		84%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.19 (dd, *J* = 6.5, 2.5 Hz, 1H), 8.11 (ddd, *J* = 9.0, 4.5, 2.5 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.71 (t, *J* = 9.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.35 – 7.31 (m, 1H), 6.98 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.31 (s, 3H).
A.14		96%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.19 – 8.08 (m, 2H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 4.80 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.74 (t, *J* = 6.0 Hz, 2H).
A.15		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 13.49 (s, 1H), 8.16 (dd, *J* = 8.5, 3.5 Hz, 1H), 8.11 – 8.02 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 3.5 Hz, 1H), 4.65 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H)

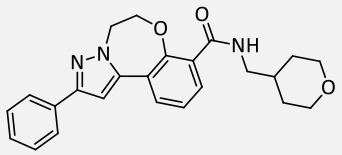
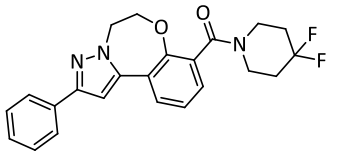
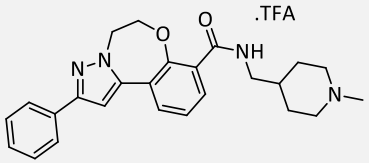
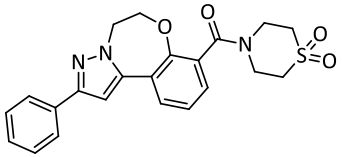
A.16		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.02 – 7.95 (m, 1H), 7.88 – 7.78 (m, 3H), 7.46 – 7.40 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 2H).
A.17		99%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.59 (dd, J = 6.0, 3.0 Hz, 1H), 8.46 - 8.42 (m, 1H), 7.88 – 7.85 (m, 2H), 7.72 (t, J = 9.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.00 (s, 1H), 4.10 (t, J = 5.5 Hz, 2H), 3.78 (t, J = 5.5 Hz, 2H).
B.01		94%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 10.52 (s, 1H), 7.93 – 7.89 (m, 2H), 7.47 – 7.42 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 8.405 Hz, 1H), 6.92 (s, 1H), 6.82 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.67 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 3.62 – 3.57 (m, 4H), 3.55 – 3.49 (m, 4H).
B.02		76%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 11.90 (s, 1H), 7.98 (dd, J = 7.5, 2.0 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 1H), 7.60 (dd, J = 7.5, 2.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.95 (s, 1H), 6.83 (dd, J = 15.0, 8.5 Hz, 1H), 5.68 (d, J = 15.0 Hz, 1H), 4.82 (d, J = 8.5 Hz, 1H).
B.03		85%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 11.28 (s, 1H), 7.91 – 7.89 (m, 2H), 7.82 – 7.78 (m, 2H), 7.47 – 7.44 (m, 2H), 7.38 – 7.35 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.95 (s, 1H), 6.80 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.67 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 8.5 Hz, 1H).

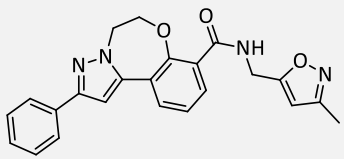
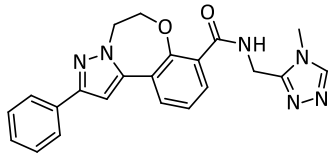
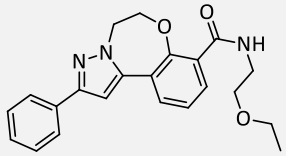
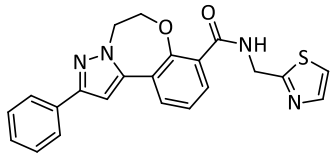
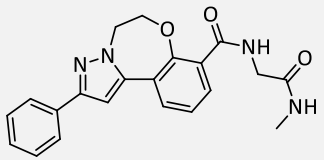
B.04		82%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 10.02 (s, 1H), 7.95 – 7.93 (m, 2H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.39 – 7.35 (m, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 6.76 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.70 (d, *J* = 15.0 Hz, 1H), 4.88 (d, *J* = 9.0 Hz, 1H).
B.05		81%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 10.85 (s, 1H), 7.93 – 7.91 (m, 2H), 7.81 (dd, *J* =8.0, 1.5 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.39 – 7.36 (m, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.77 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.69 (d, *J* = 15.0 Hz, 1H), 4.86 (d, *J* = 9.0 Hz, 1H).
B.06		63%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 10.01 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 9.0, 3.0 Hz, 1H), 7.14 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.02 - 6.96 (m, 1H), 6.91 (s, 1H), 6.82 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.67 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H)
C.01		93%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.50 (d, *J* = 2.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.83 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 (s, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.71 (m, 2H), 4.5 – 4.56 (m, 2H)
C.02		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.46 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.62 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 4.76 – 4.72 (m, 2H), 4.63 – 4.59 (m, 2H), 3.30 (s, 3H).

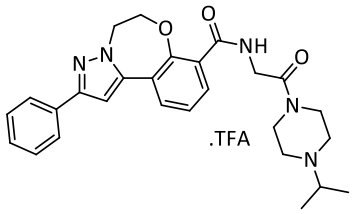
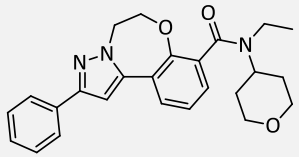
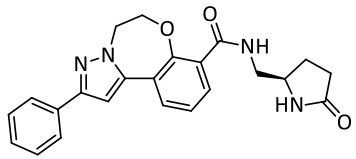
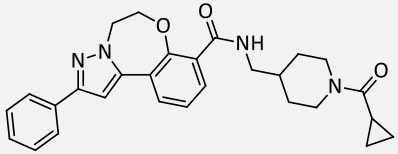
C.03		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.31 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.68 (s, 1H), 7.62 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 4.74 – 4.72 (m, 2H), 4.59 – 4.57 (m, 2H).
C.04		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 9.25 (s, 1H), 8.47 (d, *J* = 6.0 Hz, 1H), 7.86 – 7.84 (m, 2H), 7.65 (s, 1H), 7.47 – 7.43 (m, 2H), 7.37 – 7.33 (m, 1H), 7.29 (d, *J* = 6.0 Hz, 1H), 4.80 – 4.77 (m, 2H), 4.73 – 4.70 (m, 2H).
C.05		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.86 - 7.80 (m, 3H), 7.51 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 - 7.30 (m, 1H), 7.21 – 7.12 (m, 1H), 7.11 - 7.07 (m, 1H), 4.71 - 4.66 (m, 2H), 4.51 - 4.47 (m, 2H).
C.06		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.89 (d, *J* = 7.0Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 4.81 – 4.79 (m, 2H), 4.69 – 4.67 (m, 2H).
C.07		96%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.79 (d, *J* = 3.0 Hz, 1H), 8.12 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.69 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 4.76 – 4.74 (m, 2H), 4.65 – 4.63 (m, 2H).
C.08- E.01		84%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.01 (d, *J* = 2.0 Hz, 1H), 7.88 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.52 (s, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.72 – 4.68 (m, 2H), 4.55 – 4.52 (m, 2H), 3.70 – 3.46 (m, 8H).

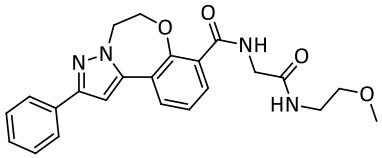
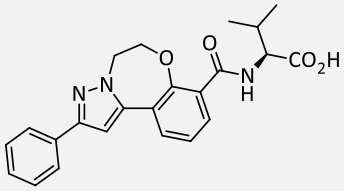
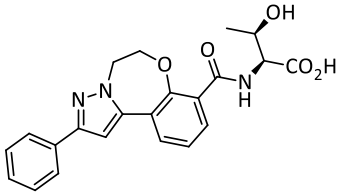
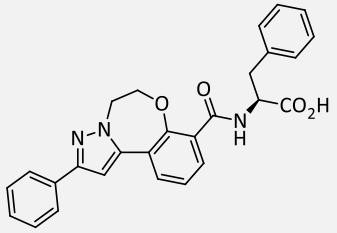
D.01		98%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.86 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.45 – 7.42 (m, 3H), 7.34 – 7.31 (m, 1H), 7.24 – 7.18 (m, 2H), 4.71 – 4.67 (m, 2H), 4.56 – 4.52 (m, 2H), 3.67 – 3.62 (m, 4H), 3.55 – 3.49 (m, 2H), 3.25 – 3.15 (m, 2H).
D.02		98%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.00 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.87 – 7.86 (m, 2H), 7.45 – 7.42 (m, 3H), 7.35 – 7.31 (m, 1H), 7.21 – 7.16 (m, 2H), 4.68 – 4.64 (m, 2H), 4.51 – 4.48 (m, 2H), 3.58 – 3.48 (m, 1H), 3.41 – 3.3.35 (m, 1H), 3.15 – 3.09 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H)
D.03		97%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.10 (t, *J* = 5.5 Hz, 1H), 8.71 (d, *J* = 5.5 Hz, 1H), 8.20 (t, *J* = 7.5 Hz, 1H), 8.10 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.88 – 7.87 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.46 – 7.42 (m, 3H), 7.35 – 7.32 (m, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 4.73 – 4.72 (m, 4H), 4.66 – 4.65 (m, 2H).
D.04		97%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.75 (s, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.87 – 7.86 (m, 2H), 7.47 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.20 (m, 2H), 4.77 – 4.68 (m, 2H), 4.62 – 4.54 (m, 2H), 3.77 – 3.74 (m, 2H), 3.65 – 3.55 (m, 2H), 3.48 – 3.35 (m, 2H), 3.27 – 3.21 (m, 2H).
D.05		84%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.03 – 7.97 (m, 2H), 7.88 – 7.86 (m, 4H), 7.45 – 7.42 (m, 6H), 7.34 – 7.31 (m, 2H), 7.21 – 7.17 (m, 4H), 4.68 – 4.66 (m, 4H), 4.51 – 4.48 (m, 4H), 3.68 – 3.58 (m, 3H), 3.53 – 3.45 (m, 2H), 3.44 – 3.34 (m, 3H), 3.24 – 3.10 (m, 4H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H).

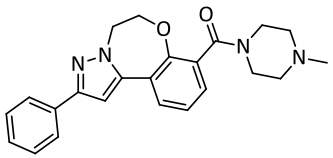
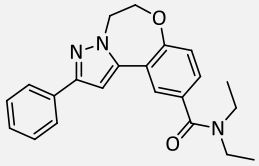
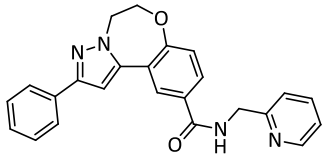
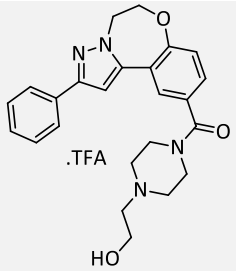
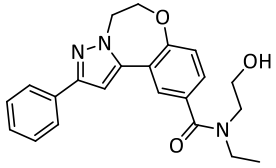
D.06		86%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.01 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.87 – 7.85 (m, 2H), 7.49 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.39 (s, 1H), 7.34 – 7.31 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 4.69 – 4.67 (m, 2H), 4.55 – 4.53 (m, 2H), 4.06 – 3.99 (m, 1H), 3.46 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.34 (dd, *J* = 10.5, 6.0 Hz, 1H), 1.73 (sep, *J* = 6.5 Hz, 1H), 1.44 – 1.36 (m, 2H), 0.93 (2d, *J* = 6.5 Hz, 6H).
D.07		97%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.01 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.87 – 7.85 (m, 4H), 7.45 – 7.41 (m, 6H), 7.34 – 7.31 (m, 2H), 7.23 – 7.17 (m, 4H), 4.69 – 4.66 (m, 5H), 4.53 – 4.50 (m, 4H), 4.35 – 4.33 (m, 1H), 4.24 – 4.22 (m, 1H), 3.58 – 3.50 (m, 3H), 3.41 – 3.37 (m, 1H), 3.32 – 3.29 (m, 2H), 3.21 – 3.15 (m, 1H), 3.01 – 2.96 (m, 1H), 2.00 – 1.86 (m, 2H), 1.86 – 1.71 (m, 2H).
D.08		98%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 9.48 (s, 1H), 8.61 (d, *J* = 6.5 Hz, 1H), 8.06 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.87 – 7.85 (m, 2H), 7.46 – 7.41 (m, 4H), 7.35 – 7.32 (m, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 4.70 – 4.69 (m, 2H), 4.57 – 4.55 (m, 2H), 4.32 – 4.28 (m, 1H), 3.74 – 3.68 (m, 1H), 3.29 – 3.21 (m, 4H), 3.10 – 3.05 (m, 1H), 2.24 – 2.21 (m, 1H), 2.13 – 2.06 (m, 1H), 1.94 – 1.90 (m, 2H), 1.81 – 1.74 (m, 1H).
D.09		99%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.01 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.87 – 7.85 (m, 4H), 7.45 – 7.42 (m, 6H), 7.35 – 7.31 (m, 2H), 7.23 – 7.18 (m, 4H), 4.68 – 4.66 (m, 4H), 4.53 – 4.50 (m, 4H), 4.35 – 4.33 (m, 1H), 4.24 – 4.22 (m, 1H), 3.57 – 3.51 (m, 3H), 3.41 – 3.37 (m, 1H), 3.33 – 3.27 (m, 2H), 3.20 – 3.16 (m, 1H), 3.00 – 2.96 (m, 1H), 1.99 – 1.87 (m, 2H), 1.86 – 1.72 (m, 2H).

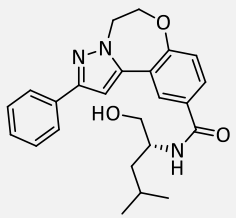
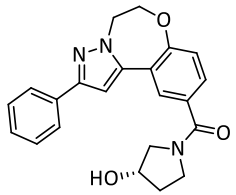
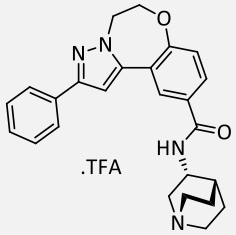
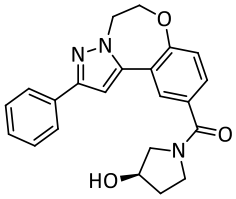
D.10		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.27 (t, *J* = 6.0 Hz, 1H), 8.02 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.86 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.40 (s, 1H), 7.35 – 7.31 (m, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 4.69 – 4.67 (m, 2H), 4.56 – 4.54 (m, 2H), 3.89 – 3.85 (m, 2H), 3.29 (td, *J* = 12.0, 2.0 Hz, 2H), 3.17 (t, *J* = 6.0 Hz, 2H), 1.84 – 1.74 (m, 1H), 1.67 – 1.60 (m, 2H), 1.23 (qd, *J* = 12.0, 4.5 Hz, 2H).
D.11		93%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.87 – 7.85 (m, 2H), 7.45 – 7.42 (m, 3H), 7.35 – 7.31 (m, 1H), 7.28 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.23 – 7.20 (m, 1H), 4.70 - 4.67 (m, 2H), 4.58 – 4.50 (m, 2H), 3.86 – 3.79 (m, 1H), 3.74 – 3.68 (m, 1H), 3.31 (t, *J* = 6.0 Hz, 2H), 2.12 – 2.01 (m, 2H), 2.00 – 1.90 (m, 2H).
D.12		98%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 9.17 (s, 1H), 8.36 (t, *J* = 6.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.87 (dd, *J* = 8.0 2.0 Hz, 2H), 7.47 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.41 (s, 1H), 7.35 – 7.31 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 4.69 – 4.68 (m, 2H), 4.57 – 4.55 (m, 2H), 3.48 – 3.41 (m, 2H), 3.18 (t, *J* = 6.0 Hz, 2H), 2.98 – 2.87 (m, 2H), 2.76 (d, *J* = 5.0 Hz, 2H), 1.96 – 1.88 (m, 2H), 1.82 – 1.76 (m, 1H), 1.41 – 1.34 (m, 2H).
D.13		68%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.46 (s, 1H), 7.45 – 7.42 (m, 2H), 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.25 – 7.21 (m, 1H), 4.71 – 4.68 (m, 2H), 4.62 – 4.50 (m,2H), 4.27 – 4.21 (m, 1H), 3.92 – 3.86 (m, 1H), 3.64 – 3.58 (m, 2H), 3.35 – 3.32 (m, 1H), 3.26 – 3.16 (m, 2H), 3.07 – 3.01 (m, 1H).

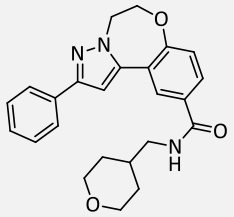
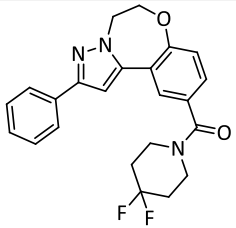
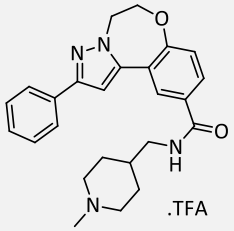
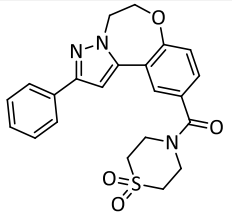
D.14		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.92 (t, *J* = 6.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.88 – 7.86 (m, 2H), 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.41 (s, 1H), 7.35 – 7.31 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.23 (s, 1H), 4.71 – 4.69 (m, 2H), 4.61 – 4.58 (m, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 2.22 (s, 3H).
D.15		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.00 (t, *J* = 5.5 Hz, 1H), 8.96 (s, 1H), 8.09 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.61 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.45 – 7.42 (m, 3H), 7.35 – 7.31 (m, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 5.5 Hz, 2H), 4.71 – 4.69 (m, 2H), 4.60 – 4.58 (m, 2H), 3.82 (s, 3H).
D.16		98%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.32 (t, *J* = 5.5 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.35 – 7.31 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 4.69 – 4.67 (m, 2H), 4.59 – 4.57 (m, 2H), 3.53 – 3.46 (m, 4H), 3.44 – 3.41 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 3H).
D.17		90%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.17 (t, *J* = 6.0 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.76 (d, *J* = 3.0 Hz, 1H), 7.65 (d, *J* = 3.0 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.35 – 7.31 (m, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 2H), 4.71 - 4.69 (m, 2H), 4.63 – 4.60 (m, 2H).
D.18		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.63 (t, *J* = 5.5 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.84 – 7.81 (m, 1H), 7.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.41 (s, 1H), 7.35 – 7.31 (m, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 4.73 – 4.69 (m, 2H), 4.67 – 4.63 (m, 2H), 3.91 (d, *J* = 5.5 Hz, 2H), 2.64 (d, *J* = 4.5 Hz, 3H).

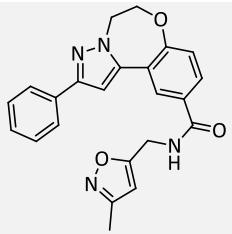
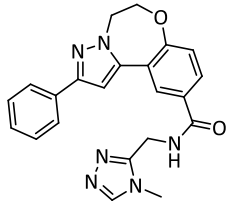
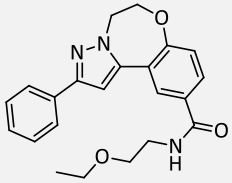
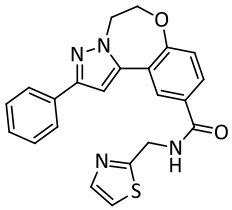
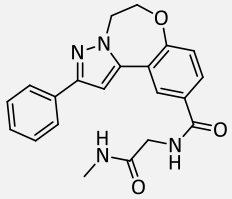
D.19		97%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.51 (s, 1H), 8.73 (t, *J* = 5.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.78 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.42 (s, 1H), 7.35 – 7.32 (m, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 4.74 – 4.71 (m, 2H), 4.69 – 4.65 (m, 2H), 4.58 – 4.52 (m, 1H), 4.39 – 4.32 (m, 1H), 4.26 – 4.20 (m, 1H), 4.15 – 4.10 (m, 1H), 3.57 – 3.50 (m, 1H), 3.47 – 3.40 (m, 3H), 3.19 – 3.13 (m, 1H), 3.04 – 2.97 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H).
D.20		92%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.03 – 7.99 (m, 1H), 7.89 – 7.84 (m, 2H), 7.46 – 7.42 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 4.69 – 4.65 (m, 2H), 4.54 – 4.46 (m, 2H), 3.97 – 3.92 (m, 0.8H), 3.83 – 3.77 (m, 1.2H), 3.48 – 3.38 (m, 2H), 3.34 (sept, *J* = 7.0 Hz, 0.7H), 3.21 – 3.05 (m, 1.6H), 3.01 – 2.95 (m, 0.7H), 1.94 – 1.72 (m, 2H), 1.71 – 1.58 (m, 1.4H), 1.46 – 1.41 (m, 0.6H), 1.18 (t, *J* = 7.0 Hz, 1.8H), 0.94 (t, *J* = 7.0 Hz, 1.2H).
D.21		93%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.35 (t, *J* = 6.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.66 (s, 1H), 7.53 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.34 – 7.30 (m, 1H), 7.23 – 7.19 (m, 1H), 4.70 – 4.66 (m, 2H), 4.58 – 4.52 (m, 2H), 4.18 – 4.12 (m, 0.2H), 3.74 – 3.69 (m, 0.8H), 3.40 – 3.35 (m, 1H), 3.31 – 3.08 (m, 1H), 2.35 – 2.10 (m, 3H), 1.90 – 1.79 (m, 1H).
D.22		82%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.30 (t, *J* = 6.0 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.46 – 7.41 (m, 3H), 7.40 (s, 1H), 7.35 – 7.31 (m, 1H), 7.22 – 7.19 (m, 1H), 4.70 – 4.66 (m, 2H), 4.57 – 4.53 (m, 2H), 4.42 – 4.21 (m, 2H), 3.20 – 3.15

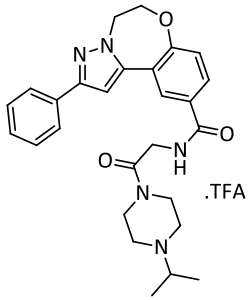
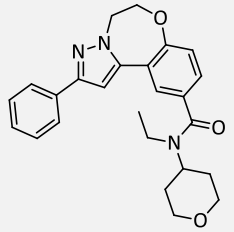
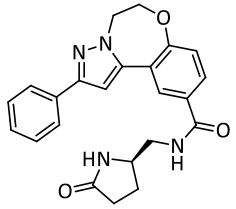
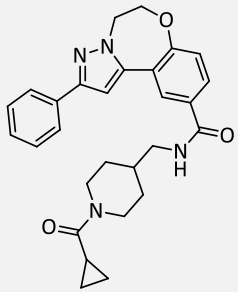
			(m, 2H), 3.12 – 3.04 (m, 1H), 2.64 – 2.54 (m, 1H), 1.99 – 1.95 (m, 1H), 1.87 – 1.66 (m, 3H), 1.23 – 0.98 (m, 2H), 0.77 – 0.63 (m, 4H).
D.23		99%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.63 (t, *J* = 5.5 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.95 (t, *J* = 6.0 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.71 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.41 (s, 1H), 7.35 – 7.31 (m, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.67 -4.63 (m, 2H), 3.93 (d, *J* = 5.5 Hz, 2H), 3.38 (t, *J* = 6.0 Hz, 2H), 3.29 (q, *J* = 6.0 Hz, 2H), 3.26 (s, 3H).
D.24		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.47 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46 - 7.41 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 4.74 – 4.69 (m, 2H), 4.64 – 4.59 (m, 2H), 4.42 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.20 (sept, *J* = 7.0 Hz, 1H), 0.98 (t, *J* = 7.0 Hz, 6H).
D.25		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.48 (d, *J* = 9.0 Hz, 1H), 8.11 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.81 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.36 – 7.27 (m, 2H), 4.76 – 4.71 (m, 2H), 4.69 – 4.64 (m, 2H), 4.45 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.26 (qd, *J* = 6.5, 3.0 Hz, 1H), 1.17 (d, *J* = 6.5 Hz, 3H).
D.26		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.51 (d, *J* = 7.5 Hz, 1H), 8.05 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.35 - 7.29 (m, 5H), 7.27 – 7.20 (m, 2H), 4.73 – 4.68 (m, 1H), 4.67 – 4.62 (m, 2H), 4.42 – 4.37 (m, 2H), 3.21 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.07 (dd, *J* = 14.0, 9.0 Hz, 1H).

