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Thesis title: Alkyaylboronate Cycloadditions Towards Aromatic Boronic Esters

Qualification: PhD

Alkynylboronate Cycloadditions Towards Aromatic Boronic Esters

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

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September 2011

Acknowledgements

Firstly, I would like to thank Joe for giving me the opportunity to work in the group. I have thoroughly enjoyed working with you over the past four years. Many thanks for your always excellent advice and encouragement. I am certain that I would not have gained as broad a knowledge of organic synthesis under anyone else. Cheers!

Many thanks to Eleanor Row at Sanofi-Aventis, who provided excellent help and advice during her brief spell as my industrial supervisor. I would also like to thank Roger Butlin, who kindly organised a placement for me at AstraZeneca, and Stuart Bennett, for his supervision in the lab. I really enjoyed my time in the CVGI group at AZ, and I thank everyone there for their support and advice. Thanks especially to Andrew Leach, for quantum mechanical studies.

Thanks to every member of the Harrity group. The lab is an excellent place to work. Apologies for the singing!

Thanks to Paddy and Lisa for their guidance during my initial months in the lab, and thanks to Nico, without doubt the best amateur French footballer in Sheffield! Many thanks to Clare for coping with sharing a fume hood with me during your last few months here. Julien, thanks for your excellent skills and knowledge, and the trips to the Dev Cat!

Jianhui, look at me! All the best for your career, I will definitely be visiting China, and I'll be bringing my music too! Duncan, thanks for all of the advice. Best of luck with your career, and more importantly the little one!

Nicole, Nimbo, thanks for always being there to answer all of my annoying questions, and for the hugs, dancing and singing. Calum, thanks for the rock, and thanks for the great times with Slash, Myles and Rooney! Jeje, mon petit ami français! Thanks for everything mate, best of luck at Sygnature. Danny, thanks for all the man-love, best of luck for you and Fran down south, we will be visiting soon.

Tom, cheers for the past three years, for both your endless knowledge and jokes. Ala, you are mental, and I love it! Good luck with your post-doc, try not to upset the French too much! Rob, best of luck with everything mate, and don't forget to bring a sausage!

Kat, thanks for all the biscuits! Best of luck with the rest of your PhD and Singapore, I know you will be fantastic! Olivier and Julong, good luck with the rest of your PhDs. Matt and Wes, thanks for all the help so far, I am looking forward to learning (and drinking) more over the next few months.

I would like to thank all of the staff in the chemistry department for keeping it running so smoothly. Thanks especially to Harry Adams for X-Ray crystallographic data.

Many thanks to the members of both the Jones and Chen group for making E26 a great place to work in. And a big thanks to all of the members of the Armes group. Nick, Morsey, Marksy, Shell and everyone else, thanks for all of the good times and all of the 'banter'. Lee, cheers for all the beer and football, long may it last! Tracy, thanks for all of the chilli and the pizza and the family outings.

Many thanks to Jonesy, Jono and the rest of the guys from Nottingham for remaining such good mates. Thanks for the unforgettable trip to Munich, and for all the non-chemistry related distractions over the past few years.

I would like to say a massive thank you to my family for everything they have done for me. Mum, Dad, thanks for giving me the best possible start in life by being loving and supporting in everything I do. Becky, thanks for being the best sister in the world, whatever you do you will be great at it. Grandma, Grandad, Grandma K and Uncle Jack, many thanks for everything you have done for me.

Kate. I dedicate this thesis to you, for all of the love and support that has got me through the last seven years with a smile on my face. I am so lucky to be married to the most beautiful, intelligent, fun and caring woman I have ever met. You are the best thing that could have possibly happened to me. I know that whatever happens next I will be facing and sharing it with you. I can't wait.

Contents

Abstract

The [4+2] cycloaddition of 2-pyrones with phenyl, trimethylsilyl and *n*-butyl substituted alkynylboronates has been studied. In general, the highest yields for the cycloadditions were obtained using trimethylsilyl alkynylboronate. The highest regioselectivities were obtained using phenyl alkynylboronate, which provided a single regioisomer irrespective of the 2-pyrone used. Mechanistic studies suggest that the high regioselectivity observed is due to stabilisation of a zwitterionic species in the transition state.

2-Pyrone cycloadditions have been shown to be a viable route for the formation of the benzyne precursors, *ortho*-silylaryltriflates. By oxidation of the aromatic boronic ester products formed from cycloadditions, followed by sulfonylation of the resulting phenol species, a mild route has been developed for the formation of these highly synthetically useful intermediates.