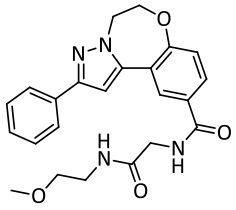
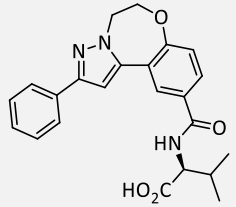
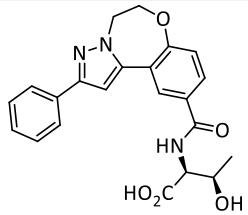
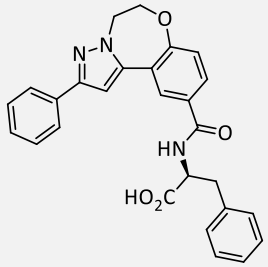
D.27		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.07 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.48 – 7.41 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.18 (m, 2H), 4.74 – 4.56 (m, 4H), 3.71 – 3.12 (m, 8H), 2.85 (s, 3H).
E.02		84%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 7.94 (d, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.53 (s, 1H), 7.44 – 7.40 (m, 2H), 7.33 – 7.30 (m, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.72 – 4.68 (m, 2H), 4.55 – 4.52 (m, 2H), 3.49 – 3.41 (m, 2H), 3.31 – 3.20 (m, 2H), 1.18 – 1.09 (m, 6H).
E.03		98%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 9.25 (t, *J* = 6.0 Hz, 1H), 8.61 (d, *J* = 4.5 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 7.98 (t, *J* = 7.5 Hz, 1H), 7.89 – 7.82 (m, 3H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.74 – 4.70 (m, 2H), 4.68 (d, *J* = 6.0 Hz, 2H), 4.58 – 4.54 (m, 2H).
E.04		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 9.75 (s, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.48 -7.42 (m, 3H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.69 (m, 2H), 4.57 – 4.53 (m, 2H), 3.79 – 3.72 (m, 2H), 3.58 - 3.40 (m, 6H), 3.24 - 3.20 (m, 2H), 3.18 – 3.09 (m, 2H).
E.05		94%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.57 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.5, 2.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.50 (s, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.62 – 4.58 (m, 2H), 4.56 – 4.50 (m, 2H), 3.44 - 3.40 (q, 7.0 Hz, 2H) 3.14 – 3.04 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H).

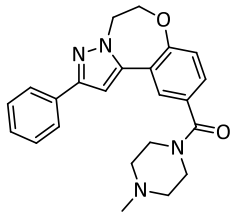
E.06		94%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.39 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.35 – 7.31 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.69 (m, 2H), 4.57 – 4.52 (m, 2H), 4.13 – 4.07 (m, 1H), 3.46 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.39 (dd, *J* = 10.5, 6.0 Hz, 1H), 1.69 – 1.61 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 – 1.38 (m, 1H), 0.90 (2d, *J* = 6.5 Hz, 6H).
E.07		88%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.09 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.53 – 7.50 (m, 1H), 7.45 – 7.40 (m, 3H), 7.34 – 7.30 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.72 – 4.69 (m, 2H), 4.56 - 4.52 (m, 2H), 4.37 – 4.33 (m, 0.5H), 4.27 – 4.24 (m, 0.5H), 3.71 – 3.64 (m, 1H), 3.62 – 3.57 (m, 1H), 3.55 – 3.48 (m, 1H), 3.41 – 3.23 (m, 1H), 2.01 – 1.89 (m, 1H), 1.87 – 1.78 (m, 1H).
E.08		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.52 (s, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.87 (m, 2H), 7.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.42 (s, 1H), 7.36 – 7.32 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 4.77 – 4.69 (m, 2H), 4.60 – 4.52 (m, 2H), 4.35 – 4.29 (m, 1H), 3.76 – 3.69 (m, 1H), 3.37 – 3.22 (m, 5H), 2.26 – 2.21 (m, 1H), 2.19 – 2.12 (m, 1H), 1.95 – 1.90 (m, 2H), 1.80 – 1.72 (m, 1H).
E.09		82%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.09 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.53 – 7.50 (m, 1H), 7.48 -7.40 (m, 3H), 7.34 – 7.30 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.72 – 4.69 (m, 2H), 4.56 – 4.52 (m, 2H), 4.37 – 4.33 (m, 0.5H), 4.27 -4.23 (m, 0.5H), 3.71 – 3.52 (m, 3H), 3.42 – 3.24 (m, 1H), 2.00 – 1.89 (m, 1H), 1.87 – 1.79 (m, 1H).

E.10		90%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.52 (t, *J* = 6.0 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 7.88 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.78 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 -7.42 (m, 3H), 7.36 – 7.31 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.72 – 4.69 (m, 2H), 4.56 – 4.53 (m, 2H), 3.85 (dd, *J* = 11.5, 2.5 Hz, 2H), 3.27 (td, *J* = 11.5, 2.5 Hz, 2H), 3.22 – 3.18 (m, 2H), 1.87 – 1.78 (m, 1H), 1.65 – 1.58 (m, 2H), 1.27 -1.18 (m, 2H).
E.11		91%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.04 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.51 (s, 1H), 7.45 – 7.41 (m, 2H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 4.72 – 4.69 (m, 2H), 4.56 – 4.53 (m, 2H), 3.82 – 3.46 (m, 4H), 2.13 – 2.02 (m, 4H).
E.12		84%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.14 (s, 1H), 8.61 (t, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.37 – 7.32 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.57 – 4.53 (m, 2H), 3.46 – 3.41 (m, 2H), 3.23 (t, *J* = 6.0 Hz, 2H), 2.95 – 2.87 (m, 2H), 2.75 (d, *J* = 5.0 Hz, 2H), 1.94 – 1.87 (m, 2H), 1.84 – 1.78 (m, 1H), 1.43 – 1.34 (m, 2H).
E.13		93%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.07 (d, *J* = 2.1 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.47 (s, 1H), 7.45 – 7.40 (m, 3H), 7.35 – 7.31 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.72 – 4.70 (m, 2H), 4.56 – 4.53 (m, 2H), 4.06 – 3.73 (m, 4H), 3.30 – 3.24 (m, 4H).

E.14		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.18 (t, *J* = 6.0 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.81 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.36 – 7.31 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.24 (s, 1H), 4.73 – 4.70 (m, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 4.57 – 4.54 (m, 2H), 2.20 (s, 3H).
E.15		96%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.26 (t, *J* = 5.5 Hz, 1H), 8.92 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.82 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 – 7.42 (m, 3H), 7.36 – 7.32 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.76 (d, *J* = 5.5 Hz, 2H), 4.73 – 4.71 (m, 2H), 4.57 – 4.54 (m, 2H), 3.80 (s, 3H).
E.16		86%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.59 (t, *J* = 5.5 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 – 7.43 (m, 3H), 7.36 – 7.32 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.56 – 4.53 (m, 2H), 3.54 – 3.50 (m, 2H), 3.49 – 3.45 (m, 4H), 1.12 (t, *J* = 7.0 Hz, 3H).
E.17		93%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.44 (t, *J* = 6.0 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.84 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.75 (d, *J* = 3.0 Hz, 1H), 7.64 (d, *J* = 3.0 Hz, 1H), 7.46 (s, 1H), 7.46 – 7.42 (m, 2H), 7.35 – 7.31 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 4.81 (d, *J* = 6.0 Hz, 2H), 4.74 – 4.71 (m, 2H), 4.58 – 4.55 (m, 2H).
E.18		75%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.82 (t, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.85 (m, 3H), 7.82 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 (s, 1H), 7.46 – 7.42 (m, 2H), 7.36 – 7.31 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.57 – 4.53 (m, 2H), 3.87 (d, *J* = 6.0 Hz, 2H), 2.61 (d, *J* = 4.5 Hz, 3H).

E.19		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 9.57 (s, 1H), 8.74 (t, *J* = 6.0 Hz, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.81 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 – 7.43 (m, 3H), 7.36 – 7.32 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.74 – 4.71 (m, 2H), 4.58 – 4.55 (m, 2H), 4.54 – 4.48 (m, 1H), 4.28 – 4.18 (m, 4H), 3.58 – 3.53 (m, 1H), 3.49 – 3.44 (m, 2H), 3.16 – 3.09 (m, 1H), 3.00 - 2.94 (M, 2H), 1.27 (d, *J* = 7.0 Hz, 6H).
E.20		97%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.94 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.52 (s, 1H), 7.44 – 7.40 (m, 2H), 7.34 – 7.30 (m, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.72 – 4.70 (m, 2H), 4.55 – 4.52 (m, 2H), 3.93 – 3.59 (m, 3H), 3.42 – 3.02 (m, 4H), 1.98 – 1.79 (m, 2H), 1.72 – 1.61 (m, 2H), 1.24 – 1.01 (m, 3H).
E.21		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.56 (t, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.81 – 7.75 (m, 2H), 7.48 – 7.42 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.74 – 4.70 (m, 2H), 4.57 – 4.53 (m, 2H), 3.77 – 3.70 (m, 1H), 3.40 – 3.23 (m, 2H), 2.23 – 2.09 (m, 3H), 1.84 – 1.73 (m, 1H).
E.22		89%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.55 (t, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 – 7.43 (m, 3H), 7.36 – 7.32 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.56 – 4.54 (m, 2H), 4.39 – 4.32 (m, 1H), 4.27 – 4.23 (m, 1H), 3.24 – 3.19 (m, 2H), 3.09 – 3.02 (m, 1H), 2.61 – 2.53 (m, 1H), 1.99 – 1.93 (m, 1H), 1.89 – 1.83 (m, 1H), 1.80 – 1.68 (m, 2H), 1.17 – 1.00 (m, 2H), 0.73 – 0.66 (m, 4H).

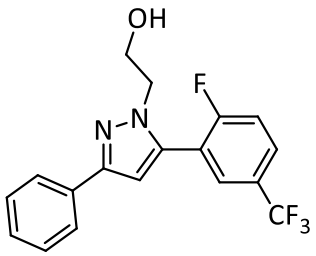
E.23		78%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.80 (t, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.00 (t, *J* = 6.0 Hz, 1H), 7.89 – 7.85 (m, 2H), 7.81 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 (s, 1H), 7.47 – 7.43 (m, 2H), 7.36 – 7.32 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.71 (m, 2H), 4.57 – 4.54 (m, 2H), 3.90 (d, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 3.27 – 3.25 (m, 5H).
E.24		97%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.53 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H), 7.90 – 7.82 (m, 3H), 7.50 – 7.41 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.77 – 4.68 (m, 2H), 4.59 – 4.54 (m, 2H), 4.33 (app t, *J* = 7.5 Hz, 1H), 2.22 (sept, *J* = 7.0 Hz, 1H), 1.00 (2d, *J* = 7.0 Hz, 6H).
E.25		99%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 12.65 (s, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.84 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 4.74 – 4.70 (m, 2H), 4.59 – 4.55 (m, 2H), 4.47 (dd, *J* = 8.5, 4.0 Hz, 1H), 4.25 – 4.19 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H).
E.26		95%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 12.78 (s, 1H), 8.77 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 3H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.68 – 4.62 (td, *J* = 10.5, 4.5 Hz, 1H), 4.56 – 4.52 (m, 2H), 3.23 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.11 (dd, *J* = 13.5, 10.5 Hz, 1H).

E.27		99%	^{1}H NMR (250 MHz, DMSO-d_6), ppm: 7.98 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.48 – 7.32 (m, 4H), 7.27 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.67 (m, 2H), 4.61 – 4.54 (m, 2H), 3.77 (dd, *J* = 5.5, 4.0 Hz, 4H), 3.16 (app t, *J* = 5.0 Hz, 4H), 2.78 (s, 3H).

Amongst the above list, the following compounds were synthesised for full characterisation.

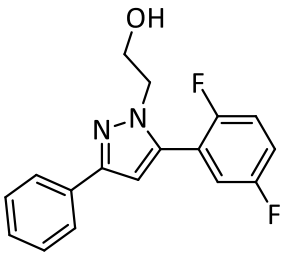
General Procedure K – A solution of potassium trifluoro(1-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-5-yl)borate **38A** (1.1 eq), coupling partner (1 eq), $Pd(OAc)_2$ (7 mol%), XPhos (14 mol%) and Na_2CO_3 (2 eq) in ethanol (0.2 M) was heated under microwave irradiation at 120 °C for 45 min (settings: high absorption, no stirring during the reaction and 60 seconds pre-stirring time). All volatiles were then removed under vacuum and the residue dissolved in water. The aqueous layer was extracted with DCM (an acidified aqueous layer was sometimes necessary in order to extract all of the crude organic material). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum before being purified by column chromatography to yield the desired coupled product.

2-(5-(2-Fluoro-5-(trifluoromethyl)phenyl)-3-phenyl-1H-pyrazol-1-yl)ethanol, A.03



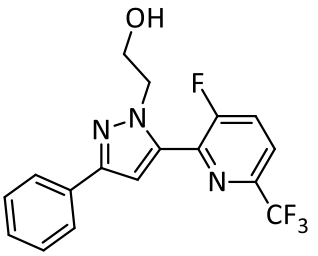
Following general procedure K, using 2-bromo-1-fluoro-4-(trifluoromethyl)benzene (123 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (87 mg, 50% yield). **^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 8.09 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.98 – 7.95 (m, 1H), 7.86 – 7.84 (m, 2H), 7.66 (t, *J* = 9.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 – 7.30 (m, 1H), 6.97 (s, 1H), 4.07 (t, *J* = 5.5 Hz, 2H), 3.77 (t, *J* = 5.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 161.1 (d, *J* = 253.0 Hz), 149.8, 137.0, 132.9, 129.6, 128.7, 127.7, 125.7 (q, *J* = 33.2 Hz), 125.1, 125.0, 122.3, 119.3 (d, *J* = 16.5 Hz), 117.4 (d, *J* = 23.5 Hz), 105.0, 60.0, 52.0. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -60.4, -107.6. **FTIR (neat, cm^{-1}), ν_{max}:** 3346 (w), 3069 (w), 2445 (w), 1629 (m), 1599 (s), 1552 (w), 1517 (m), 1071 (s). **HRMS** calculated for $C_{18}H_{14}F_4N_2O$ (ESI^+): 351.1115. Found: 351.1123.

2-(5-(2,5-Difluorophenyl)-3-phenyl-1H-pyrazol-1-yl)ethanol, A.06



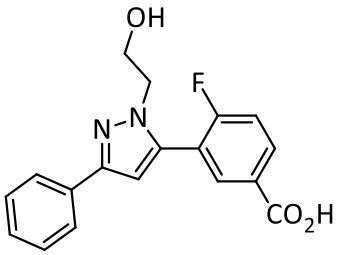
Following general procedure K, using 2-bromo-1,4-difluorobenzene (96 mg, 0.50 mmol), **38A** (171 mg, 0.55 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), XPhos (37 mg, 0.08 mmol) and Na_2CO_3 (112 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (98 mg, 65% yield**. ^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 7.85 – 7.83 (m, 2H), 7.56 (ddd, *J* = 9.0, 6.0, 3.0 Hz, 1H), 7.47 (td, *J* = 9.0, 5.0 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.34 – 7.30 (m, 1H), 6.90 (s, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.77 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 157.9 (dd, *J* = 241.5, 2.0 Hz), 155.3 (dd, *J* = 243.0, 2.0 Hz), 149.7, 137.4, 133.0, 128.7, 127.6, 125.1, 119.5 (dd, *J* = 18.0, 9.5 Hz), 118.3 (dd, *J* = 25.0, 2.5 Hz), 117.8 (dd, *J* = 9.0, 2.5 Hz), 117.5 (dd, *J* = 8.5, 4.0 Hz), 104.7 (d, *J* = 1.0 Hz), 60.0, 51.8. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -118.1, -119.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3285 (w), 3068 (w), 2981 (w), 2955 (w), 2913 (w), 1485 (s), 1462 (w), 1050 (s). **HRMS** calculated for $C_{17}H_{14}F_2N_2O$ (ESI^+): 301.1147. Found: 301.1149.

2-(5-(3-Fluoro-6-(trifluoromethyl)pyridin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, A.12



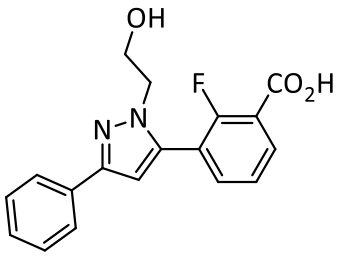
Following general procedure K, using 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine (127 mg, 0.50 mmol), **38A** (163 mg, 0.55 mmol), $Pd(OAc)_2$ (7 mg, 0.04 mmol), XPhos (33 mg, 0.08 mmol) and Na_2CO_3 (109 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (100 mg, 55% yield). **^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 8.22 (t, *J* = 9.0 Hz, 1H), 8.09 (dd, *J* = 9.0, 3.5 Hz, 1H), 7.88 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.37 – 7.32 (m, 1H), 7.25 (d, *J* = 3.5 Hz, 1H), 4.58 (t, *J* = 6.0 Hz, 2H), 3.73 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 157.6 (d, *J* = 265.5 Hz), 149.4, 141.8 (d, *J* = 34.5 Hz), 138.4 (d, *J* = 14.5 Hz), 135.5 (d, *J* = 5.5 Hz), 132.6, 128.7, 127.8, 126.7 (app d, *J* = 21.5 Hz), 125.2, 122.7, 119.7, 106.0 (d, *J* = 8.0 Hz), 60.4, 53.2. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -65.9, -114.3. **FTIR (neat, cm^{-1}), ν_{max}:** 3332 (w), 3048 (w), 2968 (w), 2934 (w), 2886 (w), 1486 (m), 1448 (m), 1339 (s), 1047 (s). **HRMS** calculated for $C_{17}H_{13}F_4N_3O$ (ESI^+): 352.1068. Found: 352.1072.

4-Fluoro-3-(1-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)benzoic acid, A.14



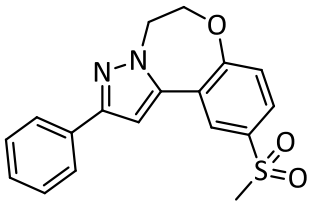
Following general procedure K, using 3-bromo-4-fluorobenzoic acid (677 mg, 3.09 mmol), **38A** (1.01 g, 3.40 mmol), $Pd(OAc)_2$ (48 mg, 0.22 mmol), XPhos (210 mg, 0.43 mmol) and Na_2CO_3 (657 mg, 6.18 mmol) in ethanol (15 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (454 mg, 45% yield). **^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 8.19 – 8.08 (m, 2H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 4.80 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.74 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (151 MHz, DMSO-d_6), ppm:** 166.0, 161.6 (d, *J* = 253.0 Hz), 149.8, 137.7, 133.4 (d, *J* = 3.5 Hz), 133.0, 132.6 (d, *J* = 9.5 Hz), 128.6, 127.7 (d, *J* = 3.0 Hz), 127.6, 125.1, 118.5 (d, *J* = 16.0 Hz), 116.5 (d, *J* = 23.0 Hz), 104.7, 59.9, 51.9. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -65.9, -114.3. **FTIR (neat, cm^{-1}), ν_{max}:** 3359 (w), 3063 (w), 2959 (w), 1713 (s), 1463 (m), 1426 (m), 1226 (s), 1040 (s). **HRMS** calculated for $C_{18}H_{15}FN_2O_3$ (ESI^+): 327.1139. Found: 327.1145.

2-Fluoro-3-(1-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)benzoic acid, A.16



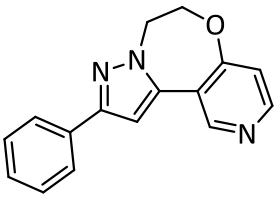
Following general procedure K, using 3-bromo-2-fluorobenzoic acid (110 mg, 0.50 mmol), **38A** (163 mg, 0.55 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (87 mg, 48% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.02 – 7.95 (m, 1H), 7.88 – 7.78 (m, 3H), 7.46 – 7.40 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 164.8, 157.9 (d, *J* = 259.0 Hz), 149.6, 137.8, 136.2, 133.0, 132.7, 128.7, 127.6, 125.1, 124.5 (d, *J* = 4.5 Hz), 120.2 (d, *J* = 11.0 Hz), 119.6 (d, *J* = 16.0 Hz), 104.7, 60.0, 51.8. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -74.9, -112.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3370 (w), 3076 (w), 2950 (w), 1696 (s), 1620 (m), 1589 (s), 1551 (w), 1294 (s), 1061 (m). **HRMS** calculated for $C_{18}H_{15}FN_2O_3$ (ESI^+): 327.1139. Found: 327.1143.

10-(Methylsulfonyl)-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine, C.02



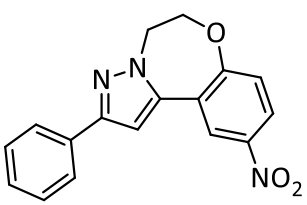
Following general procedure K, using 2-bromo-1-fluoro-4-(methylsulfonyl)benzene (127 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), XPhos (33 mg, 0.08 mmol) and Na_2CO_3 (108 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (43 mg, 25% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.46 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.62 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 4.76 – 4.72 (m, 2H), 4.63 – 4.59 (m, 2H), 3.30 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 158.6, 149.8, 139.7, 135.0, 132.7, 128.8, 128.7, 127.8, 125.1, 122.0, 117.3, 103.2, 68.8, 54.1, 43.6. **FTIR (neat, cm^{-1}), ν_{max}:** 3067 (w), 2997 (w), 2916 (w), 1601 (m), 1571 (s), 1539 (w), 1510 (m). **HRMS** calculated for $C_{18}H_{16}N_2O_3S$ (ESI^+): 341.0954. Found: 341.0958.

10-Phenyl-6,7-dihydropyrazolo[1,5-d]pyrido[3,4-f][1,4]oxazepine, C.04



Following general procedure K, using 3-bromo-4-fluoropyridine (91 mg, 0.50 mmol), **38A** (178 mg, 0.55 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), XPhos (35 mg, 0.08 mmol) and Na_2CO_3 (124 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (107 mg, 79% yield). **^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 9.25 (s, 1H), 8.47 (d, *J* = 6.0 Hz, 1H), 7.86 – 7.84 (m, 2H), 7.65 (s, 1H), 7.47 – 7.43 (m, 2H), 7.37 – 7.33 (m, 1H), 7.29 (d, *J* = 6.0 Hz, 1H), 4.80 – 4.77 (m, 2H), 4.73 – 4.70 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 163.4, 158.3 (d, *J* = 35.5 Hz), 150.0, 145.8 (d, *J* = 266.5 Hz), 137.1, 132.5, 128.8, 127.9, 125.0, 117.2, 114.3, 102.7, 69.8, 53.6. **FTIR (neat, cm^{-1}), ν_{max}:** 3052 (w), 1603 (s), 1567 (m), 1532 (w), 1508 (s). **HRMS** calculated for $C_{16}H_{13}N_3O$ (ESI^+): 264.1131. Found: 264.1135.

10-Nitro-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine, C.07

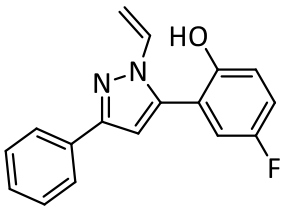


Following general procedure K, using 2-bromo-1-fluoro-4-nitrobenzene (111 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), XPhos (38 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL), the title compound was

obtained after reverse phase chromatography as a colourless oil (77 mg, 50% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.79 (d, *J* = 3.0 Hz, 1H), 8.12 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.69 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 4.76 – 4.74 (m, 2H), 4.65 – 4.63 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 159.8, 149.9, 142.3, 139.2, 132.6, 128.6, 127.8, 125.2, 125.1, 124.3, 122.4, 117.1, 103.5, 69.0, 54.0. **FTIR (neat, cm^{-1}), ν_{max}:** 3143 (w), 2931 (w), 1578 (m), 1522 (m), 1506 (m), 1483 (m), 1462 (m), 1346 (s), 1315 (m). **HRMS** calculated for $C_{17}H_{13}N_3O_3$ (ESI^+): 308.1030. Found: 308.1031.

General Procedure L – In a sealable tube, NaH (5 eq – 60% in paraffin) was added to a solution of starting material (1 eq) in *N,N*-DMF (0.07 M) at 80°C. The reaction was left to stir overnight. After completion, water was added. The aqueous layer was acidified to pH 1 with HCl 37% and it was then extracted with CH_2Cl_2. The combined organic layers were dried under Na_2SO_4, filtered and all volatiles were removed again. The residue was then purified using reversed phase chromatography to yield the desired coupled compounds.

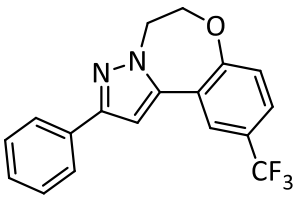
4-Fluoro-2-(3-phenyl-1-vinyl-1H-pyrazol-5-yl)phenol, B.06



Following general procedure L, using **A.06** (99 mg, 0.33 mmol), and NaH (68 mg, 1.66 mmol) in *N,N*-DMF (5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (22 mg, 22% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 10.01 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 9.0, 3.0 Hz, 1H), 7.14 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.02 - 6.96 (m, 1H), 6.91 (s, 1H), 6.82 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.67 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 155.1 (d, *J* = 235.5 Hz), 151.4 (d, *J* = 1.0 Hz), 151.0, 140.7 (d, *J* = 1.0 Hz), 132.5, 131.0, 128.8, 128.7, 128.2, 125.5, 117.6 (d, *J* = 23.5 Hz), 117.1 (d, *J* = 20.5 Hz), 117.0 (d, *J* = 7.0 Hz), 105.7, 100.1. **^{19}F NMR (101 MHz, DMSO-d_6), ppm:** -74.2, -125.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3065 (m), 2914 (w), 2861 (w), 1646 (s), 1497 (s), 1463 (s), 1448 (s), 1430 (m), 11184 (s) **HRMS** calculated for $C_{17}H_{13}FN_2O$ (ESI^+): 281.1085. Found: 281.1087.

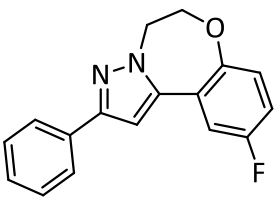
Modified General Procedure L – In a sealable tube, NaH (1.1 eq – 60% in paraffin) was added to a solution of starting material (1 eq) in *N,N*-DMF (0.07 M) at 80 °C. The reaction was left to stir overnight. After completion, water was added. The aqueous layer was acidified to pH 1 with HCl 37% and it was then extracted with CH_2Cl_2. The combined organic layers were dried under Na_2SO_4, filtered and all volatiles were removed again. The residue was then purified using reversed phase chromatography to yield the desired coupled compounds.

2-Phenyl-10-(trifluoromethyl)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine, C.03



Following modified general procedure L, using **A.03** (60 mg, 0.17 mmol), and NaH (8 mg, 0.19 mmol) in *N,N*-DMF (3 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (46 mg, 81% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.31 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.68 (s, 1H), 7.62 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 4.74 – 4.72 (m, 2H), 4.59 – 4.57 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 157.8, 149.8, 139.8, 132.7, 128.6, 127.7, 126.4 (dd, *J* = 69.8, 3.7 Hz), 125.5, 125.1, 123.4 (q, *J* = 32.4 Hz), 122.8, 122.1, 117.4, 103.3, 68.6, 54.2. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -60.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3058 (w), 2981 (w), 2926 (w), 1622 (s), 1583 (s), 1543 (w), 1516 (m). **HRMS** calculated for $C_{18}H_{13}F_3N_2O$ (ESI^+): 331.1053. Found: 331.1056.

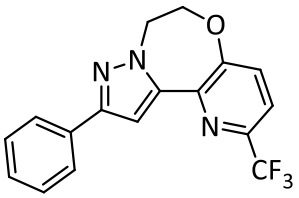
10-Fluoro-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine, C.05



Following modified general procedure L, using **A.06** (61 mg, 0.20 mmol), and NaH (11 mg, 0.22 mmol) in *N,N*-DMF (3.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (32 mg, 57% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.86 - 7.80 (m, 3H), 7.51 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 - 7.30 (m, 1H), 7.21 – 7.12 (m, 1H), 7.11 - 7.07 (m, 1H), 4.71 - 4.66 (m, 2H), 4.51 - 4.47 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 157.5 (d, *J* = 237.5 Hz), 152.0 (d, *J* = 1.6 Hz), 149.7, 140.1 (d, *J* = 2.1 Hz), 132.8, 128.8 (d, *J* = 28.0 Hz), 127.7, 125.2 (d, *J* = 27.9 Hz), 122.6 (d, *J* = 8.8 Hz), 118.7 (d, *J* = 8.5 Hz), 116.4 (d, *J* = 23.3 Hz), 114.6 (d, *J* = 25.1 Hz), 103.1, 68.4, 54.5. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -121.3.

FTIR (neat, cm^{-1}), ν_{max}: 3063 (w), 2922 (w), 1557 (m), 1497 (m), 1180 (s). **HRMS** calculated for $C_{17}H_{13}FN_2O$ (ESI^+): 281.1085. Found: 281.1091.

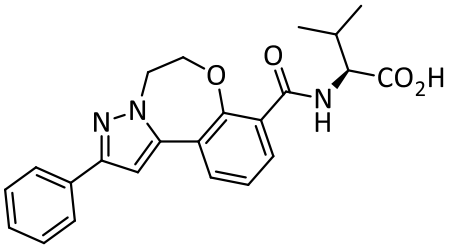
10-Phenyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-d]pyrido[2,3-f][1,4]oxazepine, C.06



Following modified general procedure L, using **A.12** (69 mg, 0.20 mmol), and NaH (12 mg, 0.22 mmol) in *N,N*-DMF (3.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (46 mg, 71% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.89 (d, *J* = 7.0 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 4.81 – 4.79 (m, 2H), 4.69 – 4.67 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 154.2, 149.6, 141.5, 140.0 (d, *J* = 34.9 Hz), 135.7, 132.5, 130.4 (broad), 128.7, 127.8, 125.2, 121.9 (d, *J* = 168.2 Hz), 120.6 (d, *J* = 102.7 Hz), 104.5, 68.5, 54.4. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -65.6. **FTIR (neat, cm^{-1}), ν_{max}:** 1593 (w), 1487 (m), 1455 (m), 1441 (m), 1354 (s), 1333 (s), 1286 (s), 1223 (s), 1163 (s), 1142 (s), 1120 (s). **HRMS** calculated for $C_{17}H_{12}F_3N_3O$ (ESI^+): 332.1005. Found: 332.1011.

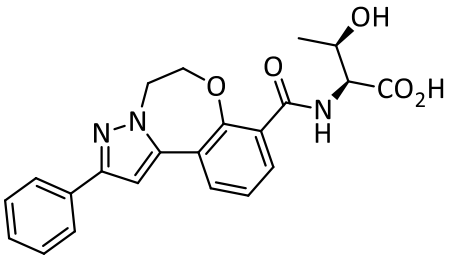
General Procedure M – TSTU (1.1 eq) and diisopropylethylamine (2 eq) were added to a solution of carboxylic acid (2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid or **C.01**, 1 eq) in THF (0.2 M). The reaction was stirred for 1 hr at rt, before all volatiles were removed. The amino acid (1.2 eq) and diisopropylamine (5 eq) were added to the residue redissolved in ethanol (0.2 M) at rt. Upon completion, all volatiles were removed and the crude was purified by reverse phase chromatography to yield the desired coupling product.

(S)-3-Methyl-2-(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxamido)butanoic acid, D.24



Following general procedure M, using 2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid (61 mg, 0.20 mmol), TSTU (73 mg, 0.22 mmol) and diisopropylethylamine (71 µL, 0.40 mmol) in THF (1 mL) then (L)-valine (29 mg, 0.24 mmol) and diisopropylamine (177 µL, 1.00 mmol) in ethanol (1 mL), the title compound was obtained as a colourless oil (54 mg, 67% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.47 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46 - 7.41 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 4.74 – 4.69 (m, 2H), 4.64 – 4.59 (m, 2H), 4.42 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.20 (sept, *J* = 7.0 Hz, 1H), 0.98 (app t, *J* = 7.0 Hz, 6H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 172.9, 165.6, 153.0, 149.8, 141.0, 132.8, 131.2, 129.8, 128.7, 128.6, 127.7, 125.0, 123.1, 119.7, 102.9, 70.0, 57.6, 53.4, 30.1, 19.2, 18.0. **FTIR (neat, cm^{-1}), ν_{max}:** 3365 (w), 2966 (w), 1784 (m), 1670 (m), 1663 (s), 1630 (m), 1478 (s), 1466 (s), 1213 (s). **HRMS** calculated for $C_{23}H_{23}N_3O_4$ (ESI^+): 406.1761. Found: 406.1766.

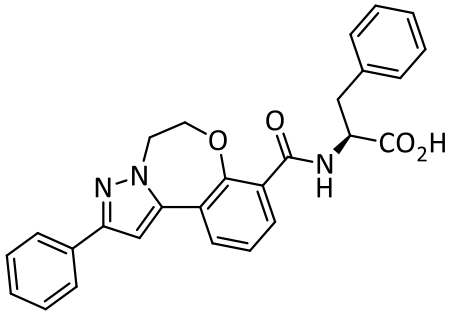
(2S,3R)-3-Hydroxy-2-(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxamido)butanoic acid, D.25



Following general procedure M, using 2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid (61 mg, 0.20 mmol), TSTU (76 mg, 0.22 mmol) and diisopropylethylamine (71 µL, 0.40 mmol) in THF (1 mL) then (L)-threonine (29 mg, 0.24 mmol) and diisopropylamine (178 µL, 1.00 mmol) in ethanol (1 mL), the title compound was obtained as a colourless oil (48 mg, 59% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.48 (d, *J* = 9.0 Hz, 1H), 8.11 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.81 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.36 – 7.27 (m, 2H), 4.76 – 4.71 (m, 2H), 4.69 – 4.64 (m, 2H), 4.45 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.26 (qd, *J* = 6.5, 3.0 Hz, 1H), 1.17 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 172.0, 164.8, 153.6, 149.8, 140.9, 132.8, 132.0, 130.7, 128.7, 127.7, 126.8, 125.1, 123.4, 120.4, 103.1, 70.4, 66.4, 58.1, 53.2, 20.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3367 (w), 2977 (w), 1729 (m), 1637

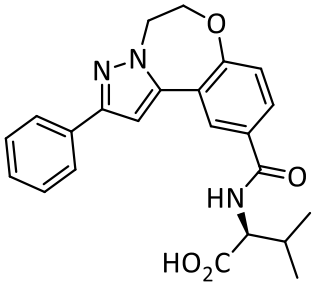
(m), 1527 (m), 1477 (m), 1460 (m). **HRMS** calculated for $C_{22}H_{21}N_3O_5$ (ESI^+): 408.1554. Found: 408.1560.

(S)-3-Phenyl-2-(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxamido)propanoic acid, D.26



Following general procedure M, using 2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid (61 mg, 0.20 mmol), TSTU (78 mg, 0.22 mmol) and diisopropylethylamine (71 µL, 0.40 mmol) in THF (1 mL) then (L)-phenylalanine (40 mg, 0.24 mmol) and diisopropylamine (178 µL, 1.00 mmol) in ethanol (1 mL), the title compound was obtained as a colourless oil (56 mg, 62% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.51 (d, *J* = 7.5 Hz, 1H), 8.05 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.35 - 7.29 (m, 5H), 7.27 – 7.20 (m, 2H), 4.73 – 4.68 (m, 1H), 4.67 – 4.62 (m, 2H), 4.42 – 4.37 (m, 2H), 3.21 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.07 (dd, *J* = 14.0, 9.0 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 172.8, 165.0, 153.2, 149.8, 140.9, 137.5, 132.8, 131.5, 129.9, 129.2, 128.7, 128.3, 127.8, 127.7, 126.6, 125.0, 123.1, 119.8, 102.9, 69.9, 53.8, 53.3, 36.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3370 (w), 2940 (w), 1737 (m), 1630 (m), 1625 (m), 1477 (m), 1456 (m). **HRMS** calculated for $C_{27}H_{23}N_3O_4$ (ESI^+): 454.1761. Found: 454.1766.

(S)-3-Methyl-2-(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-10-carboxamido)butanoic acid, E.24

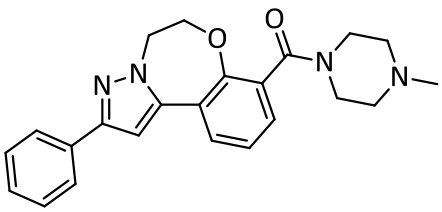


Following general procedure M, using **C.01** (62 mg, 0.20 mmol), TSTU (89 mg, 0.22 mmol) and diisopropylethylamine (71 µL, 0.40 mmol) in THF (1 mL) then (L)-valine (28 mg, 0.24 mmol) and diisopropylamine (177 µL, 1.00 mmol) in ethanol (1 mL), the title compound was obtained as a colourless oil (18 mg, 22% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.53 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H), 7.90 – 7.82 (m, 3H), 7.50 – 7.41 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.77 – 4.68 (m, 2H), 4.59 – 4.54 (m, 2H), 4.33 (app t, *J* = 7.5 Hz, 1H), 2.22 (sept, *J* = 7.0 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d,

J = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 173.2, 165.7, 157.5, 149.6, 140.7, 132.8, 129.1, 129.0, 128.7, 128.4, 127.7, 125.1, 120.9, 116.4, 102.6, 68.7, 58.5, 54.2, 29.5, 19.4, 19.0. **FTIR (neat, cm^{-1}), ν_{max}:** 2966 (w), 1727 (m), 1635 (m), 1609 (m), 1532 (m), 1512 (m), 1489 (m). **HRMS** calculated for $C_{23}H_{23}N_3O_4$ (ESI^+): 406.1761. Found: 406.1771.

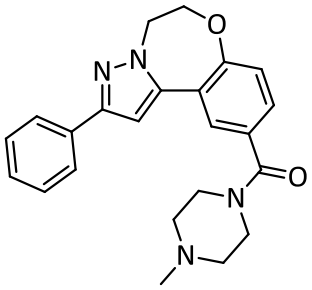
General Procedure N – To a solution of carboxylic acid (2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid or **C.01**, 1 eq) in *N,N*-DMF (0.2 M), EDC (1.2 eq), HOBt (1.1 eq), diisopropylamine (3 eq) and 1-methylpiperazine (1.1 eq) were successively added. After completion, water was added and the product extracted with CH_2Cl_2. The combined organic layers were dried under Na_2SO_4, filtered and all volatiles were removed under vacuum. The residue was then purified using reversed phase chromatography to yield the desired coupled compounds.

(4-Methylpiperazin-1-yl)(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepin-8-yl)methanone, D.27



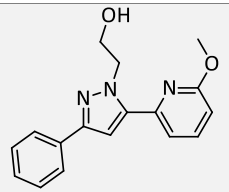
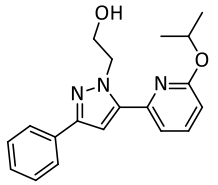
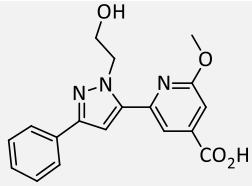
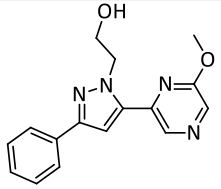
Following general procedure N, using 2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid (63 mg, 0.20 mmol), EDC (43 mg, 0.22 mmol), HOBt (35 mg, 0.22 mmol), diisopropylamine (105 µL, 0.60 mmol) and 1-methylpiperazine (24 µL, 0.22 mmol) in *N,N*-DMF (1 mL), the title compound was obtained as a colourless oil (62 mg, 78%). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.07 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.48 – 7.41 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.18 (m, 2H), 4.74 – 4.56 (m, 4H), 3.71 – 3.12 (m, 8H), 2.85 (s, 3H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 166.2, 151.2, 149.7, 140.7, 132.8, 130.3, 128.7, 128.2, 127.7, 125.0, 123.0, 118.2, 115.7, 102.8, 68.8, 54.2, 52.3, 43.2, 42.3, 38.0. **FTIR (neat, cm^{-1}), ν_{max}:** 3025 (w), 2938 (w), 1673 (s), 1197 (s), 1126 (s). **HRMS** calculated for $C_{23}H_{24}N_4O_2$ (ESI^+): 389.1972. Found: 389.1977.

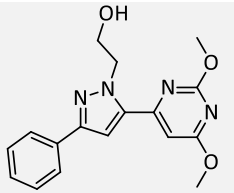
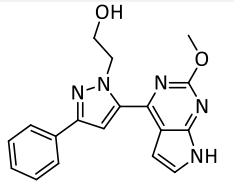
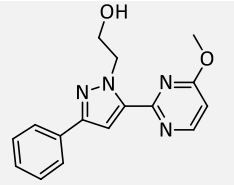
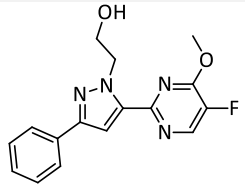
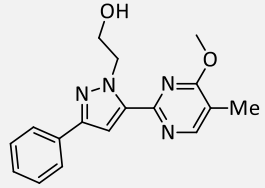
(4-Methylpiperazin-1-yl)(2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepin-10-yl)methanone, E.27

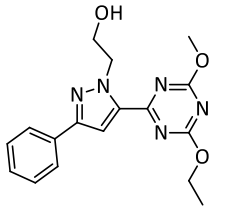
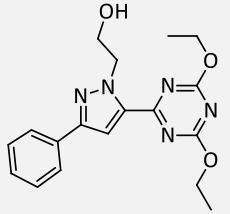
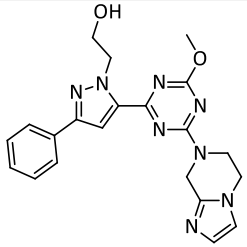
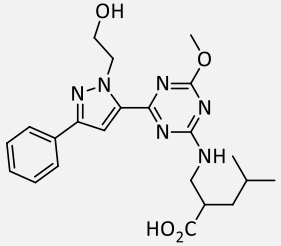


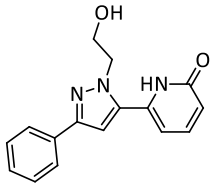
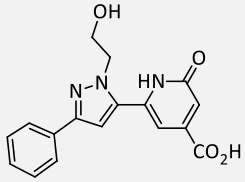
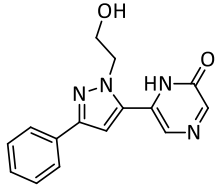
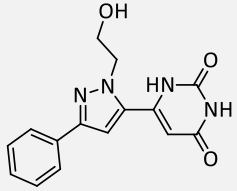
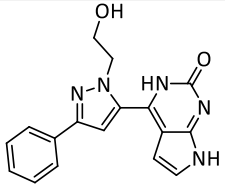
Following general procedure N, using **C.01** (58 mg, 0.20 mmol), EDC (42 mg, 0.22 mmol), HOBt (33 mg, 0.22 mmol), diisopropylamine (105 µL, 0.60 mmol) and 1-methylpiperazine (24 µL, 0.22 mmol) in *N,N*-DMF (1 mL), the title compound was obtained as a colourless oil (51 mg, 69%). **^{1}H NMR (250 MHz, DMSO-d$_6$), ppm:** 7.98 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.48 – 7.32 (m, 4H), 7.27 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.67 (m, 2H), 4.61 – 4.54 (m, 2H), 3.77 (dd, *J* = 5.5, 4.0 Hz, 4H), 3.16 (app t, *J* = 5.0 Hz, 4H), 2.78 (s, 3H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 168.4, 156.3, 149.7, 140.4, 132.8, 129.0, 128.7, 128.56, 128.52, 127.7, 125.0, 121.2, 116.7, 102.6, 68.4, 54.3, 52.2, 42.3. Both ^{1}H and ^{13}C NMR were recorded at 390 K. **FTIR (neat, cm^{-1}), ν_{max}:** 3030 (w), 2938 (w), 1674 (s), 1197 (s), 1124 (s). **HRMS** calculated for $C_{23}H_{24}N_4O_2$ (ESI$^+$): 389.1972. Found: 389.1979.

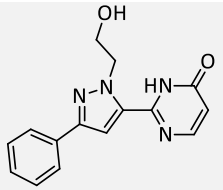
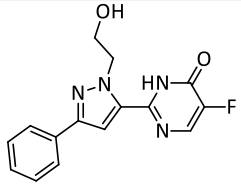
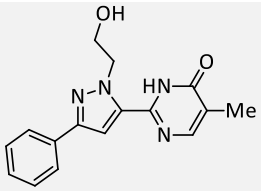
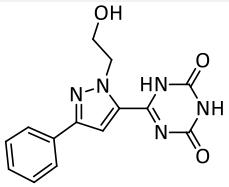
2.2.8. Library **F** of 5-6-6 tricyclic compounds

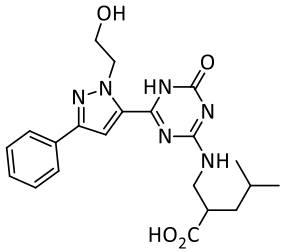
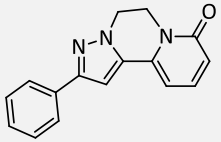
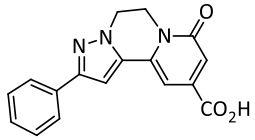
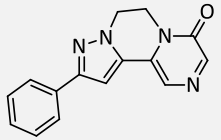
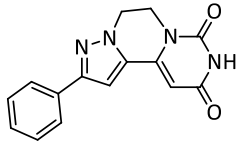
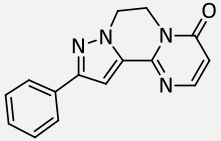
Compound ID	*Compound structure*	*LC-MS purity*	*^{1}H NMR*
F.01		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.89 – 7.80 (m, 3H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.36 – 7.30 (m, 1H), 7.27 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 1H), 4.77 (t, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 3.85 – 3.79 (m, 2H).
F.02		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.86 - 7.84 (m, 2H), 7.80 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.4'4 - 7.41 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.32 (hept, *J* = 6.0 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 2H), 3.84 -3.79 (m, 2H), 1.34 (d, *J* = 6.0 Hz, 6H).
F.03		97%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 13.79 (s, 1H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.85 (d, *J* = 1.0 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.19 (d, *J* = 1.0 Hz, 1H), 4.77 (t, *J* = 6.5 Hz, 2H), 4.00 (s, 3H), 3.80 (t, *J* = 6.5 Hz, 2H).
F.04		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.72 (s, 1H), 8.30 (s, 1H), 7.86 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 4.84 (t, *J* = 6.5 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 2H), 4.01 (s, 3H), 3.81 (app q, *J* = 6.5 Hz, 2H).

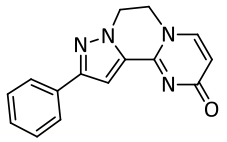
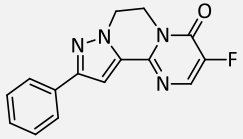
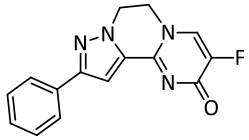
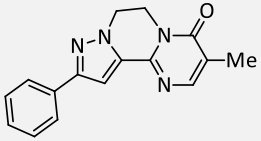
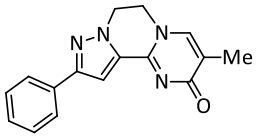
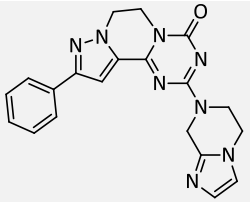
F.05		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 7.84 (d, *J* = 7.5 Hz, 2H), 7.47 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.03 (s, 1H), 4.79 (t, *J* = 6.5 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.80 (t, *J* = 6.5 Hz, 2H).
F.06		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 12.02 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 1H), 6.86 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.85 (t, *J* = 6.5 Hz, 2H), 3.99 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H).
F.07		95%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.63 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.39 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 6.0 Hz, 1H), 4.89 (t, *J* = 6.5 Hz, 2H), 4.03 (s, 3H), 3.82 (t, *J* = 6.5 Hz, 2H).
F.08		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.72 (d, *J* = 3.0 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.40 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 4.84 (t, *J* = 6.5 Hz, 2H), 4.14 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H).
F.09		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.47 (d, *J* = 1.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.40 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H), 2.15 (s, 3H).

F.10A		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.88 (d, *J* = 7.5 Hz, 2H), 7.57 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 2H), 4.50 (q, *J* = 7.0 Hz, 2H), 4.03 (s, 3H), 3.82 (t, *J* = 6.5 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H).
F.10B		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.88 (d, *J* = 7.5 Hz, 2H), 7.56 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.0 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 4H), 3.81 (t, *J* = 6.0 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 6H).
F.11		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.89 (d, *J* = 7.5 Hz, 2H), 7.70 – 7.64 (m, 2H), 7.63 – 7.57 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.39 – 5.20 (m, 2H), 4.94 – 4.84 (m, 2H), 4.48 – 4.28 (m, 4H), 4.03 (s, 3H), 3.83 (t, *J* = 6.0 Hz, 2H)
F.12		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 12.25 (s, 1H), 8.22 (app q, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.45 – 7.32 (m, 4H), 4.89 – 4.82 (m, 2H), 3.93 (d, *J* = 12.0 Hz, 3H), 3.84 – 3.76 (m 2H), 3.60 – 3.42 (m, 2H), 2.81 – 2.71 (m, 1H), 1.63 – 1.45 (m, 2H), 1.37 - 1.22 (m, 1H), 0.89 (t, *J* = 6.0 Hz, 6H).