Aromatic difluoroboranes can be formed from the cycloaddition of 2-pyrones with *in situ* generated alkynyl difluoroboranes, at mild temperatures and in short reaction times by use of a directing group. Pyridines and amides have been incorporated into the 2-pyrone ring for this purpose, and high yields of the respective cycloadducts have been obtained with only one regioisomer formed in each case. Direct functionalisation of the aromatic difluoroboranes has been achieved using palladium catalysed cross-coupling, oxidation and azidonation reactions.

Abbreviations

aq.	Aqueous
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
br	Broad
n-Bu	*normal*-Butyl
Cat	Catechol
CI	Chemical ionisation
COD	Cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
d	Doublet
o-DCB	*ortho*-Dichlorobenzene
DCM	Dichloromethane
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpy	4,4'-Di-tert-butyl bipyridine
δ	Chemical shift
eq.	Equivalents
EI	Electron impact
EWG	Electron withdrawing group

FAB	Fast atom bombardment
FTIR	Fourier transform infrared
GC	Gas chromatography
h	Hours
HRMS	High-resolution mass spectrum
Hz	Hertz
J	Coupling constant
m	Milli or medium or multiplet
max	Maximum
Me	Methyl
Mes	Mesityl
min	Minutes
mol	Moles
m.p.	Melting point
MS	Mass spectroscopy
μW	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
o/n	Overnight
Ph	Phenyl
Pin	Pinacol
i-Pr	*iso*-Propyl
Py	Pyridine

q	Quartet
R	Alkyl group
R.T.	Room temperature
s	Singlet or strong or second
SM	Starting material
t	Triplet
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Toluene
ν	Wavenumber
w	Weak

Chapter One – Alkynylboronate Cycloadditions Towards Aromatic Boronic Esters

1.1 Introduction

Organoboron compounds have become some of the most heavily utilised intermediates in modern synthetic organic chemistry. The versatility of these compounds makes them attractive for many applications. The carbon-boron bond can easily be broken, allowing the formation of a wide variety of species via various cross-coupling and functional group interconversion processes. The former characteristic of organoboron species is utilised in the palladium catalysed Suzuki-Miyaura reaction, one of the most common processes found in both industry and academia.

Figure 1 shows various chemical transformations that can be performed using vinyl- or aryl- boronate species. These processes have been summarised by Hall.[1]

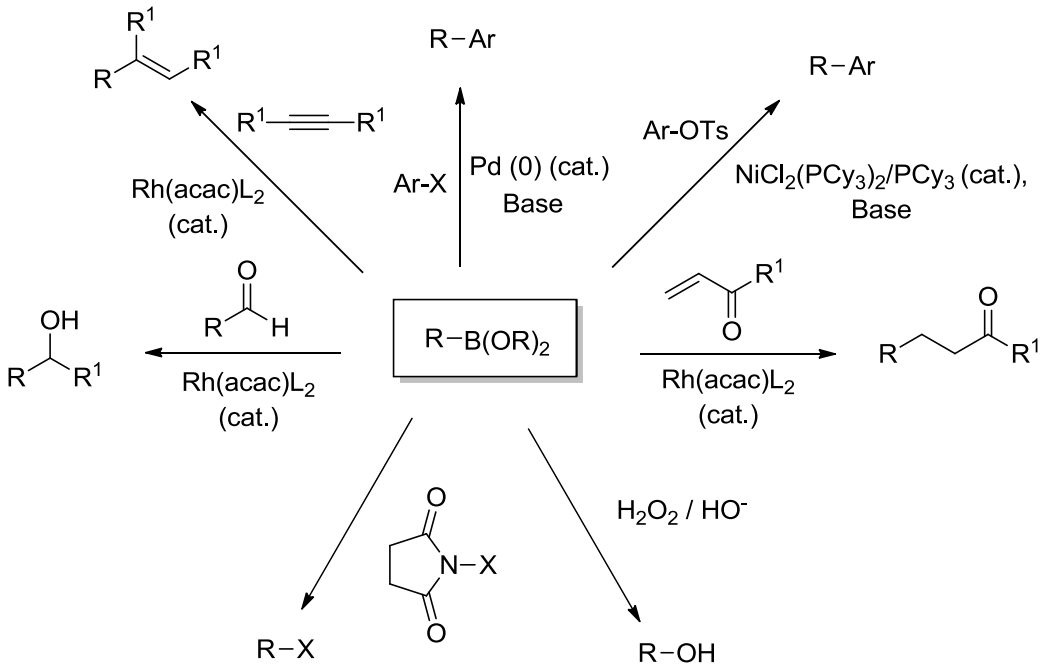
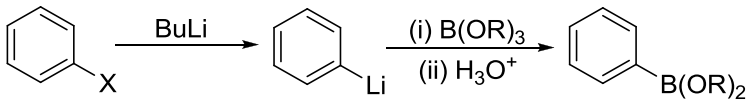