F.13		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 7.83 (d, *J* = 7.5 Hz, 2H), 7.62 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 2H), 3.82 (t, *J* = 5.5 Hz, 2H).
F.14		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.86 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.21 (s, 1H), 6.98 (s, 1H), 4.61 – 4.40 (m, 2H), 3.79 (t, *J* = 5.5 Hz, 2H).
F.15		63%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 8.10 (s, 1H), 7.85 – 7.83 (m, 2H), 7.46 - 7.39 (m, 3H), 7.36 - 7.30 (m, 1H), 7.27 (s, 1H), 4.60 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).
F.16		100%	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 11.24 (s, 1H), 11.21 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 1H), 5.89 (s, 1H), 5.49 (s, 1H), 4.31 (t, *J* = 5.0 Hz, 2H), 3.85 (t, *J* = 5.0 Hz, 2H).
F.17		na	^{1}H NMR (400 MHz, DMSO-d_6), ppm: 11.92 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.32 (m, 3H), 6.70 (d, *J* = 3.5 Hz, 1H), 4.70 (t, *J* = 5.5 Hz, 2H), 3.79 (t, *J* = 5.5 Hz, 2H).

F.18		na	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.26 – 7.95 (m, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.49 - 7.44 (m, 3H), 7.34 (t, *J* = 7.45 Hz, 1H), 6.50 – 6.26 (m, 1H), 4.73 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H).
F.19		na	^{1}H NMR (500 MHz, DMSO-d$_6$), ppm: 8.22 (d, *J* = 3.0 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.41 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 4.67 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H).
F.20		na	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.06 – 7.91 (m, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.70 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 1.99 (s, 3H).
F.21		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 12.44 (s, 1H), 11.46 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.59 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.73 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H).
F.22		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 7.79 (d, *J* = 7.5 Hz, 2H), 7.73 – 7.66 (m, 2H), 7.64 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 5.28 – 5.17 (m, 2H), 4.80 – 4.74 (m, 2H), 4.35 – 4.27 (m, 4H), 3.85 – 3.80 (m, 2H).

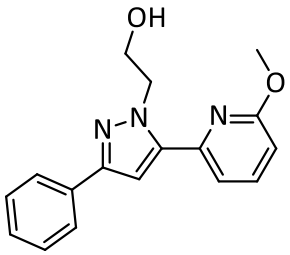
F.23		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.37 (t, *J* = 5.5 Hz, 1H), 8.05 – 7.95 (m, 1H), 7.84 – 7.74 (m, 4H), 7.60 (s, 1H), 7.52 (s, 1H), 7.46 – 7.42 (m, 4H), 7.37 – 7.32 (m, 2H), 4.83 – 4.74 (m, 4H), 3.83 – 3.74 (m, 4H), 3.66 – 3.39 (m, 4H), 3.38 – 3.30 (m, 1H), 2.80 – 2.67 (m, 2H), 1.66 – 1.43 (m, 4H), 1.36 – 1.26 (m, 2H), 0.91 – 0.87 (m, 12H).
F.24		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 7.84 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.54 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 6.79 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.46 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.55 – 4.47 (m, 2H), 4.47 – 4.41 (m, 2H).
F.25		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.79 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.64 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 1.5 Hz, 1H), 4.55 – 4.51 (m, 2H), 4.49 – 4.51 (m, 2H).
F.26		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.02 (s, 1H), 7.93 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.57 – 4.53 (m, 2H), 4.45 – 4.41 (m, 2H).
F.27		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 11.41 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.56 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.19 (d, *J* = 2.0 Hz, 1H), 4.54 – 4.44 (m, 2H), 4.30 – 4.19 (m, 2H)
F.28A		100%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 8.02 (d, *J* = 6.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 6.5 Hz, 1H), 4.61 – 4.56 (m, 2H), 4.51 – 4.46 (m, 2H).

F.28B		na	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 7.91 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.43 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 6.03 (d, *J* = 7.5 Hz, 1H), 4.64 – 4.61 (m, 2H), 4.45 – 4.42 (m, 2H).
F.29A		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.34 (d, *J* = 6.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.42 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.68 – 4.62 (m, 2H), 4.50 – 4.44 (m, 2H).
F.29B		na	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.23 (d, *J* = 2.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.47 - 7.42 m, 3H), 7.36 (t, *J* = 7.45 Hz, 1H), 4.60 - 4.57 (m, 2H), 4.55 - 4.51 (m, 2H).
F.30A		na	^{1}H NMR (500 MHz, DMSO-d$_6$), ppm: 7.95 (d, *J* = 1.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.46 - 7.35 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 4.59 – 4.54 (m, 2H), 4.53 – 4.47 (m, 2H), 2.02 (s, 3H).
F.30B		na	^{1}H NMR (500 MHz, DMSO-d$_6$), ppm: 7.90 (d, *J* = 7.5 Hz, 2H), 7.80 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.41 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 4.64 – 4.59 (m, 2H), 4.43 – 4.39 (m, 2H), 1.89 (s, 3H).
F.31		86%	^{1}H NMR (400 MHz, DMSO-d$_6$), ppm: 7.91 (d, *J* = 7.5 Hz, 2H), 7.68 (s, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 5.35 – 5.16 (m, 2H), 4.63 – 4.56 (m, 2H), 4.47 – 4.42 (m, 1H), 4.40 – 4.34 (m, 2H), 4.33 – 4.21 (m, 3H).

na: not applicable. These substrates were not submitted for testing therefore no purity assessment was carried out.

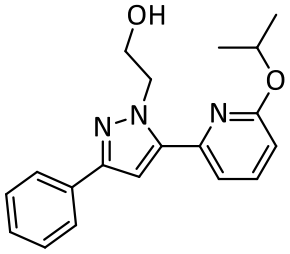
The above library was synthesised by hand, therefore whenever possible, the compounds were fully characterised. The method for the Suzuki cross-coupling step (general method K) can be found page 202.

2-(5-(6-Methoxypyridin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.01



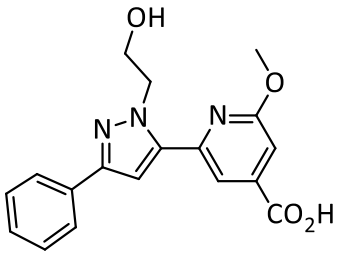
Following general procedure K, using 2-bromo-6-methoxypyridine (370 µL, 3.00 mmol), **38A** (970 mg, 3.30 mmol), $Pd(OAc)_2$ (48 mg, 0.21 mmol), XPhos (207 mg, 0.42 mmol) and Na_2CO_3 (637 mg, 6.00 mmol) in ethanol (15 mL). The title compound was obtained after flash chromatography as an orange oil (851 mg, 96% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.89 – 7.80 (m, 3H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.36 – 7.30 (m, 1H), 7.27 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 1H), 4.77 (t, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 3.85 – 3.79 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 163.0, 149.1, 146.5, 141.9, 140.1, 133.0, 128.7, 127.6, 125.1, 115.8, 109.7, 103.9, 60.6, 53.4, 53.3. **FTIR (neat, cm^{-1}), ν_{max}:** 3340 (br), 3070 (w), 2948 (w), 2875 (w), 1591 (m), 1575 (s), 1470 (s), 1449 (s), 1414 (s), 1301 (s), 1245 (s), 1064 (s). **HRMS** calculated for $C_{17}H_{17}N_3O_2$ (ESI^+): 296.1394. Found: 296.1392.

2-(5-(6-Isopropoxypyridin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.02



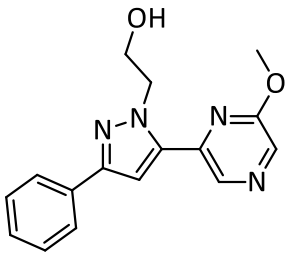
Following general procedure K, using 2-bromo-6-isopropoxypyridine (639 mg, 3.00 mmol), **38A** (970 mg, 3.30 mmol), $Pd(OAc)_2$ (48 mg, 0.21 mmol), XPhos (207 mg, 0.42) and Na_2CO_3 (637 mg, 6.00 mmol) in ethanol (15 mL), the title compound was obtained after flash chromatography on silica as an orange oil (946 mg, 99% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.86 - 7.84 (m, 2H), 7.80 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.44 - 7.41 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.32 (hept, *J* = 6.0 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 2H), 3.84 -3.79 (m, 2H), 1.34 (d, *J* = 6.0 Hz, 6H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 162.2, 149.1, 146.5, 142.2, 140.1, 133.0, 128.7, 127.6, 125.1, 115.6, 110.4, 104.0, 67.7, 60.6, 53.0, 21.9. **FTIR (neat, cm^{-1}), ν_{max}:** 3287 (br), 3062 (w), 3039 (w), 2982 (w), 2959 (w), 2919 (w), 1587 (m), 1575 (s), 1455 (s), 1427 (s), 1289 (s), 1241 (s), 1070 (s). **HRMS** calculated for $C_{19}H_{21}N_3O_2$ (ESI^+): 324.1707. Found: 324.1710.

2-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)-6-methoxyisonicotinic acid, F.03



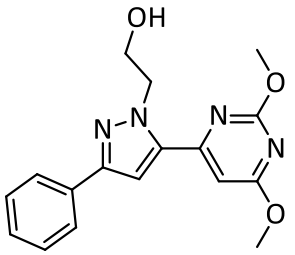
Following general procedure K, using 2-bromo-6-methoxyisonicotinic acid (118 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a colourless oil (118 mg, 69% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 13.79 (s, 1H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.85 (d, *J* = 1.0 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.19 (d, *J* = 1.0 Hz, 1H), 4.77 (t, *J* = 6.5 Hz, 2H), 4.00 (s, 3H), 3.80 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 165.6, 163.7, 149.2, 147.5, 142.6, 141.3, 132.9, 128.6, 127.6, 125.1, 114.6, 109.1, 104.5, 60.6, 54.1, 53.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3375 (br), 3188 (br), 2968 (w), 2946 (w), 1724 (s), 1609 (m), 1570 (s), 1447 (s), 1382 (s), 1336 (s), 1239 (s), 1208 (s), 1041 (s). **HRMS** calculated for $C_{18}H_{17}N_3O_4$ (ESI^+): 340.1292. Found: 340.1299.

2-(5-(6-Methoxypyrazin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.04



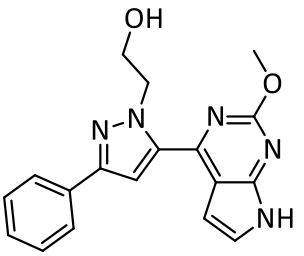
Following general procedure K, using 2-bromo-6-methoxypyrazine (97 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a colorless oil (98 mg, 66% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.72 (s, 1H), 8.30 (s, 1H), 7.86 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 4.84 (t, *J* = 6.5 Hz, 1H), 4.73 (t, *J* = 6.5 Hz, 2H), 4.01 (s, 3H), 3.81 (app q, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 158.9, 149.4, 141.1, 139.0, 135.0, 133.5, 132.7, 128.7, 127.7, 125.1, 104.4, 60.6, 53.8, 53.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3298 (br), 3125 (w), 3055 (w), 2980 (w), 2956 (w), 2908 (w), 2869 (w), 1531 (s), 1472 (m), 1451 (s), 1394 (s), 1307 (s), 1272 (m), 1158 (s), 1150 (m), 1079 (s). **HRMS** calculated for $C_{16}H_{16}N_4O_2$ (ESI^+): 297.1346. Found: 297.1350.

2-(5-(2,6-Dimethoxypyrimidin-4-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.05



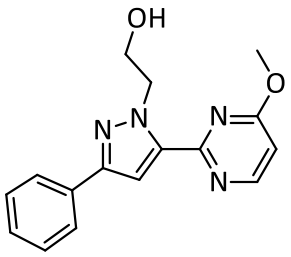
Following general procedure K, using 4-chloro-2,6-dimethoxypyrimidine (88 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (7.9 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (106 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a colorless oil (109 mg, 66% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.84 (d, *J* = 7.5 Hz, 2H), 7.47 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.03 (s, 1H), 4.79 (t, *J* = 6.5 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.80 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 172.0, 164.9, 157.5, 149.3, 140.1, 132.7, 128.7, 127.7, 125.1, 105.5, 98.7, 60.6, 54.7, 54.0, 53.7. **FTIR (neat, cm^{-1}), ν_{max}:** 3340 (br), 2987 (w), 2953 (w), 2922 (w), 2875 (w), 1584 (s), 1563 (s), 1471 (m), 1446 (s), 1397 (m) 1346 (s), 1214 (s), 1200 (s), 1094 (s), 1078 (s). **HRMS** calculated for $C_{17}H_{18}N_4O_3$ (ESI^+): 327.1452. Found: 327.1457.

2-(5-(2-Methoxy-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.06



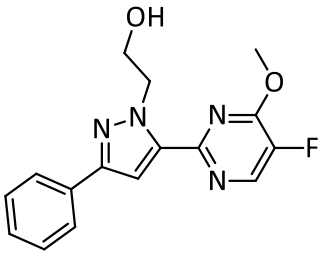
Following general procedure K, using 4-chloro-2-methoxy-7*H*-pyrrolo[2,3-d]pyrimidine (93 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a yellow oil (83 mg, 49% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 12.02 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 1H), 6.86 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.85 (t, *J* = 6.5 Hz, 2H), 3.99 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 160.8, 154.8, 149.5, 148.3, 139.7, 132.8, 128.6, 127.7, 126.1, 125.4, 111.0, 106.2, 100.5, 60.6, 54.4, 53.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3328 (br), 3219 (w), 3123 (w), 2957 (w), 2844 (w), 1616 (m), 1566 (s), 1510 (m), 1481 (m), 1450 (s), 1336 (s), 1089 (s). **HRMS** calculated for $C_{18}H_{17}N_5O_2$ (ESI^+): 336.1455. Found: 336.1459.

2-(5-(4-Methoxypyrimidin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.07



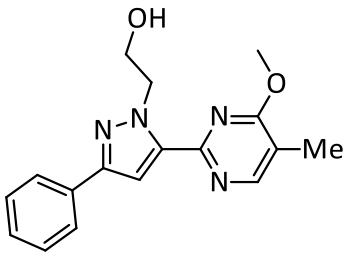
Following general procedure K, using 2-bromo-4-methoxypyrimidine (189 mg, 1.00 mmol), **38A** (323 mg, 1.10 mmol), $Pd(OAc)_2$ (16.5 mg, 0.08 mmol), XPhos (71 mg, 0.16 mmol) and Na_2CO_3 (211 mg, 2.00 mmol) in ethanol (5 mL). The title compound was obtained after reverse phase chromatography as a colorless oil (169 mg, 57% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.63 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.39 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 6.0 Hz, 1H), 4.89 (t, *J* = 6.5 Hz, 2H), 4.03 (s, 3H), 3.82 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 168.9, 158.0, 157.1, 148.9, 141.3, 132.8, 128.7, 127.7, 125.1, 106.3, 60.6, 53.9, 53.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3216 (br), 3047 (w), 2986 (w), 2941 (w), 2882 (w), 1581 (s), 1563 (s), 1476 (s), 1448 (s), 1412 (s), 1315 (m), 1266 (s), 1108 (s), 1039 (s). **HRMS** calculated for $C_{16}H_{16}N_4O_2$ (ESI^+): 297.1346. Found: 297.1350.

2-(5-(5-Fluoro-4-methoxypyrimidin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol , F.08



Following general procedure K, using 2-chloro-5-fluoro-4-methoxypyrimidine (86 mg, 0.50 mmol), **38A** (169 mg, 0.55 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a colorless oil (93 mg, 56% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.72 (d, *J* = 3.0 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.40 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 4.84 (t, *J* = 6.5 Hz, 2H), 4.14 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm**: 157.7 (d, *J* = 10.5 Hz), 152.3 (d, *J* = 8.0 Hz), 148.9, 145.9, 143.3 (d, J = 8.0 Hz), 140.7, 132.7, 128.7, 127.7, 125.1, 106.2, 60.5, 54.7, 53.7. **^{19}F NMR (377 MHz, DMSO-d_6), ppm:** -155.2 (d, *J* = 3.0 Hz). FTIR (neat, cm^{-1}), ν_{max}: 3244 (br), 2952 (w), 2877 (w), 1588 (m), 1484 (s), 1456 (m), 1406 (s), 1349 (m), 1212 (m), 1070 (m). **HRMS** calculated for $C_{16}H_{15}FN_4O_2$ (ESI^+): 315.1252. Found: 315.1259.

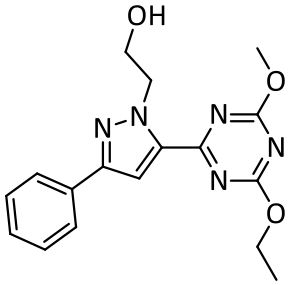
2-(5-(4-Methoxy-5-methylpyrimidin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.09



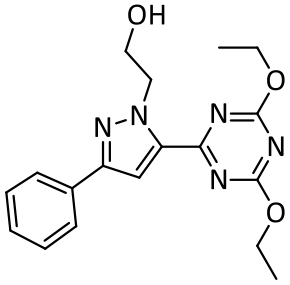
Following general procedure K, using 2-chloro-4-methoxy-5-methylpyrimidine (81 mg, 0.50 mmol), **38A** (191 mg, 0.55 mmol), $Pd(OAc)_2$ (8.2 mg, 0.04 mmol), XPhos (35 mg, 0.08 mmol) and Na_2CO_3 (109 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after reverse phase chromatography as a colorless oil (93 mg, 60% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.47 (d, *J* = 1.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.40 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 3.81 (t, *J* = 6.5 Hz, 2H), 2.15 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 167.2, 156.6, 155.0, 148.8, 141.4, 132.8, 128.6, 127.6, 125.1, 115.9, 105.8, 60.6, 54.0, 53.7, 12.2. **FTIR (neat, cm^{-1}), ν_{max}:** 3241 (br), 2998 (w), 2978 (w), 2955 (w), 2920 (w), 2859 (w), 1587 (m), 1566 (m), 1549 (m), 1472 (s), 1451 (s), 1399 (s), 1314 (s), 1084 (s). **HRMS** calculated for $C_{17}H_{18}N_4O_2$ (ESI^+): 311.1503. Found: 311.1508.

2-(5-(4-Ethoxy-6-methoxy-1,3,5-triazin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.10A and 2-(5-(4,6-Diethoxy-1,3,5-triazin-2-yl)-3-phenyl-1H-pyrazol-1-yl)ethanol, F.10B

Following general procedure K, using 2-chloro-4,6-dimethoxy-1,3,5-triazine (88 mg, 0.50 mmol), **38A** (168 mg, 0.55 mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol), XPhos (35 mg, 0.08 mmol) and Na_2CO_3 (107 mg, 1.00 mmol) in ethanol (2.5 mL). The title compounds were obtained after reverse phase chromatography 2-(5-(4-ethoxy-6-methoxy-1,3,5-triazin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)ethanol **F.10A** as a colorless oil (46 mg, 27% yield) and 2-(5-(4,6-diethoxy-1,3,5-triazin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)ethanol **F.10B** as a colorless oil (23 mg, 13% yield).



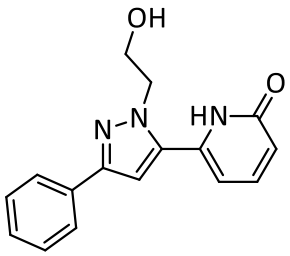
F.10A: ^{1}H NMR (400 MHz, DMSO-d_6), ppm: 7.88 (d, *J* = 7.5 Hz, 2H), 7.57 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.5 Hz, 2H), 4.50 (q, *J* = 7.0 Hz, 2H), 4.03 (s, 3H), 3.82 (t, *J* = 6.5 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 172.2, 171.6, 166.8, 149.2, 139.6, 132.3, 128.7, 127.9, 125.2, 108.0, 64.0, 60.5, 55.2, 54.2, 14.1**. FTIR (neat, cm^{-1}), ν_{max}:** 3379 (m), 2985 (w), 2936 (w), 2873 (w), 1541 (s), 1519 (m), 1495 (s), 1452 (s), 1032 (s). **HRMS** calculated for $C_{17}H_{19}N_5O_3$ (ESI^+): 342.1561. Found: 342.1566.



F.10B: **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.88 (d, *J* = 7.5 Hz, 2H), 7.56 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.87 (t, *J* = 6.0 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 4H), 3.81 (t, *J* = 6.0 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 171.6, 166.8, 149.1, 139.6, 132.4, 128.7, 127.9, 125.1, 107.9, 64.0, 60.5, 54.1, 14.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3363 (m), 3145 (w), 3051 (w), 2970 (w), 2929 (w), 1559 (s), 1537 (s), 1517 (m), 1490 (m), 1035 (s). **HRMS** calculated for $C_{18}H_{21}N_5O_3$ (ESI$^+$): 356. 1717. Found: 356.1723.

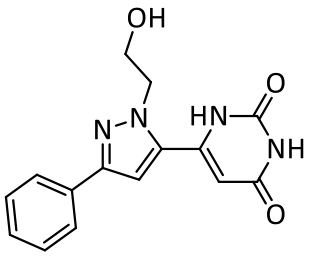
General Procedure O – A solution of HCl (4 M in 1,4-dioxane or water) was added to a solution of pyridinol methyl ether (1 eq) in 1,4-dioxane (0.15 M). The mixture was heated at reflux in a sealed tube. Upon completion, all volatiles were removed and the crude was purified by column chromatography to yield the desired coupled product.

6-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)pyridin-2(1H)-one, F.13



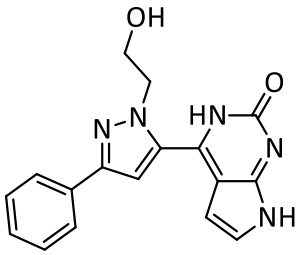
Following general procedure O, using **F.01** (204 mg, 0. 62 mmol), HCl in 1,4-dioxane (3.1 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (161 mg, 91% yield). **^{1}H NMR (600 MHz, DMSO-d$_6$), ppm:** 7.83 (d, *J* = 7.5 Hz, 2H), 7.62 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 4.43 (t, J = 5.5 Hz, 2H), 3.82 (t, J = 5.5 Hz, 2H). **^{13}C NMR (126 MHz, DMSO-d$_6$), ppm:** 162.8, 149.5, 140.8, 140.3, 140.1, 132.9, 128.8, 127.8 125.2, 115.8, 109.9, 104.5, 60.4, 52.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3438 (br), 3107 (w), 3028 (w), 2953 (w), 2876 (w), 1645 (s), 1620 (s), 1558 (m), 1510 (m), 1074 (s). **HRMS** calculated for $C_{16}H_{15}N_3O_2$ (ESI$^+$): 282.1237. Found: 282.1237.

6-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)pyrimidine-2,4(1H,3H)-dione, F.16



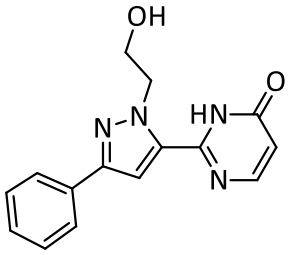
Following general procedure O, using **F.05** (70 mg, 0. 21 mmol), HCl in 1,4-dioxane (1 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (58 mg, 90% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.24 (s, 1H), 11.21 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 1H), 5.89 (s, 1H), 5.49 (s, 1H), 4.31 (t, *J* = 5.0 Hz, 2H), 3.85 (t, *J* = 5.0 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 163.8, 151.2, 149.9, 142.6, 137.1, 132.4, 128.8, 127.9, 125.1, 105.3, 101.1, 60.2, 52.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3351 (br), 3028 (w), 2879 (w), 2812 (w), 1706 (s), 1652 (s), 1077 (m). **HRMS** calculated for $C_{15}H_{14}N_4O_3$ (ESI$^+$): 299.1139. Found: 299.1144.

4-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)-3,7-dihydro-2H-pyrrolo[2,3-d]pyrimidin-2-one, F.17



Following general procedure O, using **F.06** (83 mg, 0. 25 mmol), HCl in 1,4-dioxane (1.3 mL) and water (0.4 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (51 mg, 70% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.92 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.32 (m, 3H), 6.70 (d, *J* = 3.5 Hz, 1H), 4.70 (t, *J* = 5.5 Hz, 2H), 3.79 (t, *J* = 5.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 158.4, 158.0, 154.5, 149.9, 138.3, 132.6, 128.7, 127.9, 126.2, 125.4, 109.5, 106.5, 101.1, 60.6, 53.2. **FTIR (neat, cm^{-1}), ν_{max}:** 3375 (br), 2938 (w), 2807 (w), 1722 (m), 1612 (s), 1198 (s), 1077 (s). **HRMS** calculated for $C_{17}H_{15}N_5O_2$ (ESI$^+$): 322.1299. Found: 322.1305.