Figure 1 - Applications of Vinyl- and Aryl-Boronic Esters and Acids

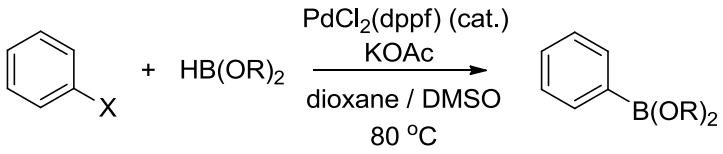
1.1.1 Synthesis of Aromatic Boronic Esters

Aromatic boronic esters are traditionally formed via lithium-halogen exchange reactions from an aromatic halide followed by a transmetallation with a boronate reagent (Scheme 1).[2] This method is fairly robust, has a number of variants (e.g. Grignard reagents can be employed) but has many problems associated with it. The main disadvantages are the limitations associated with the scope of starting aromatic halides as well as the requirement for strongly basic organometallic reagents that may lead to incompatibility issues.



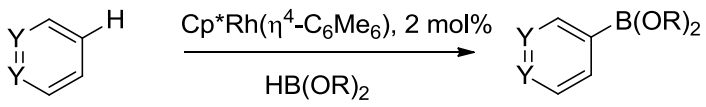
Scheme 1 – Traditional Synthesis of Aromatic Boronic Esters

More recently, Miyaura has developed a palladium catalysed cross coupling route to aromatic boronic esters (Scheme 2).[3] This method is useful as it is more functional group tolerant than the lithium-halogen exchange method. However it does require a transition metal catalyst, which is expensive, and it does not address the issue of having a limited range of readily available starting materials.

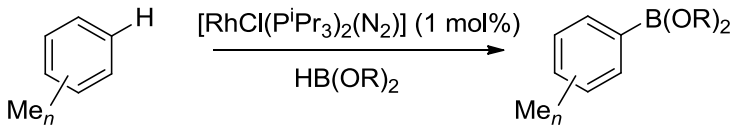


Scheme 2 - Miyaura's Synthesis of Aromatic Boronic Esters

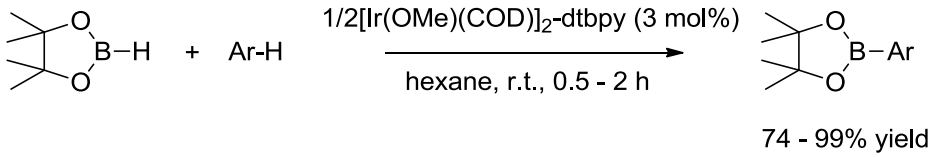
The direct borylation of aromatics can also be achieved, via metal catalysed C-H activation. Initially, this method was developed, using different metal catalysts, independently by Smith, Marder and Miyaura.[4-6] These methods demonstrate a mild method for aromatic boronic ester functionalisation, and do not require substrates to be pre-functionalised. However, these again suffer from the need to use expensive metal catalysts, and also regioselectivity issues, as any of the hydrogens on the aromatic ring can potentially be activated (Scheme 3).