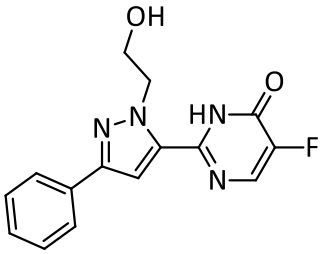
2-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)pyrimidin-4(3H)-one, F.18



Following general procedure O, using **F.07** (68 mg, 0. 23 mmol), HCl in 1,4-dioxane (1.2 mL) and water (0.4 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (45 mg, 70% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.26 – 7.95 (m, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.49 - 7.44 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.50 – 6.26 (m, 1H), 4.73 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (126 MHz, DMSO-**

d_6), ppm: 162.1, 154.2, 150.6, 149.1, 136.6, 132.5, 128.9, 128.0, 125.1, 114.0, 106.2, 60.5, 53.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3419 (w), 3321 (w), 3131 (w), 3056 (w), 2941 (w), 2863 (w), 1667 (s), 1591 (s), 1563 (m), 1530 (s), 1498 (s), 1289 (m). **HRMS** calculated for $C_{15}H_{14}N_4O_2$ (ESI^+): 283.1190. Found: 283.1190**.**

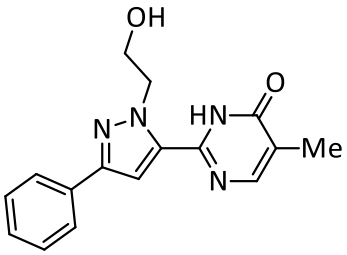
5-Fluoro-2-(1-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)pyrimidin-4(3H)-one, F.19



Following general procedure O, using **F.08** (84 mg, 0. 27 mmol), HCl in 1,4-dioxane (1.4 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (59 mg, 74% yield). **^{1}H NMR (500 MHz, DMSO-d_6), ppm:** 8.22 (d, *J* = 3.0 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.41 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 4.67 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (126 MHz, DMSO-d_6), ppm:** 155.6, 149.6, 149.1, 147.7, 145.7, 136.0, 132.4, 128.8, 128.0, 125.1, 106.1, 60.4, 53.2. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -152.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3365 (w), 3227 (w), 3045 (w), 2937 (w), 1676 (s), 1605 (s), 1578 (m), 1576 (m), 1535 (s), 1079 (m). **HRMS** calculated for $C_{15}H_{13}FN_4O_2$ (ESI^+): 301.1095. Found: 301.1101.

No decoupling of the signals on the ^{13}C NMR as the signals had broaden to the point where specific parameters had to be used to record the analysis.

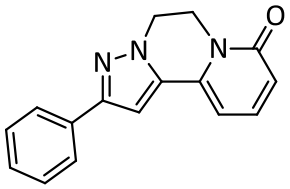
2-(1-(2-Hydroxyethyl)-3-phenyl-1H-pyrazol-5-yl)-5-methylpyrimidin-4(3H)-one, F.20



Following general procedure O, using **F.09** (74 mg, 0. 24 mmol), HCl in 1,4-dioxane (1.2 mL) and water (0.3 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (56 mg, 79% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.06 – 7.91 (m, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 4.70 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 1.99 (s, 3H). **^{13}C NMR (126 MHz, DMSO d_6), ppm:** 162.8, 150.4, 149.1, 148.0, 136.3, 132.5, 128.8, 127.9, 125.1, 123.1, 105.8, 60.4, 53.3, 12.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3348 (br), 3132 (w), 2977 (w), 1656 (s), 1597 (s), 1574 (m), 1071 (m). **HRMS** calculated for $C_{16}H_{16}N_4O_2$ (ESI^+): 297.1346. Found: 297.1352.

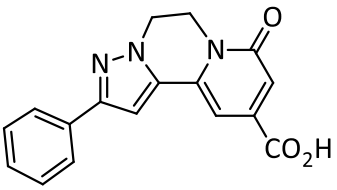
General procedure P – Tosyl chloride (2 eq) and cesium carbonate (6 eq) were added to a solution of pyridinol (1 eq) in *N,N*-DMF (0.04 M) and the mixture was heated at reflux. Upon completion, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered. All volatiles were removed and the crude was purified by column chromatography to afford the desired compounds.

2-Phenyl-5H-pyrazolo[1,5-a]pyrido[2,1-c]pyrazin-8(6H)-one, F.24



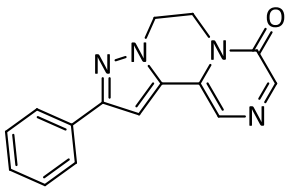
Following general procedure P, using **F.13** (145 mg, 0.52 mmol), tosyl chloride (204 mg, 1.03 mmol) and cesium carbonate (1.02 g, 3.09 mmol) in *N,N*-DMF (14 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (116 mg, 85% yield). **^{1}H NMR (400 MHz, DMSO- d$_6$), ppm:** 7.84 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.54 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 6.79 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.46 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.55 – 4.47 (m, 2H), 4.47 – 4.41 (m, 2H). **^{13}C NMR (101 MHz, DMSO- d$_6$), ppm:** 160.6, 150.9, 139.5, 135.3, 134.3, 132.5, 128.8, 128.0, 125.1, 118.7, 102.7, 100.8, 45.1, 39.7. **FTIR (neat, cm^{-1}), ν_{max}:** 3111 (w), 3065 (w), 2923 (w), 1653 (s), 1575 (s), 1529 (s), 1514 (m), 1458 (m), 1143 (s). **HRMS** calculated for $C_{16}H_{13}N_3O$ (ESI^+): 264.1131. Found: 264.1134.

8-Oxo-2-phenyl-6,8-dihydro-5H-pyrazolo[1,5-a]pyrido[2,1-c]pyrazine-10-carboxylic acid, F.25



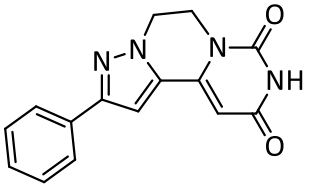
Following general procedure P, using **F.14** (15 mg, 0.05 mmol), tosyl chloride (20 mg, 0.09 mmol) and cesium carbonate (90 mg, 0.28 mmol) in *N,N*-DMF (1.3 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (6 mg, 45% yield). **^{1}H NMR (600 MHz, DMSO-d$_6$), ppm:** 13.79 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.64 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 1.5 Hz, 1H), 4.55 – 4.51 (m, 2H), 4.49 – 4.51 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 165.5, 160.6, 151.1, 141.3, 135.9, 134.1, 132.4, 128.8, 128.0, 125.1, 119.1, 101.4, 100.8, 44.9, 40.2. **FTIR (neat, cm^{-1}), ν_{max}:** 3375 (br), 3082 (w), 3000 (w), 1696 (m), 1643 (s), 1248 (s), 1236 (s). **HRMS** calculated for $C_{17}H_{13}N_3O_3$ (ESI^+): 308.1030. Found: 308.1035.

10-Phenyl-6,7-dihydro-4H-pyrazino[1,2-a]pyrazolo[5,1-c]pyrazin-4-one, F.26



Following general procedure P, using **F.15** (24 mg, 0.09 mmol), tosyl chloride (36 mg, 0.17 mmol) and cesium carbonate (170 mg, 0.50 mmol) in *N,N*-DMF (2.4 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (7 mg, 29% yield). **^{1}H NMR (600 MHz, DMSO-d$_6$), ppm:** 8.02 (s, 1H), 7.93 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.57 – 4.53 (m, 2H), 4.45 – 4.41 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d$_6$), ppm:** 154.2, 151.2, 146.4, 132.3, 131.8, 128.8, 128.11, 128.07, 125.1, 119.7, 101.0, 44.6, 40.3. Not enough material could be isolated to further characterise the compound.

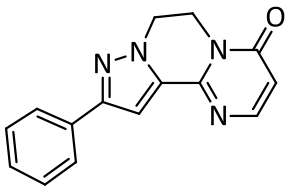
2-Phenyl-5H-pyrazolo[5',1':3,4]pyrazino[1,2-c]pyrimidine-8,10(6H,9H)-dione, F.27



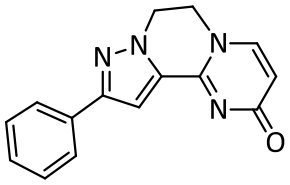
Following general procedure P, using **F.16** (29 mg, 0.01 mmol), tosyl chloride (37 mg, 0.19 mmol) and cesium carbonate (188 mg, 0.57 mmol) in *N,N*-DMF (2.6 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (21 mg, 78% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 11.41 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.56 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.19 (d, *J* = 2.0 Hz, 1H), 4.54 – 4.44 (m, 2H), 4.30 – 4.19 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 162.9, 151.0, 150.7, 140.8, 132.8, 132.2, 128.8, 128.1, 125.1, 102.5, 96.5, 45.4, 40.2. **FTIR (neat, cm^{-1}), ν_{max}:** 3003 (w), 2807 (w), 1701 (s) 1673 (s). **HRMS** calculated for $C_{15}H_{12}N_4O_2$ (ESI^+): 281.1033. Found: 281.1038.

10-Phenyl-6,7-dihydro-4H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, F.28A and 10-phenyl-6,7-dihydro-2H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, F.28B

Following general procedure P, using **F.18** (22 mg, 0.07 mmol), tosyl chloride (27 mg, 0.14 mmol) and cesium carbonate (142 mg, 0.41 mmol) in *N,N*-DMF (1.9 mL), the title compounds were obtained after reverse phase chromatography 10-phenyl-6,7-dihydro-4*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, **F.28A** as a colourless oil (12 mg, 42% yield) and 10-phenyl-6,7-dihydro-2*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, **F.28B** as a colourless oil (4 mg, 14% yield).



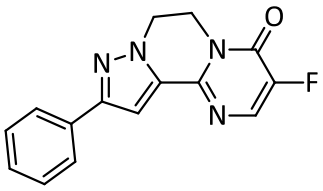
F.28A: ^{1}H NMR (400 MHz, DMSO- d_6), ppm: 8.02 (d, *J* = 6.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 6.5 Hz, 1H), 4.61 – 4.56 (m, 2H), 4.51 – 4.46 (m, 2H). **^{13}C NMR (101 MHz, DMSO- d_6), ppm:** 159.6, 153.0, 151.1, 147.9, 134.6, 132.2, 128.8, 128.1, 125.3, 113.2, 103.5, 44.8, 39.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3060 (w), 3045 (w), 3015 (w), 2856 (w), 2811 (w), 1660 (s), 1582 (m), 1564 (m), 1522 (s), 1515 (s). **HRMS** calculated for $C_{15}H_{12}N_4O$ (ESI^+): 265.1084. Found: 265.1085.



F.28B: **^{1}H NMR (600 MHz, DMSO-d_6), ppm:** 7.91 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.43 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 6.03 (d, *J* = 7.5 Hz, 1H), 4.64 – 4.61 (m, 2H), 4.45 – 4.42 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d_6), ppm:** 169.1, 150.9, 148.0, 143.8, 134.7, 132.2, 128.8, 128.1, 125.2, 110.4, 103.5, 48.8, 45.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3068 (w), 3015 (w), 2924 (w), 1634 (s), 1561 (s), 1519 (m), 1504 (m), 1474 (m). **HRMS** calculated for $C_{15}H_{12}N_4O$ (ESI^+): 265.1084. Found: 265.1089.

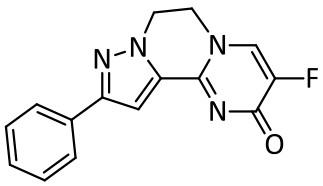
3-Fluoro-10-phenyl-6,7-dihydro-4H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, F.29A and 3-Fluoro-10-phenyl-6,7-dihydro-2H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, F.29B

Following general procedure P, using **F.19** (54 mg, 0.18 mmol), tosyl chloride (70 mg, 0.36 mmol) and cesium carbonate (356 mg, 1.08 mmol) in *N,N*-DMF (5.0 mL), the title compounds were obtained after reverse phase chromatography 3-fluoro-10-phenyl-6,7-dihydro-4*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, **F.29A** as a colourless oil (17 mg, 34% yield) and 3-fluoro-10-phenyl-6,7-dihydro-2*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, **F.29B** as a colourless oil (5 mg, 10% yield).



F.29A: ^{1}H NMR (600 MHz, DMSO- d_6), ppm: 8.23 (d, *J* = 2.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.47 - 7.42 m, 3H), 7.36 (t, *J* = 7. 5 Hz, 1H), 4.60 - 4.57 (m, 2H), 4.55 - 4.51 (m, 2H). **^{13}C NMR (126 MHz, DMSO-d_6), ppm:** 154.1 (d, *J* = 25.0 Hz), 151.1, 148.6 (d, *J* = 252.5 Hz), 143.9 (d, *J* = 4.5 Hz), 135.8 (d, *J* = 20.5 Hz), 134.4, 132.1, 128.8, 128.2, 125.3, 103.3, 44.5, 40.3. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -150.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3068 (w), 3008 (w), 2977(w),

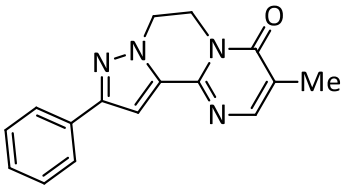
2942 (w), 2924 (w), 1688 (s), 1566 (m), 1537 (m) 1484 (m), 1461 (m). **HRMS** calculated for $C_{15}H_{11}FN_4O$ (ESI^+): 283.0990. Found: 283.0991.



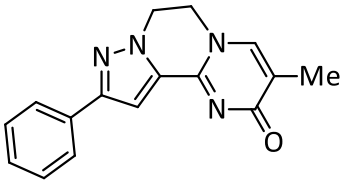
F.29B: ^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.34 (d, *J* = 6.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.42 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.68 – 4.62 (m, 2H), 4.50 – 4.44 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d_6), ppm:** 162.1 (d, *J* = 14.5 Hz), 150.9, 146.3 (d, *J* = 164.5 Hz), 145.5 (d, *J* = 87.0 Hz), 134.2, 132.1, 129.1 (d, *J* = 35.5 Hz), 128.8, 128.2, 125.3, 103.8, 49.2, 44.9. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -152.0 (d, *J* = 6.6 Hz). **FTIR (neat, cm^{-1}), ν_{max}:** 3083 (w), 3061 (w), 3023 (w), 2985 (w), 1642 (s), 1563 (s), 1529 (s), 1463 (s), 1436 (m). **HRMS** calculated for $C_{15}H_{11}FN_4O$ (ESI^+): 283.0990. Found: 283.0993.

3-Methyl-10-phenyl-6,7-dihydro-4H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, F.30A and 3-Methyl-10-phenyl-6,7-dihydro-2H-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, F.30B

Following general procedure P, using **F.20** (26 mg, 0.09 mmol), tosyl chloride (33 mg, 0.18 mmol) and cesium carbonate (172 mg, 0.53 mmol) in *N,N*-DMF (2.5 mL), the title compounds were obtained after reverse phase chromatography 3-methyl-10-phenyl-6,7-dihydro-4*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-4-one, **F.30A** as a colourless oil (14 mg, 57% yield) and 3-methyl-10-phenyl-6,7-dihydro-2*H*-pyrazolo[5',1':3,4]pyrazino[1,2-a]pyrimidin-2-one, **F.30B** as a colourless oil (5 mg, 20% yield).



F.30A: **^{1}H NMR (500 MHz, DMSO- d_6), ppm:** 7.95 (d, *J* = 1.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.46 - 7.35 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 4.59 – 4.54 (m, 2H), 4.53 – 4.47 (m, 2H), 2.02 (s, 3H). **^{13}C NMR (126 MHz, DMSO- d_6), ppm:** 160.5, 151.1, 149.6, 145.7, 134.8, 132.3, 128.8, 128.1, 125.2, 122.3, 102.9, 44.8, 39.9, 13.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3061 (w), 3023 (w), 2992 (w), 2923 (w), 1659 (s), 1600 (m), 1565 (m), 1537(s), 1480 (s). **HRMS** calculated for $C_{16}H_{14}N_4O$ (ESI^+): 279.1240. Found: 279.1243.



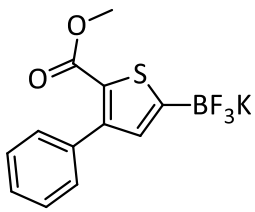
F.30B: ^{1}H NMR (500 MHz, DMSO- d$_6$), ppm: 7.90 (d, *J* = 7.5 Hz, 2H), 7.80 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.41 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 4.64 – 4.59 (m, 2H), 4.43 – 4.39 (m, 2H), 1.89 (s, 3H). **^{13}C NMR (126 MHz, DMSO- d$_6$), ppm:** 169.8, 150.8, 147.1, 139.9, 134.7, 132.2, 128.8, 128.1, 125.2, 119.4, 103.2, 48.7, 45.1, 13.8. **FTIR (neat, cm^{-1}), ν_{max}:** 3068 (w), 3023 (w), 2970(w), 2909 (w), 1659 (s), 1600 (m), 1565 (m), 1536 (s), 1479 (m). **HRMS** calculated for $C_{16}H_{14}N_4O$ (ESI$^+$): 279.1240. Found: 279.1247.

2.3. Synthesis of thiophene-5-trifluoroborates

2.3.1. Condensation of ynone trifluoroborates and methylthioglycolate

General procedure Q - Methylthioglycolate (1.1 eq) was added to a solution of ynone trifluoroborate (1.0 eq) in anhydrous acetonitrile (0.30 M) at 0 °C. The reaction was left to stir for 2 hrs at 0 °C before sequential addition of methanol (2/3, v/v, methanol/acetonitrile) and potassium carbonate (2.0 eq). The conversion was monitored by ^{19}F NMR spectroscopy. When complete conversion was reached, all volatiles were removed under vacuum. The residue was extracted with acetone (3 times the volume of acetonitrile) by stirring for 30 min and then the solid was removed by filtration and washed with acetone. The solvent from the combined extracts was removed under vacuum and the products were obtained by precipitation from acetone and ether (Et_2O or TBME).

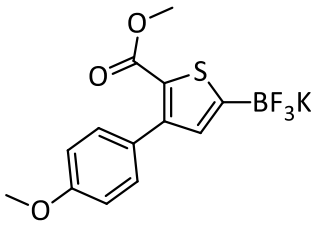
Methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 67



Following general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (2.0 g, 8.5 mmol), methylthioglycolate (0.9 mL, 9.0 mmol) in acetonitrile (30 mL), with subsequent addition of methanol (20 mL) and K_2CO_3 (2.0 g, 17.0 mmol), the title compound was obtained as a pink solid (2.52 g, 92% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.41 – 7.30 (m, 5H), 6.86 (s, 1H), 3.64 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 162.5, 148.1, 136.6, 132.1, 129.1, 127.6, 127.1, 124. 8, 51.3. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -135.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 2.0. **m. pt.** 228 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2945 (w), 1667 (m),

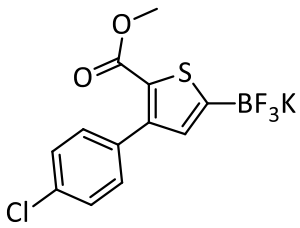
1493 (w), 1269 (s), 1117 (s), 1085 (s). **HRMS** calculated for $C_{12}H_9{}^{11}BF_3O_2S$ (ESI^-): 285.0376. Found: 285.0390.

Methyl 3-(4-methoxyphenyl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 68



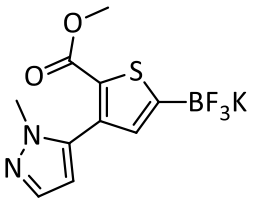
Following general procedure Q, using potassium trifluoro(3-oxo-3-(4-methoxyphenyl)prop-1-yn-1-yl)borate **17** (0.54 g, 2.0 mmol), methylthioglycolate (0.2 mL, 2.2 mmol) in acetonitrile (7 mL), with subsequent addition of methanol (4.7 mL) and K_2CO_3 (0.57 g, 4.0 mmol), the title compound was obtained as a pink solid (0.49 g, 68% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.35 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.84 (s, 1H), 3.79 (s, 3H), 3.64 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 162.6, 158.5, 147.9, 132.1, 130.3, 128.9, 124.0, 113.0, 55.0, 51.2. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -135.4. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 1.9. **m. pt.** 188-189 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2936 (w), 1685 (m), 1505 (m), 1441 (m), 1244 (s), 1118 (s), 1081 (s). **HRMS** calculated for $C_{13}H_{11}{}^{11}BF_3O_3S$ (ESI^-): 315.0482. Found: 315.0494.

Methyl 3-(4-chlorophenyl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 69



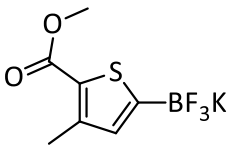
Following general procedure Q, using potassium trifluoro(3-oxo-3-(4-chlorophenyl)prop-1-yn-1-yl)borate **18** (0.20 g, 0.7 mmol), methylthioglycolate (0.1 mL, 1.0 mmol) in acetonitrile (2.4 mL), with subsequent addition of methanol (1.6 mL) and K_2CO_3 (0.20 g, 1.4 mmol), the title compound was obtained as a pink solid (0.18 g, 73% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.41 (s, 4H), 6.86 (s, 1H), 3.65 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 162.4, 146.7, 135.4, 131.91, 131.89, 130.9, 127.6, 125.1, 51.4. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -135.4. **^{11}B NMR (128 MHz, DMSO), ppm:** 2.0. **m. pt.** 263-264 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2949 (w), 1685 (m), 1663 (s), 1438 (m), 1278 (s), 1171 (m), 1115 (s), 1083 (s), 828 (s). **HRMS** calculated for $C_{12}H_8{}^{11}B^{35}ClF_3O_2S$ (ESI^-): 318.9986. Found: 318.9996.

Methyl 3-(1-methyl-1H-pyrazol-5-yl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 70



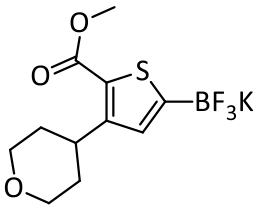
Following general procedure Q, using potassium 1-(1-methyl-*1H*-pyrazol-5-yl)-3-(trifluoroboranyl)prop-2-yn-1-one **19** (142 mg, 0.60 mmol), methylthioglycolate (0.1 mL, 0.66 mmol) in acetonitrile (2.0 mL), with subsequent addition of methanol (1.3 mL) and K_2CO_3 (165 mg, 1.20 mmol), the title compound was obtained as a pink solid (160 mg, 82% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.40 (d, *J* = 2.0 Hz, 1H), 6.81 (s, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 161.7, 137.9, 137.3, 135.9, 131.8, 127.9, 106.1, 51.6, 36.6. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -135.5. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.7. **m. pt.** 215 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3031 (w), 2957 (w), 2357 (w), 1705 (m), 1283 (m), 1090 (s). **HRMS** calculated for $C_{10}H_9{}^{11}BF_3N_2O_2S$ (ESI^-): 289.0435. Found: 289.0443.

Methyl 3-methyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 71



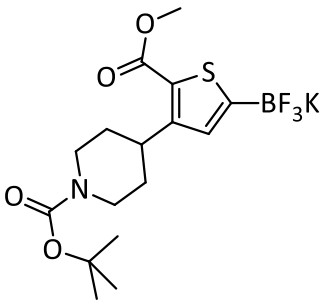
Following general procedure Q, using potassium trifluoro(3-oxobut-1-yn-1-yl)borate (100 mg, 0.60 mmol), methylthioglycolate **20** (0.1 mL, 0.66 mmol) in acetonitrile (2.0 mL), with subsequent addition of methanol (1.5 mL) and K_2CO_3 (160 mg, 1.20 mmol), the title compound was obtained as a pink solid (130 mg, 87% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 6.73 (s, 1H), 3.71 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 163.2, 145.7, 132.7, 124.2, 51.2, 15.7. **^{19}F NMR (377 MHz, DMSO-d_6), ppm:** -135.3. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 2.1. **m. pt.** > 300 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2949 (w), 1708 (s), 1540 (m), 1443 (m), 1264 (s), 1128 (s), 1093 (s). **HRMS** calculated for $C_7H_7{}^{11}BF_3O_2S$ (ESI^-): 223.0219. Found: 223.0224.

Methyl 3-(tetrahydro-2H-pyran-4-yl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 72



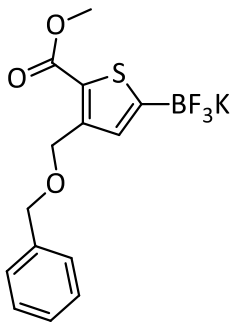
Following general procedure Q, using potassium 1-(tetrahydro-*2H*-pyran-4-yl)-3-(trifluoroboranyl)prop-2-yn-1-one **21** (198 mg, 0.82 mmol), methylthioglycolate (0.08 mL, 0.90 mmol) in acetonitrile (2.8 mL), with subsequent addition of methanol (1.9 mL) and K_2CO_3 (233 mg, 1.64 mmol), the title compound was obtained as a deep purple solid (143 mg, 53% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 6.89 (s, 1H), 3.96 - 3.89 (m, 2H), 3.74 – 3.63 (m, 4H), 3.43 – 3.36 (m, 2H), 1.67 - 1.62 (m, 4H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 162.8, 154.4, 128.1, 123.5, 67.6, 51.2, 34.9, 33.2. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -135.3. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.8. **m. pt.** 227-228 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 2967 (w), 2940 (w), 2859 (w), 2360 (w), 1695 (s), 1526 (m), 1449 (m), 1240 (s), 1120 (s). **HRMS** calculated for $C_{11}H_{13}{}^{11}BF_3O_3S$ (ESI^-): 293.0636. Found: 293.0628.

tert-Butyl 4-(2-(methoxycarbonyl)-5-(trifluoro-l4-boranyl)thiophen-3-yl)piperidine-1-carboxylate, potassium salt, 73



Following general procedure Q, using potassium *tert*-butyl 4-(3-(trifluoroboranyl)porpioloyl)piperidine-1-carboxylate **22** (201 mg, 0.58 mmol), methylthioglycolate (0.06 mL, 0.64 mmol) in acetonitrile (2.0 mL), with subsequent addition of methanol (1.3 mL) and K_2CO_3 (161 mg, 1.16 mmol), the title compound was obtained as an orange solid (140 mg, 55% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 6.85 (s, 1H), 4.11 - 4.00 (m, 2H), 3.73 (s, 3H), 3.62 (tt, *J* = 7.5, 3.5 Hz, 1H), 2.82 - 2.72 (m, 2H), 1.75 - 1.66 (m, 2H), 1.50 – 1.41 (m, 11H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 162.8, 154.1, 153.9, 128.0, 123.6, 78.5, 51.2, 44.3, 35.8, 32.3, 28.1. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -135.3. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.9. **m. pt.** 157 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 2975 (w), 1671 (s), 1430 (m), 1247 (s), 1122 (s), 1083 (s). **HRMS** calculated for $C_{16}H_{22}{}^{11}BF_3NO_4S$ (ESI^-): 392.1320. Found: 392.1338.

Methyl 3-((benzyloxy)methyl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, 74

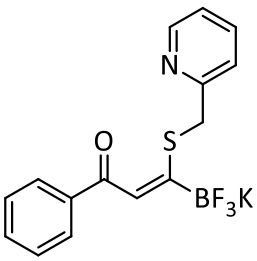


Following general procedure Q, using potassium 1-(benzyloxy)-4-(trifluoroboranyl)but-3-yn-2-one **23** (114 mg, 0.41 mmol), methylthioglycolate (0.04 mL, 0.45 mmol) in acetonitrile (1.4 mL), with subsequent addition of methanol (0.75 mL) and K_2CO_3 (115 mg, 0.81 mmol), the title compound was obtained as a deep purple solid (84 mg, 56% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.38 – 7.28 (m, 5H), 7.05 (s, 1H), 4.79 (s, 2H), 4.56 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 162.7, 147.3, 138.5, 129.6, 128.3, 127.4, 127.3, 124.4, 66.9, 64.9, 51.4. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm**: -135.4. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.8. **m. pt.** 134 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3031 (w), 2951 (w), 2860 (w), 1700 (s), 1540 (m), 1450 (m), 1347 (m), 1278 (s), 1089 (s). **HRMS** calculated for $C_{14}H_{13}{}^{11}BF_3O_3S$ (ESI^-): 329.0636. Found: 329.0646.

2.3.2. Condensation with various methylthiols

When using another thiol, *general procedure Q* (page 232) gave 1,4-adduct which were isolated in the following cases.

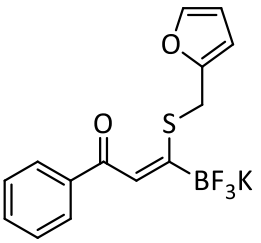
Potassium trifluoro(3-oxo-3-phenyl-1-((pyridin-2-ylmethyl)thio)prop-1-en-1-yl)borate, 82



Following general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (208 mg, 0.88 mmol), pyridine-2-methanethiol (150 mg, 1.06 mmol) in acetonitrile (2.8 mL), with subsequent addition of methanol (1.9 mL) and K_2CO_3 (244 mg, 1.76 mmol), the title compound was obtained as a brown oil (180 mg, 60% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.49 (m, 1H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.74 (td, *J* = 8.0, 1.5 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.26 – 7.22 (m, 1H), 4.40 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 186.5, 158.7, 149.0, 139.5, 136.6, 131.2, 128.5, 127.2, 123.5, 121.8, 115.8, 39.7. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -137.0. **^{11}B NMR**

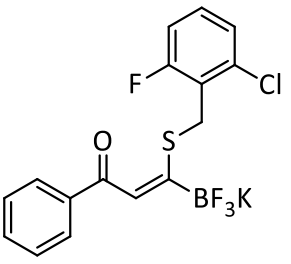
(128 MHz, DMSO), ppm: 1.4. **FTIR (neat, cm^{-1}), ν_{max}:** 3108 (w), 3064 (w), 2955 (w), 1700 (s), 1599 (m), 1576 (m). **HRMS** calculated for $C_{15}H_{12}{}^{11}BF_3NOS$ (ESI^-): 322.0690. Found: 322.0696.

Potassium trifluoro(1-((furan-2-ylmethyl)thio)-3-oxo-3-phenylprop-1-en-1-yl)borate, 83



Following general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (199 mg, 0.84 mmol), furfuryl mercaptan (132 mg, 1.01 mmol) in acetonitrile (2.8 mL), with subsequent addition of methanol (1.9 mL) and K_2CO_3 (234 mg, 1.69 mmol), the title compound was obtained as a light yellow solid (207 mg, 70% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.82 (d, *J* = 7.0 Hz, 2H), 7.57 (m, 1H), 7.53 – 7.44 (m, 3H), 7.25 (s, 1H), 6.39 (m, 1H), 6.29 (d, *J* = 3.0 Hz, 1H), 4.31 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 186.6, 152.1, 142.1, 139.4, 131.3, 128.5, 127.3, 115.8, 110.6, 107.4, 29.2. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -137.1. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.2. **m. pt.** 48 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3124 (w), 1615 (s), 1598 (s), 1576 (s), 1513 (s), 1490 (s). **HRMS** calculated for $C_{14}H_{11}{}^{11}BF_3O_2S$ (ESI^-): 311.0530. Found: 311.0538.

Potassium (1-((2-chloro-6-fluorobenzyl)thio)-3-oxo-3-phenylprop-1-en-1-yl)trifluoroborate, 84

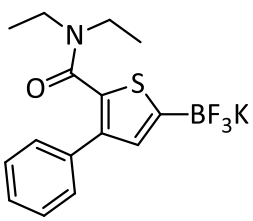


Following general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (207 mg, 0.88 mmol), (2-chloro-6-fluorophenyl)methanethiol (190 mg, 1.05 mmol) in acetonitrile (2.8 mL), with subsequent addition of methanol (1.9 mL) and K_2CO_3 (243 mg, 1.75 mmol), the title compound was obtained as a light yellow solid (202 mg, 56 % yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.82 (d, *J* = 7.0 Hz, 2H), 7.53 – 7.44 (m, 3H), 7.42 – 7.33 (m, 2H), 7.29 – 7.21 (m, 2H), 4.47 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 186.6, 161.2 (d, *J* = 248.0 Hz), 139.3, 134.8 (d, *J* = 5.5 Hz), 131.3, 129.6 (d, *J* = 10.0 Hz), 128.5, 127.3, 125.5 (d, *J* = 3.5 Hz), 124.1 (d, *J* = 18.5 Hz), 115.9 (s), 114.5 (d, *J* = 22.5 Hz), 39.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -113.1, -137.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.2. **m. pt.** 195 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3094 (w), 3063 (w), 2975 (w), 2963 (w), 1624 (m), 1578 (m), 1520 (s), 1452 (s), 1232 (s). **HRMS** calculated for$C_{16}H_{11}{}^{11}B^{35}ClF_4OS$: 373.0254. Found: 373.0264.

Modified General Procedure Q -Condensation of phenyl-ynone trifluoroborates and other substituted-methanethiols

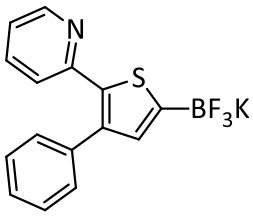
Methanethiol (1.1 eq) was added to a solution of potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (1.0 eq) in anhydrous acetonitrile (0.30 M) at 0 °C. The reaction was left to stir for 2 hrs at 0°C before sequential addition of *tert*-butanol (2/3, v/v, methanol/acetonitrile) and potassium *tert*-butoxide (2.0 eq). The conversion was monitored by ^{19}F NMR spectroscopy. When complete conversion was reached, all volatiles were removed under vacuum. The residue was extracted with acetone (3 times the volume of acetonitrile) by stirring for 30 min and then the solid was removed by filtration and washed with acetone. The solvent from the combined extracts was removed under vacuum and the products were obtained by precipitation from acetonitrile and TBME.

N,N-Diethyl-3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxamide, potassium salt, 75



Following the modified general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (204 mg, 0.88 mmol), *N,N*-diethyl-2-sulfanylacetamide (157 mg, 0.96 mmol) in acetonitrile (2.8 mL), with subsequent addition of *tert*-butanol (1.9 mL) and KO^{t}Bu (193 mg, 1.75 mmol), the title compound was obtained as a brown solid (180 mg, 61% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 7.43 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 3.22 (q, *J* = 7.0 Hz, 4H), 0.93 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 166.3, 139.1, 137.1, 131.6, 128.7, 128.0, 127.8, 127.1, 40.7, 13.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -134.5. **^{11}B NMR (128 MHz, DMSO), ppm:** 2.0. **m. pt.** 60-61 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 2975 (w), 1598 (s), 1484 (m), 1461 (m), 1441 (m), 1123 (s). **HRMS** calculated for $C_{15}H_{16}{}^{11}BF_3NOS$ (ESI^-): 326.1003. Found: 326.1019.

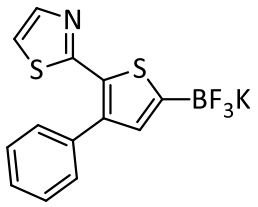
2-(3-Phenyl-5-(trifluoro-l4-boranyl)thiophen-2-yl)pyridine, potassium salt, 76



Following the modified general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (207 mg, 0.88 mmol), pyridine-2-methanethiol (127 mg, 0.96 mmol) in acetonitrile (2.8 mL), with subsequent addition of *tert*-butanol (1.9 mL) and KO^{t}Bu (196 mg,

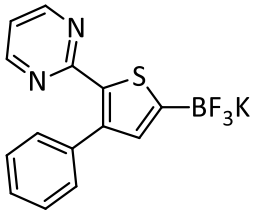
1.75 mmol), the title compound was obtained as a brown solid (180 mg, 60% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.49 (d, *J* = 5.0 Hz, 1H), 7.48 (td, *J* = 8.0, 2.0 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.30 - 7.27 (m, 3H), 7.11 (dd, *J* = 6.5, 5.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 153.7, 149.3, 139.6, 137.9, 137.4, 135.8, 131.5, 128.6, 128.5, 126.8, 121.2, 121.0. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -134.7. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 2.1. **m. pt.** 122 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3282 (w), 1587 (w), 1563 (w), 1475 (w), 1429 (w). **HRMS** calculated for $C_{15}H_{10}{}^{11}BF_3NS$ (ESI^-): 304.0585. Found: 304.0594.

Potassium trifluoro(4-phenyl-5-(thiazol-2-yl)thiophen-2-yl)borate, 80



Following the modified general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (102 mg, 0.42 mmol), thiazol-2-ylmethanethiol (68 mg, 0.47 mmol) in acetonitrile (1.5 mL), with subsequent addition of *tert*-butanol (0.75 mL) and KO^{t}Bu (96 mg, 0.85 mmol), the title compound was obtained as a brown solid (104 mg, 69% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.68 (d, *J* = 3.0 Hz, 1H), 7.45 – 7.33 (m, 6H), 6.77 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 161.1, 141.9, 141.8, 136.8, 131.3, 130.8, 129.2, 128.7, 127.7, 118.9. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -134.8. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.8. **m. pt.** 132 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3055 (w), 1610 (m), 1599 (m), 1576 (w), 1547 (s). **HRMS** calculated for $C_{13}H_8{}^{11}BF_3NS_2$ (ESI^-): 310.0149. Found: 310.0160.

Potassium trifluoro(4-phenyl-5-(pyrimidin-2-yl)thiophen-2-yl)borate, 81



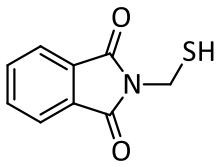
Following the modified general procedure Q, using potassium trifluoro(3-oxo-3-phenylprop-1-yn-1-yl)borate **16** (103 mg, 0.42 mmol), pyrimidin-2-ylmethanethiol (78 mg, 0.47 mmol) in acetonitrile (1.5 mL), with subsequent addition of *tert*-butanol (0.75 mL) and KO^{t}Bu (102 mg, 0.85 mmol), the title compound was obtained as a brown solid (100 mg, 66% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.58 (d, *J* = 5.0 Hz, 1H), 7.34 – 7.20 (m, 3H), 7.16 (t, *J* = 5.0 Hz, 1H), 6.85 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 162.3, 156.9, 143.0, 138.2, 135.3, 132.7, 129.0, 127.6, 126.4, 118.1. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -134.9. **^{11}B NMR (128 MHz, DMSO), ppm:** 1.9. **m. pt.** 165 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3048

(w), 1601 (m), 1569 (s), 1553 (s), 1532 (m). **HRMS** calculated for $C_{14}H_9{}^{11}BF_3N_2S$ (ESI^-): 305.0537. Found: 305.0542.

2.3.3. General procedure R. Synthesis of methanethiols

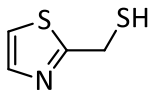
A solution of sodium thiophosphate dodecahydrate (1.1 eq) in water (0.2 M) was added to a solution of halogenated substrate (1.0 eq) in *N,N*-DMF (1 M) at rt. After 5 hrs, the reaction is acidified to pH 4 with 1 M HCl. After 18-20 hrs, the product was extracted with ethyl acetate, washed with brine, dried on $MgSO_4$ and the volatiles removed under vacuum. The product thiols were used directly as obtained

2-(Mercaptomethyl)isoindoline-1,3-dione, 77



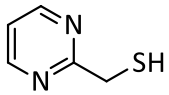
Following general procedure R, using 2-(chloromethyl)isoindoline-1,3-dione (508 mg, 2.6 mmol) in *N,N*-DMF (3 mL) and sodiumthiophosphate dodecahydrate (2.03 g, 5.1 mmol) in water (13 mL). The title compound[120] was obtained as a colourless oil (114 mg, 22% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.87 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 1H), 4.74 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 166.9, 134.4, 132.1, 123.6, 32.1.

Thiazol-2-ylmethanethiol, 78



Following general procedure R, using 2-(bromomethyl)thiazole (656 mg, 5.0 mmol) in *N,N*-DMF (5 mL) and sodiumthiophosphate dodecahydrate (2.18 g, 5. 5 mmol) in water (25 mL). The title compound[121] was obtained as a colourless oil (208 mg, 32% yield) and used directly because of its instability. **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.75 (d, *J* = 3.5 Hz, 1H), 7.39 (d, *J* = 3.5 Hz, 1H), 4.76 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 165.8, 143.2, 121.4, 26.6. **FTIR (neat, cm^{-1}), ν_{max}:** 3080 (w), 2921 (m), 1664 (m), 1496 (s), 1078 (s). **HRMS** calculated for $C_4H_5NS_2$ (ESI^+): 130.9858. Found: 130.9863.

Pyrimidin-2-ylmethanethiol, 79

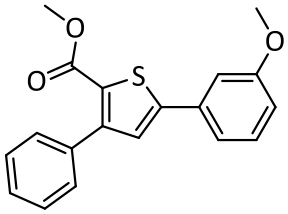


Following general procedure R, using 2-(chloromethyl)pyrimidine (744 mg, 5.8 mmol) in *N,N*-DMF (6 mL) and sodiumthiophosphate dodecahydrate (2.56 g, 6.4 mmol) in water (30 mL). The title compound was as a colourless oil (259 mg, 36% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 8.70 (d, *J* = 5.0 Hz, 2H), 7.18 (t, *J* = 5.0 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 2H), 2.14 (t, *J* = 8.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 169.5, 157.5, 119.1, 31.9**. FTIR (neat, cm^{-1}), ν_{max}:** 3040 (w), 2921 (w), 1561 (s), 1413 (s). **HRMS** calculated for $C_5H_6N_2S$ (ESI^+): 127.0324. Found: 127.0326.

2.3.4. General Procedure S - Suzuki-Miyaura cross coupling

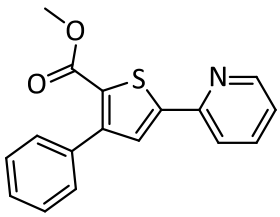
In a sealable microwave tube, were sequentially introduced **79** (1.1 eq), the brominated coupling partner (1.0 eq), $Pd(PPh_3)_4$ (7 mol %), K_3PO_4 (3.0 eq) and the mixture of solvent (0.2 M - 1,4-dioxane/water, 4/1). The mixture was placed in the microwave oven for 45 min at 140 °C, with 60 s of pre-stirring at 'High Absorption' and no stirring during the reaction. All volatiles were removed from the mixture and the residue was dissolved in water. The crude was extracted with dichloromethane and purified by reversed phase chromatography to yield the pure compound.

Methyl 5-(3-methoxyphenyl)-3-phenylthiophene-2-carboxylate, 85



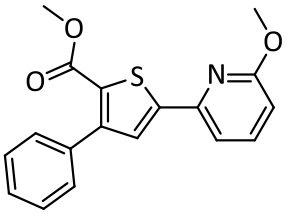
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (102 mg, 0.31 mmol), 1-bromo-3-methoxybenzene (36 µL, 0.28 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), K_3PO_4 (178 mg, 0.84 mmol) in 1,4-dioxane/water (1.4 mL - 4/1 mixture). The title compound was obtained after purification by reversed phase chromatography as a colourless oil (63 mg, 68% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.70 (s, 1H), 7.54 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.45 – 7.40 (m, 3H), 7.37-7.35 (m, 3H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 161.5, 159.8, 149.0, 147.3, 135.0, 133.6, 130.4, 129.2, 128.4, 128.0, 127.8, 124.5, 118.3, 115.2, 111.0, 55.3, 52.0. **FTIR (neat, cm^{-1}), ν_{max}:** 3063 (w), 3016 (w), 3008 (w), 2949 (w), 2935 (w), 1717 (s), 1598 (m), 1579 (w), 1454 (s), 1436 (s), 1247 (s), 1076 (s). **HRMS** calculated for $C_{19}H_{16}O_3S$ (ESI^+): 325.0893. Found: 325.0898.

Methyl 3-phenyl-5-(pyridin-2-yl)thiophene-2-carboxylate, 86



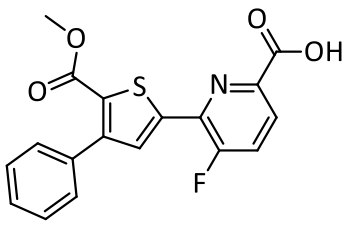
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (180 mg, 0.55 mmol), 2-bromopyridine (48 µL, 0.50 mmol), $Pd(PPh_3)_4$ (41 mg, 0.04 mmol), K_3PO_4 (329 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by silica gel chromatography as a light brown solid (146 mg, 99% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 8.62 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.55 (s, 1H), 7.51 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.45 – 7.37 (m, 3H), 7.26 – 7.21 (m, 1H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.6, 151.6, 150.0, 149.5, 148.5, 137.0, 135.9, 129.3, 128.4, 128.2, 128.0, 127.9, 123.3, 119.4, 52.1. **m. pt.** 114-115 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3043 (w), 2998 (w), 2950 (w), 1684 (s), 1446 (m), 1430 (m), 1373 (m), 1298 (s), 1279 (s), 1034 (s). **HRMS** calculated for $C_{17}H_{13}NO_2S$ (ESI^+): 296.0740. Found: 296.0745.

Methyl 5-(6-methoxypyridin-2-yl)-3-phenylthiophene-2-carboxylate, 87



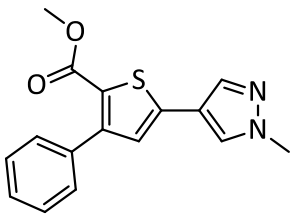
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (178 mg, 0.55 mmol), 2-bromo-6-methoxypyridine (61.5 µL, 0.50 mmol), $Pd(PPh_3)_4$ (42 mg, 0.04 mmol), K_3PO_4 (337 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by reversed phase chromatography as a colourless solid (135 mg, 83% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 7.88 (s, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 6.0 Hz, 2H), 7.46 – 7.39 (m, 3H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 163.0, 161.7, 148.8, 148.0, 140.2, 135.1, 129.2, 128.6, 128.0, 127.8, 126.4, 112.5, 110.7, 53.1, 51.9. **m. pt.** 109 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3109 (w), 2952 (w), 1715 (s), 1574 (m), 1465 (m), 1420 (m), 1210 (s), 1086 (s). **HRMS** calculated for $C_{15}H_{16}{}^{11}BF_3NOS$ (ESI^+): 326.0845. Found: 326.0852.

5-Fluoro-6-(5-(methoxycarbonyl)-4-phenylthiophen-2-yl)picolinic acid, 88



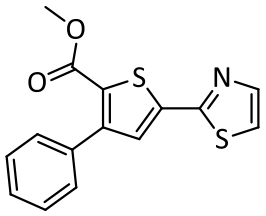
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (180 mg, 0.55 mmol), 6-bromo-5-fluoropicolinic acid (109 mg, 0.50 mmol), $Pd(PPh_3)_4$ (40 mg, 0.04 mmol), K_3PO_4 (322 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by reversed phase chromatography as a colourless solid (100 mg, 56% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 13.48 (s, 1H), 8.11 (dd, *J* = 8.5, 4.0 Hz, 1H), 8.04 (dd, *J* = 10.5, 8.5 Hz, 1H), 7.82 (d, *J* = 1.5 Hz, 1H), 7.53 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.48 – 7.38 (m, 3H), 3.75 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 164.6, 161.5, 157.4 (d, *J* = 267.0 Hz), 148.4, 144.6 (d, *J* = 4.0 Hz), 141.7 (d, *J* = 8.0 Hz), 138.5 (d, *J* = 12.5 Hz), 134.8, 131.7 (d, *J* = 11.0 Hz), 129.1, 128.2, 128.0 (d, *J* = 4.0 Hz), 127.9, 126.8 (d, *J* = 6.0 Hz), 126.0 (d, *J* = 20.0 Hz), 52.2. **^{19}F NMR (376 MHz, DMSO-d_6), ppm:** -115.7**. m. pt.** 190-191 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2961 (w), 2865 (w), 2605 (w), 1716 (s), 1701 (s), 1444 (m), 128° (s), 1250 (s), 1083 (s). **HRMS** calculated for $C_{18}H_{12}FNO_4S$ (ESI^+): 358.0544. Found: 358.0548.

Methyl 5-(1-methyl-1H-pyrazol-4-yl)-3-phenylthiophene-2-carboxylate, 89



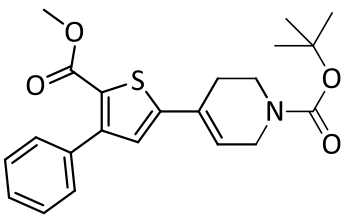
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (180 mg, 0.55 mmol), 4-bromo-1-methyl-*1H*-pyrazole (83 mg, 0.50 mmol), PdSPhosG2 (26 mg, 0.04 mmol), Na_2CO_3 (110 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after purification by reversed phase chromatography as a colourless oil (15 mg, 10% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.76 (s, 1H), 7.63 (s, 1H), 7.47 (d, *J* = 6.5 Hz, 2H), 7.44 – 7.37 (m, 3H), 7.04 (s, 1H), 3.96 (s, 3H), 3.77 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm**: 162.5, 149.7, 139.5, 137.0, 135.7, 129.3, 128.2, 128.04, 127.99, 127.0, 123.7, 116.5, 52.0, 39.2. **FTIR (neat, cm^{-1}), ν_{max}:** 2951 (w), 1686 (s), 1584 (m), 1534 (w), 1394 (s), 1273 (s), 1078 (s). **HRMS** calculated for $C_{16}H_{14}N_2O_2S$ (ESI^+): 299.0849. Found: 299.0858.