Scheme 3a – Smith's C-H Activation for Synthesis of Aromatic Boronic Esters

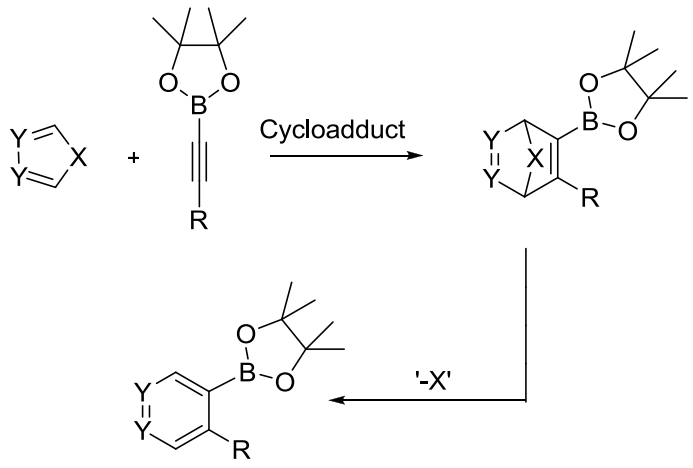


Scheme 3b – Marder's C-H Activation for Synthesis of Aromatic Boronic Esters



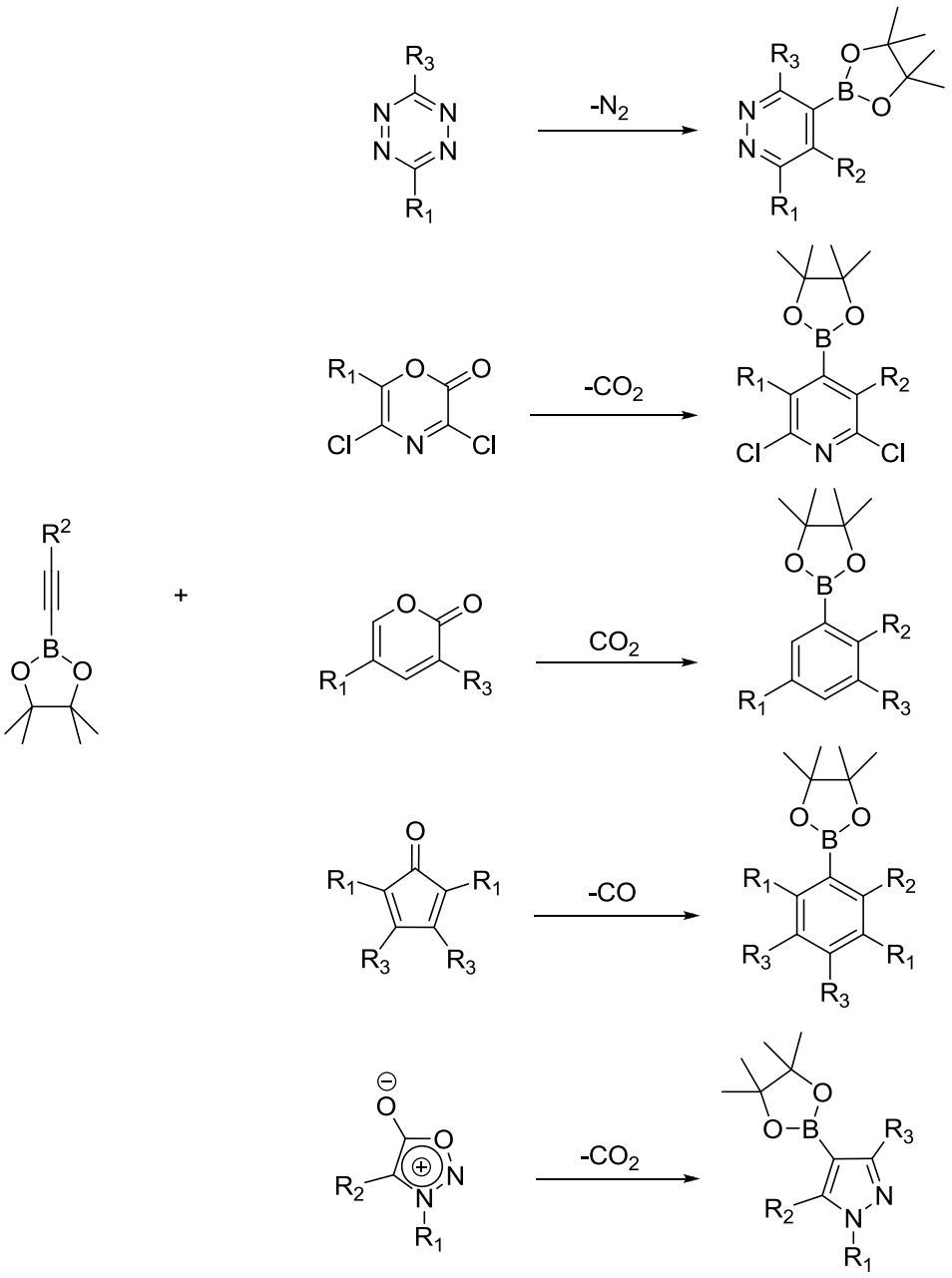
Scheme 3c - Miyaura's C-H Activation for Synthesis of Aromatic Boronic Esters

Recent work in the Harrity group has focused on the formation of the aromatic ring and addition of the boronic ester group in a single operation. This can be done via a [4+2] Diels-Alder type cycloaddition. It requires a diene that contains a small molecule that can act as a leaving group, and an alkynylboronate as the dienophile (Scheme 4). This route could provide access to aromatic boronic esters bearing a wide range of functionality.