Methyl 3-phenyl-5-(thiazol-2-yl)thiophene-2-carboxylate, 90



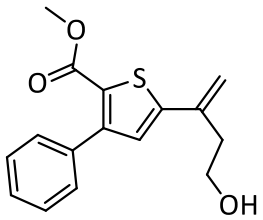
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (180 mg, 0.55 mmol), 2-bromothiazole (45 µL, 0.50 mmol), $Pd(PPh_3)_4$ (42 mg, 0.04 mmol), K_3PO_4 (333 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by reversed phase chromatography as a colourless solid (77 mg, 51% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.85 (d, *J* = 3.0 Hz, 1H), 7.50 – 7.39 (m, 6H), 7.36 (d, *J* = 3.0 Hz, 1H), 3.80 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.3, 160.7, 149.2, 144.1, 140.7, 135.2, 130.0, 129.3, 128.4, 128.1, 127.8, 119.8, 52.3. **m. pt.** 107-108 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3120 (w), 3093 (w), 3068 (w), 2949 (w), 1716 (s), 1483 (m), 1452 (m), 1259 (s), 1210 (s), 1122 (s), 1081 (s). **HRMS** calculated for $C_{15}H_{11}NO_2S_2$ (ESI^+): 302.0304. Found: 302.0312.

tert-Butyl 4-(5-(methoxycarbonyl)-4-phenylthiophen-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate, 91



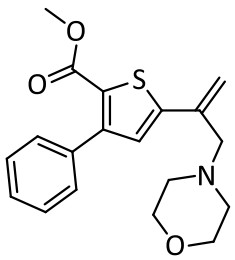
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (206 mg, 0.55 mmol), *tert*-butyl 4-bromo-3,6-dihydropyridine-1(*2H*)-carboxylate (140 mg, 0.50 mmol), PdSPhosG2 (24 mg, 0.04 mmol), Na_2CO_3 (114 mg, 1.00 mmol) in ethanol (2.5 mL). The title compound was obtained after purification by reversed phase chromatography as an orange oil (124 mg, 62% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.47 – 7.39 (m, 5H), 6.98 (s, 1H), 6.25 (s, 1H), 4.15 - 4.09 (m, 2H), 3.77 (s, 3H), 3.65 (t, *J* = 5.5 Hz, 2H), 2.57 - 2.51 (m, 2H), 1.51 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.5, 154.8, 149.1, 148.8, 135.8, 129.6, 129.2, 128.1, 127.9, 126.5, 124.2, 122.7, 80.1, 52.0, 43.8, 39.8, 28.5, 27.3. **FTIR (neat, cm^{-1}), ν_{max}:** 2964 (w), 1697 (s), 1429 (s), 1250 (s), 1211 (s), 1081 (s). **HRMS** calculated for $C_{22}H_{25}NO_4S$ (ESI^+): 400.1577. Found: 400.1581.

Methyl 5-(4-hydroxybut-1-en-2-yl)-3-phenylthiophene-2-carboxylate, 92



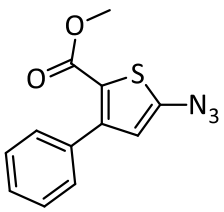
Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (180 mg, 0.55 mmol), 3-bromobut-3-en-1-ol (78 mg, 0.50 mmol), $Pd(PPh_3)_4$ (42 mg, 0.04 mmol), K_3PO_4 (333 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by silica gel chromatography as a light yellow oil (48 mg, 33% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.46 – 7.38 (m, 5H), 7.05 (s, 1H), 5.67 (s, 1H), 5.21 (s, 1H), 3.85 (t, *J* = 6.5 Hz, 2H), 3.76 (s, 3H), 2.75 (td, *J* = 6.5, 1.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.4, 149.2, 148.5, 137.7, 135.7, 129.2, 128.2, 128.1, 128.0, 125.2, 115.8, 61.1, 52.1, 38.5. **FTIR (neat, cm^{-1}), ν_{max}:** 3408 (w), 2950 (w), 1716 (s), 1452 (m), 1440 (m), 1253 (s), 1080 (s). **HRMS** calculated for $C_{16}H_{16}O_3S$ (ESI^+): 289.0893. Found: 289.0898.

Methyl 5-(3-morpholinoprop-1-en-2-yl)-3-phenylthiophene-2-carboxylate, 93



Following general procedure S, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (178 mg, 0.55 mmol), 4-(2-bromoallyl)morpholine (107 mg, 0.50 mmol), $Pd(PPh_3)_4$ (42 mg, 0.04 mmol), K_3PO_4 (317 mg, 1.50 mmol) in 1,4-dioxane/water (2.5 mL - 4/1 mixture). The title compound was obtained after purification by silica gel chromatography as a yellow oil (45 mg, 26% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.47 – 7.37 (m, 5H), 7.24 (s, 1H), 5.67 (s, 1H), 5.27 (d, *J* = 1.0 Hz, 1H), 3.76 (s, 3H), 3.74 (t, *J* = 4.5 Hz, 4H), 3.28 (s, 2H), 2.51 (t, *J* = 4.5Hz, 4H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.8, 148.5, 147.4, 137.5, 136.1, 129.2, 128.5, 128.0, 127.9, 125.8, 116.5, 67.1, 63.8, 53.4, 52.0. **FTIR (neat, cm^{-1}), ν_{max}:** 2957 (w), 2856 (w), 2807 (w), 1706 (s), 1447 (m), 1269 (s), 1251 (s). **HRMS** calculated for $C_{19}H_{21}NO_3S$ (ESI^+): 344.1315. Found: 344.1322.

2.3.5. Azidonation of thiophene-5-trifluoroborates

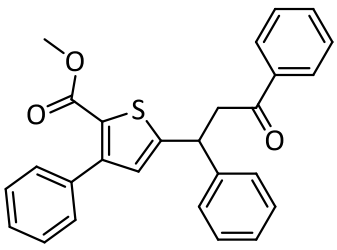


To a solution of methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, **67** (50 mg, 0.15 mmol) in methanol (0.8 mL) was added sodium azide (16 mg, 0.23 mmol) as a solution in water (0.2 mL) followed by tetrakis(acetonitrile)copper(I) tetrafluoroborate (24 mg, 0.08 mmol). The mixture was heated at 55 °C overnight. After being allowed to cool down to rt, the mixture was filtered through Celite and washed with acetone. The solvent was removed under vacuum and the residue purified by flash chromatography on silica gel (petrol/EtOAc, 100/0 to 90/10) to yield ***methyl 5-azido-3-phenylthiophene-2-carboxylate, 94*** as a colorless oil (9 mg, 23% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.46 – 7.39 (m, 5H), 6.66 (s, 1H), 3.77 (s, 3H). **MS**, $[M+H]^+$: 260.0. This compound decomposes too rapidly to allow for a clean measurement of ^{13}C NMR and IR spectra.

2.3.7. Addition of thiophene-5-trifluoroborates to enone

General procedure T - Boron trifluoride diethyl etherate (1.5 eq) was added to a solution of methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (2.0 eq) in dry CH_2Cl_2 (0.2 M) under inert atmosphere. After a few minutes, enone (1.0 eq) was added and the mixture warmed to reflux and left stirring for 18-20 hrs. Saturated aqueous NaCl was then added, and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ before all volatiles were removed. The desired adduct was obtained after purification by silica gel chromatography.

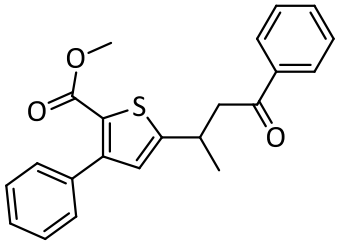
Methyl 5-(3-oxo-1,3-diphenylpropyl)-3-phenylthiophene-2-carboxylate, 96



Following general procedure **T**, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (62 mg, 0.19 mmol), boron trifluoride diethyl etherate (18 µL, 0.14 mmol) and €-chalcone (20 mg, 0.10 mmol) in dry CH_2Cl_2 (0.6 mL). The title compound was obtained after purification by flash chromatography as a colourless oil (27 mg, 66% yield).**^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.96

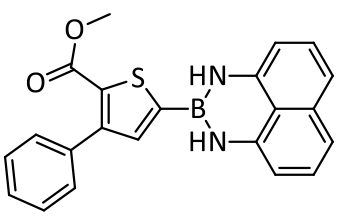
(d, *J* = 8.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.32 (m, 9H), 7.27 - 7.25 (m, 1H), 6.86 (d, *J* = 0.5 Hz, 1H), 5.06 (t, *J* = 7.0 Hz, 1H), 3.86 (dd, *J* = 17.5, 7.0 Hz, 1H), 3.76 (dd, *J* = 17.5, 7.0 Hz, 1H), 3.71 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 197.0, 162.5, 153.8, 148.9, 142.8, 136.7, 135.8, 133.6, 129.33, 129.30, 129.0, 128.8, 128.2, 128.1, 127.9, 127.8, 127.4, 124.8, 51.9, 45.8, 41.9. **FTIR (neat, cm^{-1}), ν_{max}:** 3039 (w), 3028 (w), 2949 (w), 2930 (w), 1716 (s), 1683 (s), 1597 (m), 1580 (w), 1545 (w), 1494 (s), 1250 (s), 1074 (s). **HRMS** calculated for $C_{27}H_{22}O_3S$ (ESI^+): 427.1362. Found: 427.1358.

Methyl 5-(4-oxo-4-phenylbutan-2-yl)-3-phenylthiophene-2-carboxylate, 97



Following general procedure **T**, using methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **67** (62 mg, 0.15 mmol), boron trifluoride diethyl etherate (12 µL, 0.11 mmol) and (E)-1-phenylbut-2-en-1-one (11.3 mg, 0.07 mmol) in dry CH_2Cl_2 (0.4 mL). The title compound was obtained after purification by flash chromatography as a colourless oil (27 mg, 66% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.96 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.51 – 7.35 (m, 7H), 6.89 (s, 1H), 3.92 – 3.79 (m, 1H), 3.74 (s, 3H), 3.42 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.26 (dd, *J* = 17.0, 7.5 Hz, 1H), 1.46 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 197.9, 162.6, 156.0, 148.9, 136.9, 136.0, 133.5, 129.3, 128.8, 128.3, 128.2, 128.0, 127.9, 124.0, 51.9, 47.4, 31.3, 22.6. **FTIR (neat, cm^{-1}), ν_{max}:** 3059 (w), 2951 (w), 2922 (w), 2846 (w), 1716 (s), 1683 (s), 1597 (m), 1580 (w), 1546 (w), 1495 (m), 1254 (s), 1075 (s). **HRMS** calculated for $C_{22}H_{20}O_3S$ (ESI^+): 365.1206. Found: 365.1207.

2.3.8. Ligand exchange on the boron

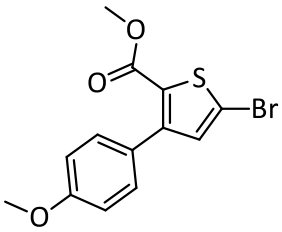


To a solution of methyl 3-phenyl-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt, **67** (100 mg, 0.31 mmol) and 1,8-diaminonaphthalene (55 mg, 0.34 mmol) in toluene (7 mL) under nitrogen, NEt_3 (90 µL, 0.62 mmol) was added. After 5 min, TMS-Cl (0.12 mL, 0.93 mmol) was added dropwise then the mixture was heated at reflux overnight. The solvent was removed under vacuum and the crude was purified by flash

chromatography on silica gel (petrol/CH_2Cl_2, gradient from 100/0 to 0/100) to yield ***methyl 5-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-3-phenylthiophene-2-carboxylate, 98*** as a yellow oil (69 mg, 58% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.47 (s, 2H), 7.89 (s, 1H), 7.56 - 7.40 (m, 5H), 7.10 (t, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 7.0 Hz, 2H), 3.75 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 161.8, 148.4, 141.8, 138.7, 136.0, 135.2, 130.1, 129.3, 128.0, 127.9, 127.7, 119.9, 116.8, 105.9, 52.1. **FTIR (neat, cm^{-1}), ν_{max}:** 3419 (m), 3405 (m), 3058 (w), 3020 (w), 1678 (s), 1598 (s), 1539 (s), 1510 (s), 1485 (m), 1335 (s), 1284 (s), 1090 (s). **HRMS** calculated for $C_{22}H_{17}{}^{11}BN_2O_2S$ (ESI^+): 385.1177. Found: 385.1191

2.3.9. Bromination reaction

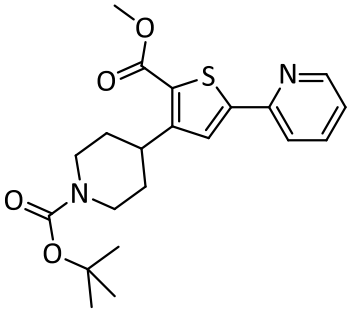
Methyl 5-bromo-3-(4-methoxyphenyl)thiophene-2-carboxylate, 99



A solution of *N*-bromosuccinide (79.2 mg, 1 eq) in MeCN (2 mL) was added to a solution of methyl 3-(4-methoxyphenyl)-5-(trifluoro-l4-boranyl)thiophene-2-carboxylate, potassium salt **68** (150.3 mg, 1 eq) in MeCN (1.2 mL) under nitrogen. After 1 hr, all volatiles were removed under vacuum. The title compound was obtained after purification by silica gel chromatography as a colorless solid (114 mg, 82% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 7.41 (d, *J* = 9.0 Hz, 2H), 7.07 (s, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 161.6, 159.9, 149.2, 134.5, 130.6, 126.8, 118.7, 113.5, 55.4, 52.2. **m. pt.** 135-136 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3080 (w), 3002 (w), 2977 (w), 2949 (w), 1725 (s), 1609 (m), 1581 (m), 1541 (w), 1502 (s), 1432 (s), 1249 (s), 1206 (s). **HRMS** calculated for $C_{13}H_{11}{}^{81}BrO_3S$ (ESI^+): 327.9587. Found: 327.9602.

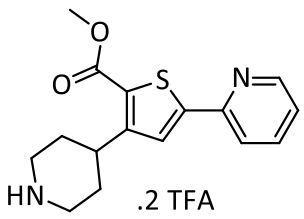
2.3.10. Library synthesis

tert-Butyl 4-(2-(methoxycarbonyl)-5-(pyridin-2-yl)thiophen-3-yl)piperidine-1-carboxylate, 111



Following general procedure S (see page 241), using tert-butyl 4-(2-(methoxycarbonyl)-5-(trifluoro-l4-boranyl)thiophen-3_yl)piperidine-1-carboxylate, potassium salt **73** (671 mg, 1.57 mmol), 2-bromopyridine (135 µL, 1.42 mmol), $Pd(PPh_3)_4$ (120 mg, 0.99 mmol), K_3PO_4 (934 mg, 4.25 mmol) in 1,4-dioxane/water (7.5 mL - 4/1 mixture). The title compound was obtained after purification by silica gel chromatography as an orange oil (277 mg, 49% yield). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 8.59 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.72 (td, *J* = 7.5, 1.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.52 (s, 1H), 7.22 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 4.33 – 4.17 (m, 2H), 3.88 (s, 3H), 3.79 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.86 (t, *J* = 12.0 Hz, 2H), 1.89 (d, *J* = 12.5 Hz, 2H), 1.63 (qd, *J* = 12.5, 3.5 Hz, 2H), 1.49 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 163.1, 155.4, 154.9, 151.6, 150.0, 149.0, 137.0, 126.9, 124.6, 123.2, 119.5, 79.6, 53.6, 52.0, 36.6, 32.7, 28.7. **FTIR (neat, cm^{-1}), ν_{max}:** 2942 (w), 2859 (w), 1700 (s), 1683 (s), 1420 (m), 1365 (m), 1245 (s). **HRMS** calculated for $C_{21}H_{26}N_2O_4S$ (ESI^+): 403.1686. Found: 403.1694.

Methyl 3-(piperidin-4-yl)-5-(pyridin-2-yl)thiophene-2-carboxylate, 112



Trifluoroacetic acid (3 mL, 20% v/v, TFA/CH_2Cl_2) was added to tert-butyl 4-(2-(methoxycarbonyl)-5-(pyridin-2-yl)thiophen-3-yl)piperidine-1-carboxylate **111** (1.29 g, 3.21 mmol) in dichloromethane (16 mL, 0.2 M) at 0 °C. The reaction was left to stir at 0 °C and the conversion followed by LC-MS. After for 5 hrs, complete conversion was observed. The volatiles were removed under vacuum to yield methyl 3-(piperidin-4-yl)-5-(pyridin-2-yl)thiophene-2-carboxylate, **112** as an orange oil (1.34 g, 100%). **^{1}H NMR (400 MHz, $CDCl_3$), ppm:** 9.52 (s, 1H), 9.04 (s, 1H), 8.65 (d, *J* = 5.0 Hz, 1H), 7.82 (td, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.31 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.00 – 3.91 (m, 1H), 3.89 (s, 3H), 3.60 – 3.54 (m, 2H), 3.20 – 3.01 (m, 2H), 2.19 – 2.05 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$), ppm:** 162.9, 152.7, 150.8, 149.2, 148.4, 138.1, 128.0, 124.8, 123.7, 120.2, 52.3, 44.8, 34.3, 29.2. **FTIR**

(neat, cm^{-1}), ν_{max}: 3359 (w), 2993 (w), 2813 (w), 2750 (w), 2532 (w), 1682 (s), 1656 (s), 1446 (m), 1428 (m), 1174 (s), 1125 (s). **HRMS** calculated for $C_{16}H_{18}N_2O_2S$ (ESI^+): 303.1162. Found: 303.1159.

General procedure for library G - For each of the 24 selected substrates, the library production was carried out according to the following procedure:

In a 4 mL Parr parallel microwave reactor, the mixture of aryl bromide partner (0.25 mmol, 1 eq), **72** (0.25 mmol, 1 eq) and potassium phosphate tribasic (0.75 mmol, 4 eq) were put under argon atmosphere. Subsequent addition of palladium(0)-tetrakis(triphenylphosphine) (0.01 mmol, 0.05 eq) and a 4/1 mixture of 1,4-dioxane and water (1.25 mL) was carried out. Microvawe irradiation was carried out (700 W, 140 °C) for 45 min (LC-MS monitoring). The resulting mixture was transferred into a RG24-flask and stirred with Si-TMT-Scavenger (100 mg) for 4 hours. It was then filtered and washed with DME (2 mL). The crude was evaporated and redissolved in *N,N*-DMF and purified by prep. HPLC.

Resulting compounds were then saponified as follows:

In a RG24 vial, compounds from the first step were dissolved in a 1/1 mixture of methanol and water (4 mL). Then an aqueous solution of sodium hydroxide (2M - 0.5 mL, 4 eq) was added and the mixture heated to 40°C until the reaction was complete (LC-MS monitoring). *N,N*-DMF (2 mL) was added to the crude and it was purified by prep. HPLC to yield compounds **G.01** to **G.11**.

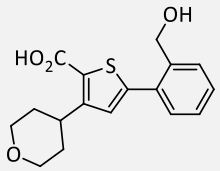
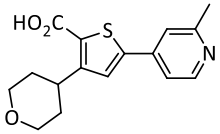
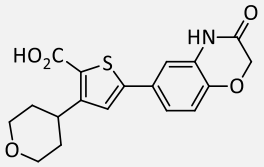
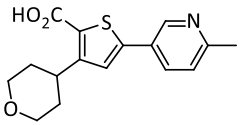
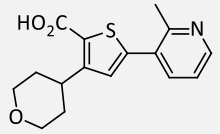
General procedure for library H - For each of the 20 selected substrates, the library production was carried out according to the following procedure:

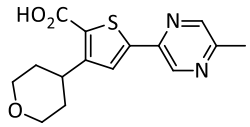
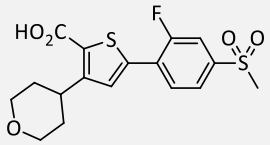
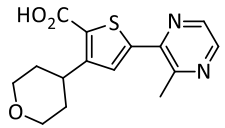
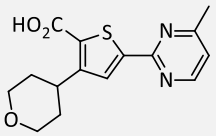
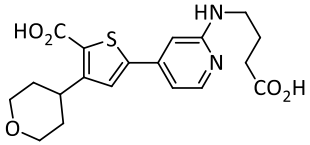
In a RG2-flask, the mixture of acid partner (0.20 mmol, 1.25 eq), **112** (0.16 mmol, 1 eq) were dissolved in *N,N*-DMF (2 mL). *N*-methylmorpholine (0.80 mmol, 5 eq), dimethylaminopyridine (0.01 mmol, 0.05 eq) and 1-hydroxy-7-azabenzotriazole (0.2 mmol, 1.25 eq) were added. After stirring for 5 min at rt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.2 mmol, 1.25 eq)

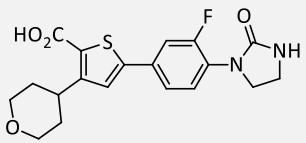
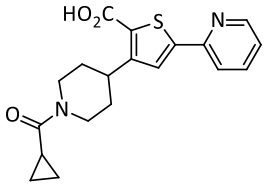
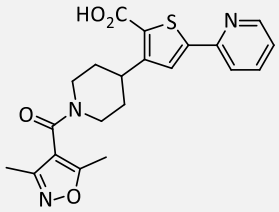
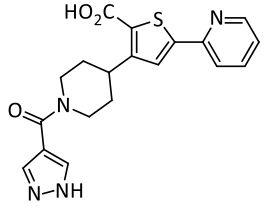
was added in tetrahydrofuran (0.25 mL). The resulting mixture was stirred at rt until completion (LC-MS monitoring). The crude was evaporated, neutralised with sodiumbicarbonate (10% aqueous solution – 5 mL) extracted with ethylacetate (15 mL). The crude was then redissolved in *N,N*-DMF and purified by prep. HPLC.

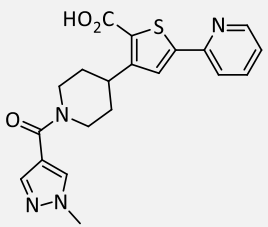
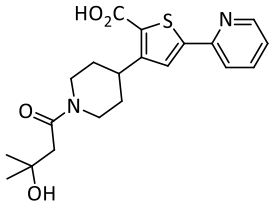
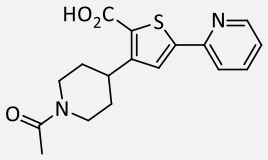
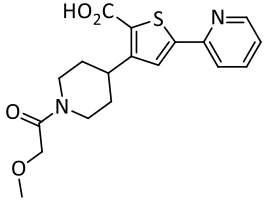
Resulting compounds were then saponified as follows:

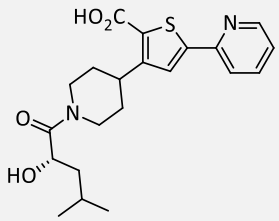
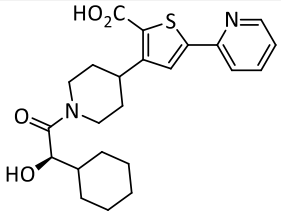
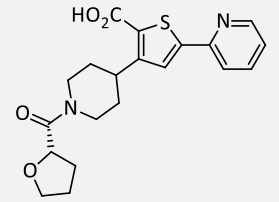
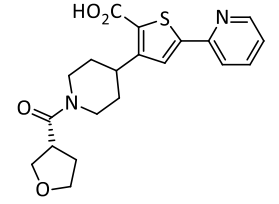
In a RG24 vial, compounds from the first step were dissolved in a 1/1 mixture of methanol and tetrahydrofuran (4 mL). Then an aqueous solution of sodium hydroxide (2M - 0.5 mL, 4 eq) was added and the mixture stirred at rt until the reaction was complete (LC-MS monitoring). After evaporation, *N,N*-DMF (2 mL) was added to the crude and it was purified by prep. HPLC to yield compounds **G.01** to **G.11**.

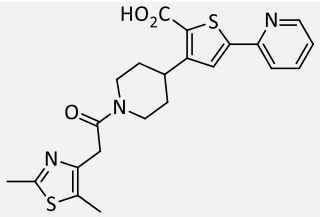
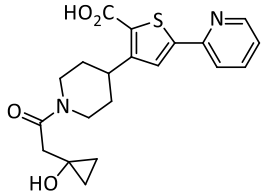
Compound ID	*Compound structure*	*LC-MS purity*	*^{1}H NMR*
G.01		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.00 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.38 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 4.56 (s, 2H), 3.96 – 3.92 (m, 2H), 3.89 – 3.77 (m, 1H), 3.45 – 3.39 (m, 2H), 1.78 – 1.70 (m, 4H).
G.02		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.46 (s, 1H), 8.66 (d, *J* = 5.5 Hz, 1H), 8.13 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 5.5 Hz, 1H), 3.98 – 3.94 (m, 2H), 3.82 (tt, *J* = 12.0, 4.0 Hz, 1H), 3.46 – 3.40 (m, 2H), 2.63 (s, 3H), 1.85 – 1.76 (m, 2H), 1.73 – 1.68 (m, 2H).
G.03		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 12.99 (s, 1H), 10.75 (s, 1H), 7.46 (s, 1H), 7.36 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 4.63 (s, 2H), 3.97 – 3.92 (m, 2H), 3.79 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.44 – 3.38 (m, 2H), 1.81 – 1.72 (m, 2H), 1.71 – 1.66 (m, 2H).
G.04		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.15 (s, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 8.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.79 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 3.98 – 3.93 (m, 2H), 3.82 (tt, *J* = 12.0, 4.0 Hz, 1H), 3.46 – 3.39 (m, 2H), 2.55 (s, 3H), 1.85 – 1.76 (m, 2H), 1.71 – 1.67 (m, 2H).
G.05		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.00 (s, 1H), 7.88 – 7.85 (m, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 3.97 – 3.93 (m, 2H), 3.796 (tt, *J* = 12.0,

			4.0 Hz, 1H), 3.45 – 3.39 (m, 2H), 2.49 (s, 3H), 1.83 – 1.74 (m, 2H), 1.72 – 1.68 (m, 2H).
G.06		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.14 (s, 1H), 9.21 (d, *J* = 1.0 Hz, 1H), 8.52 (d, *J* = 1.0 Hz, 1H), 8.04 (s, 1H), 3.98 – 3.94 (m, 2H), 3.81 (tt, *J* = 12.0, 4.0 Hz, 1H), 3.45 – 3.41 (m, 2H), 2.52 (s, 3H), 1.85 – 1.76 (m, 2H), 1.72 – 1.68 (m, 2H).
G.07		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.29 (s, 1H), 8.26 (t, *J* = 8.0 Hz, 1H), 7.94 (dd, *J* = 10.5, 2.0 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.98 – 3.94 (m, 2H), 3.83 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.46 – 3.40 (m, 2H), 3.32 (s, 3H), 1.85 – 1.76 (m, 2H), 1.73 – 1.68 (m, 2H).
G.08		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.19 (s, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 7.71 (s, 1H), 3.98 – 3.94 (m, 2H), 3.83 (tt, *J* = 12.0, 4.0 Hz, 1H), 3.47 – 3.40 (m, 2H), 2.82 (s, 3H), 1.86 – 1.77 (m, 2H), 1.74 – 1.70 (m, 2H).
G.09		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.22 (s, 1H), 8.69 (d, *J* = 5.0 Hz, 1H), 7.90 (s, 1H), 7.33 (d, *J* = 5.0 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.81 – 3.74 (m, 1H), 3.45 – 3.40 (m, 2H), 2.52 (s, 3H), 1.75 – 1.70 (m, 4H).
G.10		95%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.00 – 7.94 (m, 2H), 7.20 – 7.09 (m, 2H), 3.98 – 3.93 (m, 2H), 3.81 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.46 – 3.39 (m, 2H), 3.38 – 3.34 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.86 – 1.76 (m, 4H), 1.71 – 1.67 (m, 2H).

G.11		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.05 (s, 1H), 7.73 – 7.69 (m, 2H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.99 (s, 1H), 3.97 – 3.93 (m, 2H), 3.87 (t, *J* = 7.5 Hz, 2H), 3.80 (tt, *J* = 12.0, 3.55 Hz, 1H), 3.45 – 3.39 (m, 4H), 1.84 – 1.75 (m, 2H), 1.71 – 1.66 (m, 2H).
H.01		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.07 (s, 1H), 8.57 – 8.55 (m, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.87 (td, *J* = 8.0, 1.0 Hz, 1H), 7.34 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.61 – 4.50 (m, 1H), 4.45 – 4.35 (m, 1H), 3.84 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.20 – 3.14 (m, 1H), 2.65 – 2.59 (m, 1H), 2.04 – 1.98 (m, 1H), 1.90 – 1.75 (m, 2H), 1.74 – 1.52 (m, 2H), 0.80 – 0.70 (m, 4H).
H.02		97%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.09 (s, 1H), 8.56 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H) , 8.06 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 7.89 (td, *J* = 8.0, 1.5 Hz, 1H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.69 – 4.51 (m, 1H), 3.83 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.75 – 3.58 (m, 1H), 3.35 – 3.10 (m, 1H), 2.94 – 2.76 (m, 1H), 2.42 (s, 3H), 2.23 (s, 3H), 1.91 – 1.80 (m, 2H), 1.77 – 1.51 (m, 2H).
H.03		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.56 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.94 – 7.85 (m, 3H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.81 – 4.04 (m, 2H), 3.86 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.16 – 2.65 (m, 2H), 1.90 – 1.80 (m, 2H), 1.77 – 1.65 (m, 2H).

H.04		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.09 (s, 1H), 8.57 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.97 (s, 1H), 7.89 (td, *J* = 8.0, 2.0 Hz, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.70 – 4.60 (m, 1H), 3.93 – 3.84 (m, 5H), 3.30 – 3.17 (m, 1H), 2.92 – 2.81 (m, 1H), 1.94 – 1.78 (m, 2H), 1.78 – 1.69 (m, 2H).
H.05		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.07 (s, 1H), 8.56 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H), 8.06 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.89 (s, 1H), 7.89 – 7.85 (m, 1H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.66 – 4.61 (m, 1H), 4.15 – 4.09 (m, 1H), 3.80 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.12 – 3.05 (m, 1H), 2.63 – 2.56 (m, 1H), 2.53 (d, *J* = 15.0 Hz, 1H), 2.47 (d, *J* = 15.0 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.70 – 1.56 (m, 2H), 1.20 (d, *J* = 1.0 Hz, 5H).
H.06		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 8.56 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H), 8.05 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.91 (s, 1H), 7.87 (td, *J* = 8.0, 2.0 Hz, 1H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.58 – 4.52 (m, 1H), 3.97 – 3.90 (m, 1H), 3.80 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.15 – 3.08 (m, 1H), 2.60 – 2.53 (m, 1H), 2.04 (s, 3H), 1.85 – 1.75 (m, 2H), 1.73 – 1.64 (m, 1H), 1.61 – 1.52 (m, 1H).
H.07		100%	^{1}H NMR (600 MHz, DMSO-d$_6$), ppm: 13.08 (s, 1H), 8.61 – 8.54 (m, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.94 – 7.83 (m, 2H), 7.39 – 7.31 (m, 1H), 4.57 – 4.53 (m, 1H), 4.50 – 4.44 (m, 2H), 4.13 – 4.08 (m, 1H), 3.86 – 3.78 (m, 1H), 3.08 (t, *J* = 12.5

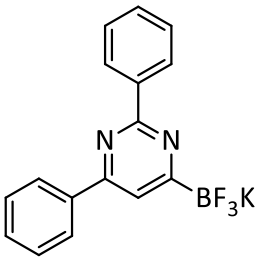
			Hz, 1H), 2.65 (t, *J* = 12.5 Hz, 1H), 1.84 – 1.81 (m, 2H), 1.74 – 1.55 (m, 2H), 1.26 -1.19 (m, 3H).
H.08		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.56 (d, *J* = 5.0 Hz, 1H), 8.06 (t, *J* = 7.0 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.35 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.38 – 4.33 (m, 1H), 4.08 – 4.00 (m, 1H), 3.86 – 3.76 (m, 1H), 3.14 – 3.05 (m, 1H), 2.68 – 2.60 (m, 1H), 1.89 – 1.58 (m, 5H), 1.48 – 1.33 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 6H).
H.09		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.08 (s, 1H), 8.56 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.38 – 7.32 (m, 1H), 4.61 – 4.52 (m, 1H), 4.18 – 4.05 (m, 2H), 3.87 – 3.76 (m, 1H), 3.14 – 3.03 (m, 1H), 2.72 – 2.62 (m, 1H), 1.91 – 1.80 (m, 2H), 1.74 – 1.53 (m, 8H), 1.27 – 0.97 (m, 6H).
H.10		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.56 (d, *J* = 4.5 Hz, 1H), 8.11 – 8.04 (m, 1H), 7.91 (d, *J* = 4.5 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.35 (dd, *J* = 7.5, 4.5 Hz, 1H), 4.71-4.66 (m, 1H), 4.54 – 4.49 (m, 1H), 4.16 – 4.10 (m, 1H), 3.85 – 3.72 (m, 3H), 3.14 – 3.03 (m, 1H), 2.66 – 2.58 (m, 1H), 2.13 – 1.96 (m, 2H), 1.91 – 1.79 (m, 4H), 1.71 – 1.54 (m, 2H).
H.11		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 13.09 (s, 1H), 8.56 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 7.87 (td, *J* = 8.0, 1.5 Hz, 1H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.61 – 4.55 (m, 1H), 4.11 – 4.06 (m, 1H), 3.94 –

			3.86 (m, 1H), 3.85 – 3.66 (m, 4H), 3.42 – 3.35 (m, 1H), 3.15 – 3.07 (m, 1H), 2.66 – 2.59 (m, 1H), 2.11 – 2.00 (m, 2H), 1.87 – 1.77 (m, 2H), 1.70 – 1.54 (m, 2H).
H.12		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.56 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.35 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.16 – 4.10 (m, 1H), 3.95 (s, 2H), 3.83 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.71 – 2.61 (m, 4H), 2.29 (s, 3H), 1.88 - 1.80 (m, 2H), 1.73 – 1.56 (m, 2H).
H.13		100%	^{1}H NMR (600 MHz, DMSO-d_6), ppm: 8.56 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 8.06 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.88 (dt, *J* = 8.0, 1.5 Hz, 2H), 7.35 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H), 4.57 – 4.52 (m, 1H), 3.85 – 3.76 (m, 2H), 3.70 (d, *J* = 16.0 Hz, 1H), 3.60 (d, *J* = 16.0 Hz, 1H), 3.11 – 3.05 (m, 1H), 2.65 – 2.59 (m, 1H), 2.57 – 2.51 (m, 2H), 1.84 – 1.78 (m, 2H), 1.70 – 1.57 (m, 2H), 0.95 (t, *J* = 7.0 Hz, 3H).

2.4. Synthesis of pyrimidine-6-trifluoroborates

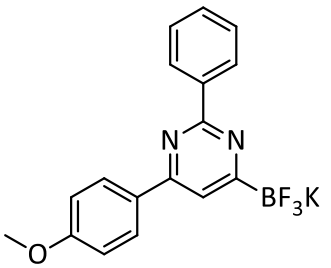
General procedure U – To a solution of ynone (1.0 eq) in toluene (0.07 M) in a sealable tube, amidine (1.2 or 2.4 eq) was added. The tube was then sealed and the mixture heated at reflux o/n. All volatiles were then removed and pyrimidine products were obtained after a precipitation from acetone and Et_2O.

Potassium (2,6-diphenylpyrimidin-4-yl)trifluoroborate, 100



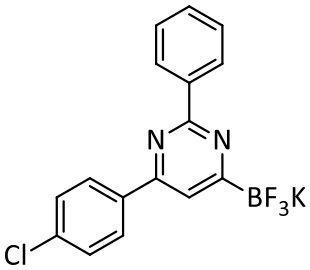
Following general procedure U, using **16** (104 mg, 0.42 mmol), and benzamidine (68 mg, 0.51 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a colourless solid (100 mg, 67% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.45 (d, *J* = 7.5 Hz, 2H), 8.37 – 8.26 (m, 3H), 7.75 – 7.58 (m, 6H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 165.5, 158.7, 134.5, 133.1, 132.7, 131.8, 129.8, 129.4, 128.6, 128.5, 117.9. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -142.2. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 0.6. **m. pt.** 267-268 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3268 (w), 3207 (w), 3172 (w), 1621 (m), 1603 (m), 1591 (m), 1560 (s). **HRMS** calculated for $C_{16}H_{11}{}^{11}BF_3N_2$ (ESI^-): 299.0973. Found: 299.0986.

Potassium trifluoro(6-(4-methoxyphenyl)-2-phenylpyrimidin-4-yl)borate, 101



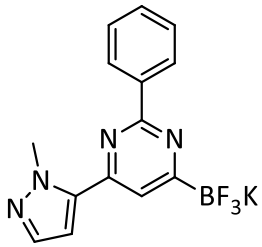
Following general procedure U, using **17** (115 mg, 0.42 mmol), and benzamidine (69 mg, 0.51 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a colourless solid (117 mg, 73% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.54 (dd, *J* = 8.0, 1.5 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.72 (s, 1H), 7.55 – 7.44 (m, 3H), 7.10 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 161.6, 161.0, 159.2, 139.2, 130.1, 129.6, 128.2, 128.1, 127.7, 115.9, 114.2, 55.3. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -142.6. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.5. **m. pt.** 257 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3085 (w), 3047 (w), 2960 (w), 2936 (w), 2836 (w), 1610 (m), 1588 (m), 1572 (m), 1509 (s), 1370 (s), 1354 (s), 966 (s). **HRMS** calculated for $C_{17}H_{13}{}^{11}BF_3N_2O$ (ESI^-): 329.1079. Found: 329.1089.

Potassium (6-(4-chlorophenyl)-2-phenylpyrimidin-4-yl)trifluoroborate, 102



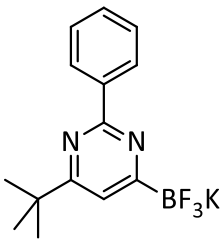
Following general procedure U, using **18** (120 mg, 0.42 mmol), and benzamidine (130 mg, 1.01 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a colourless solid (125 mg, 76% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.54 (d, *J* = 6.5 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H), 7.80 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.48 (m, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 161.8, 158.3, 138.9, 136.6, 134.9, 129.8, 128.9, 128.5, 128.3, 127.8, 116.6. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -142.7. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.5. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 3042 (w), 2597 (m), 1569 (m), 1513 (s), 1492 (m). **HRMS** calculated for $C_{16}H_{10}{}^{11}B^{35}ClF_3N_2$ (ESI^-): 333.0583. Found: 333.0598.

Potassium trifluoro(6-(1-methyl-1H-pyrazol-5-yl)-2-phenylpyrimidin-4-yl)borate, 103



Following general procedure U, using **19** (108 mg, 0.42 mmol), and benzamidine (123 mg, 1.01 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a colourless solid (129 mg, 84% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.47 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.56 – 7.46 (m, 4H), 6.95 (d, *J* = 2.0 Hz, 1H), 4.33 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 161.4, 153.1, 139.7, 138.8, 137.9, 130.0, 128.5, 127.7, 118.8, 107.5, 40.1. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -142.8. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** 263-264 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 1570 (m), 1511 (m), 1454 (m), 1424 (w). **HRMS** calculated for $C_{14}H_{11}{}^{11}BF_3N_4$ (ESI^-): 303.1034. Found: 303.1047.

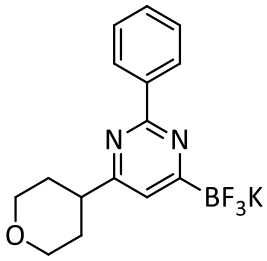
Potassium (6-(tert-butyl)-2-phenylpyrimidin-4-yl)trifluoroborate, 104



Following general procedure U, using potassium (4,4-dimethyl-3-oxopent-1-yn-1-yl)trifluoroborate (54 mg, 0.23 mmol), and benzamidine (42 mg, 0.28 mmol) in toluene (3 mL). The title compound was obtained after precipitation as a colourless solid (45 mg, 56% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.46 – 8.41 (m, 2H), 7.51 – 7.43 (m, 3H), 7.32 (s, 1H), 1.34 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 172.9, 160.8, 139.5, 129.4, 128.2, 127.6, 116.4, 64.9, 29.4. **^{19}F NMR (377 MHz, DMSO-d$_6$), ppm:** -142.4. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.6. **m. pt.** > 290 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2962 (w), 2922 (w), 2903 (w), 2870 (w), 1569 (w),

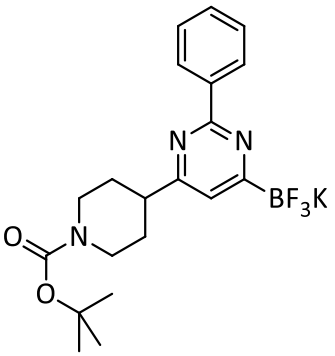
1516 (m), 1478 (w), 1456 (w). **HRMS** calculated for $C_{14}H_{15}{}^{11}BF_3N_2$ (ESI^-): 279.1286. Found: 279.1288.

Potassium trifluoro(2-phenyl-6-(tetrahydro-2H-pyran-4-yl)pyrimidin-4-yl)borate, 105



Following general procedure U, using **21** (111 mg, 0.42 mmol), and benzamidine (69 mg, 0.51 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a light brown solid (98 mg, 62% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.42 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.49 – 7.43 (m, 3H), 7.17 (s, 1H), 4.01 – 3.92 (m, 2H), 3.47 (td, *J* = 11.0, 4.0 Hz, 2H), 2.91 – 2.83 (m, 1H), 1.85 – 1.73 (m, 4H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 168.5, 161.3, 139.2, 129.5, 128.2, 127.7, 118.9, 67.0, 41.9, 31.4. **^{19}F NMR (377 MHz, DMSO-d_6), ppm:** -142.5. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 1.3. **m. pt.** 209 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 2953 (w), 2858 (w), 1568 (m), 1516 (s), 1492 (w), 1463 (w), 1088 (m). **HRMS** calculated for $C_{15}H_{15}{}^{11}BF_3N_2O$ (ESI^-): 307.1235. Found: 307.1246.

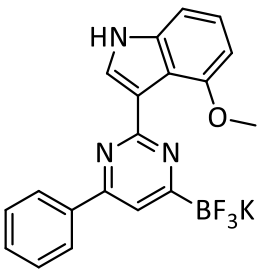
Potassium (6-(1-(tert-butoxycarbonyl)piperidin-4-yl)-2-phenylpyrimidin-4-yl)trifluoroborate, 106



Following general procedure U, using **21** (149 mg, 0.42 mmol), and benzamidine (64 mg, 0.51 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a light yellow solid (119 mg, 61% yield). **^{1}H NMR (400 MHz, DMSO-d_6), ppm:** 8.41 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.16 (s, 1H), 4.10 – 4.06 (m, 2H), 2.99 – 2.73 (m, 3H), 1.91 – 1.85 (m, 2H), 1.67 – 1.57 (m, 2H), 1.43 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6), ppm:** 168.5, 161.2, 154.0, 139.2, 129.5, 128.2, 127.6, 119.0, 78.6, 42.8, 39.1, 30.7, 28.1. **^{19}F NMR (377 MHz, DMSO-d_6), ppm:** -142.6. **^{11}B NMR (128 MHz, DMSO-d_6), ppm:** 1.4. **m. pt.** 127-128 °C. **FTIR (neat, cm^{-1}), ν_{max}:** 2974 (w), 2931 (w), 2857 (w), 1671 (s), 1518 (s), 1427 (s), 1232 (s), 1166 (s). **HRMS** calculated for $C_{20}H_{24}{}^{11}BF_3N_3O_2$ (ESI^-): 406.1919. Found: 406.1926.

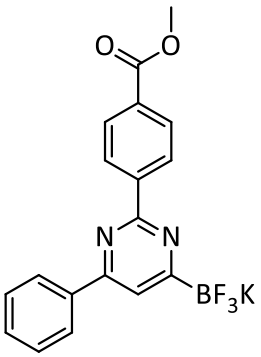
Potassium trifluoro(2-(4-methoxy-1H-indol-3-yl)-6-phenylpyrimidin-4-yl)borate, 107

Following general procedure U, using **16** (101 mg, 0.42 mmol), and 4-methoxy-1*H*-indole-3-carboximidamide (96 mg, 0.51 mmol) in toluene (6 mL). The title compound was obtained after precipitation as a colourless solid (87 mg, 50% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.38 – 8.30 (m, 2H), 8.24 - 8.10 (m, 1H), 7.78 (s, 1H), 7.56 (s, 3H), 7.18 - 7.10 (m, 2H), 6.72 (d, *J* = 5.5 Hz, 1H), 3.93 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 160.3, 153.1, 151.6, 139.1, 138.8, 137.0, 131.0, 128.9, 127.5, 123.3, 114.3, 106.1, 103.4, 102.0, 55.7. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -143.3. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.4. **m. pt.** 196 °C (decomp.). **FTIR (neat, cm^{-1}), ν_{max}:** 3351 (w), 3069 (w), 1576 (s), 1525 (m), 1509 (s), 1485 (w), 1086 (s). **HRMS** calculated for $C_{19}H_{14}{}^{11}BF_3N_3O$ (ESI^-): 368.1188. Found: 368.1196.



Potassium trifluoro(2-(4-(methoxycarbonyl)phenyl)-6-phenylpyrimidin-4-yl)borate, 110

To a solution of **16** (50 mg, 0.21 mmol, 1.0 eq) in toluene (3 mL, 0.17 M) in a microwave tube, methyl 4-carbamimidoylbenzoate (95 mg, 0.51 mmol, 2.4 eq) was added. The tube was sealed in submitted to the following microwave method: 1 min pre-stirring at 140 °C for 2 hrs under high stirring. All volatiles were then removed and the title compound was obtained after a precipitation from acetone and Et_2O as a colourless solid (12 mg, 15% yield). **^{1}H NMR (400 MHz, DMSO-d$_6$), ppm:** 8.69 (d, *J* = 8.5 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.85 (s, 1H), 7.63 – 7.51 (m, 3H), 3.91 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d$_6$), ppm:** 166.2, 160.9, 159.8, 143.4, 137.6, 130.5, 130.3, 129.3, 129.0, 128.0, 126.8, 117.3, 52.2. **^{19}F NMR (376 MHz, DMSO-d$_6$), ppm:** -142.7. **^{11}B NMR (128 MHz, DMSO-d$_6$), ppm:** 1.5. **m. pt.** 276-277 °C .**FTIR (neat, cm^{-1}), ν_{max}:** 3057 (w), 2953 (w), 1712 (s), 1568 (m), 1508 (s), 1437 (m), 1422 (w), 1280 (s), 1136 (s). **HRMS** calculated for $C_{18}H_{13}{}^{11}BF_3N_2O_2$ (ESI^-): 357.1028. Found: 357.1041.



Conclusions and Outlook

Conclusions

The purpose of this work was to show the versatility of ynone trifluoroborates in the synthesis of heteroaromatic compounds bearing a boron handle. Indeed, we have shown this in three heterocycle syntheses: in the generation of pyrazoles, thiophenes and pyridimines.

In a first part, we have shown that the scope of ynone trifluoroborates could be extended to a wide range of substituents, incorporating heteroaromatics such as pyrazole, as well as alkyl groups, namely, pyran, piperidine and benzyl protected alcohol.

The desired 5-trifluoroborated pyrazole substrates could be obtained in excellent yields as well as excellent regioselectivities in most cases. Furthermore, we have continued this work by studying the funtionalisation of these compounds. We could achieve the regioselective halogenation at *C*4 of our pyrazole substrates yielding a variety of bifunctional compounds. Using those compounds, the orthogonal functionalisation of the *C*5 and *C*4 position was realised via a sequence of two Suzuki-Miyaura cross-coupling reactions. We have also explored the compatibility of our substrates with the automated library production process and found that we could use our substrates to synthesise a wide range of new tricyclic pyrazole scaffolds. We have also tested their early ADME properties. All this was made possible by the eighteen months stay in the facilities of Sanofi Deutschland in Frankfurt.

As a second project, we have studied in great detail the condensation of ynone trifluoroborate salts with methanethiol-type reagents to synthesise thiophene-5-trifluoroborates. We have found that the trifluoroborate handle was stable to basic conditions (as potassium carbonate was required to carry out the transformation). Studying the mechanism of this reaction, we could also provide a rationale as to why some methanethiols failed to produce the desired thiophenes. We could also show that a broader scope of methanethiol reagents (beyond methylthioglycolate) could be used in such condensation reaction. As for the pyrazole scaffolds, we have investigated their functionalisation as well as their compatibility with automated production. We found that the borylated thiophenes could undergo several reactions that are unprecedented on thiophenes in the literature. Also, two

libraries could be successfully synthesised giving compounds that could be potentially relevant to medicinal chemistry.

Finally, we also started investigating the synthesis of pyrimidine-6-trifluoroborates via the condensation of amidine-type reagents and our ynone trifluoroborates. We found that all our ynones were compatible with the condensation procedure, despite heating at 110 °C, no sign of degradation was observed. This method allowed us to synthesise a range of 2-phenyl-6-trifluoroborate pyrimidines in high to excellent yields. We have also found some alternative amidines which could undergo the condensation to give the desired pyrimidine products.

Outlook

Our various investigations in the synthesis of trifluoroborated molecules has revealed areas for which improvements that could be investigated. As a general comment, the insolubility of potassium trifluoroborates in most organic solvents is usually a valuable property as it allows for easy purification by precipitation. However, precipitation of products derived from alkyl substituted ynones can be quite challenging due to their propensity to coordinate to solvent, turning solids into oily residues. Also, we have noted that the oxidation of potassium alkyl-ynol trifluoroborates into the corresponding ynones was low yielding. Our hypothesis was that, due to the use of manganese(IV) oxide as the oxidant, coordination of the products to the manganese was the reason for this poor mass recovery. We are currently conducting experiments into the synthesis of the more soluble tetrabutylammonium trifluoroborated ynones. Our hypothesis is that the increased solubility of those trifluoroborates would help in developing higher yielding oxidation conditions.

The chemistry reported here towards thiophenes has been quite well developed. However, we are interested in exploring the potential of thiophene 2-methanethiol to undergo condensation to our ynones in order to generate monomers for polymeric thiophenes that are important in materials chemistry.

Finally, the chemistry of pyrimidine-6-trifluoroborates is still in its infancy. We have observed the successful condensation of benzamidine on a range of ynones. Unfortunately, when changing the amidine reagent we have had more difficulties in carrying out the

formation of the desired product. Microwave irradiation seems to be a promising avenue to explore. However, remains to develop conditions in which the competing reaction, namely protodeboration, is minor. We report the initial studies in this thesis and follow up is ongoing within our group.

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