Scheme 4 - Cycloaddition Route to Aromatic Boronic Esters

A selection of approaches that have been successfully realised by this methodology are outlined in Scheme 5 below. The examples include the synthesis of aromatic boronic esters based on pyridazines, pyridines, benzenes and pyrazoles.[7-15]



Scheme 5 - Aromatic Boronic Esters in the Harrity Group

If a non-symmetrical diene is used, two potential regioisomers of the cycloadduct can be obtained (Figure 2). Therefore the regioselectivity of the cycloaddition is the

key element of this methodology. Previous work has found that this regioselectivity is highly variable but is often controlled by steric effects.[7, 13]

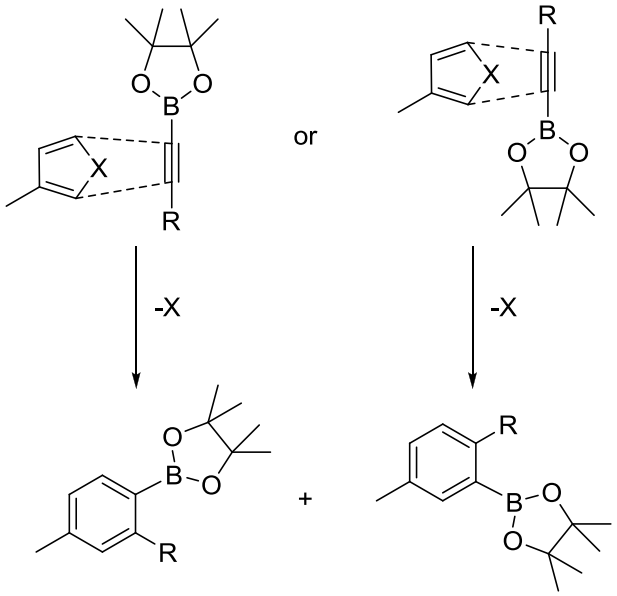


Figure 2 - Possible Regiocontrol in Cycloaddition Reactions

1.1.2 Synthesis of Alkynylboronates

Various alkynylboron reagents can be found in the literature. The most common of these are alkynylboranes, alkynylboronic acids, alkynyldiaminoboranes, and alkynylboronates (Figure 3). Alkynylboronates are possibly the most heavily exploited of these compounds, due to their relatively high stability, making them useful for various chemical transformations.

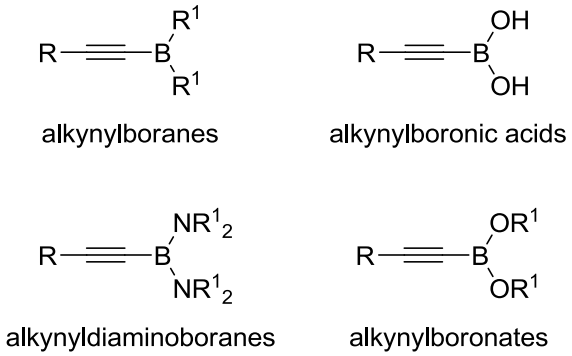
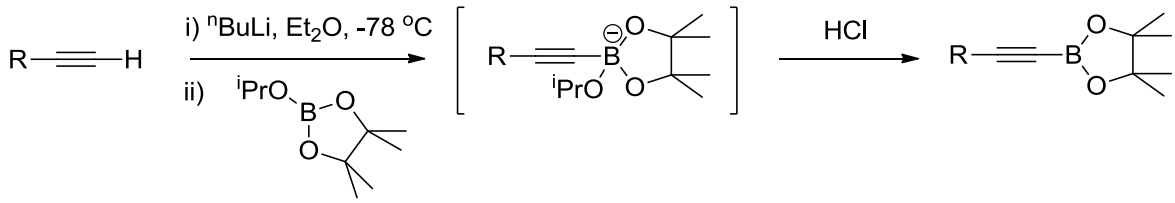


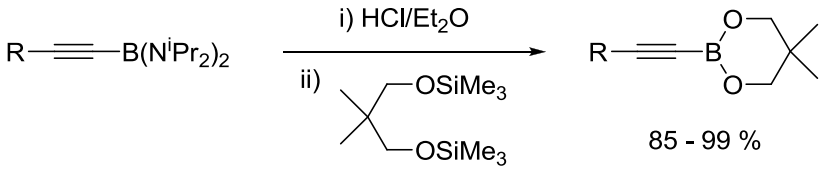
Figure 3 – Alkynylboron Reagents

The synthesis of alkynylboronates was first reported by Matteson in 1960.[16] The chemistry involved a low temperature deprotonation of a terminal alkyne, followed by addition of a boronate, with a subsequent room temperature acid quench (Scheme 6). Brown subsequently expanded on this initial methodology and made the synthesis more general and reliable.[17] This technique remains the most commonly used method today for alkynylboronate formation.



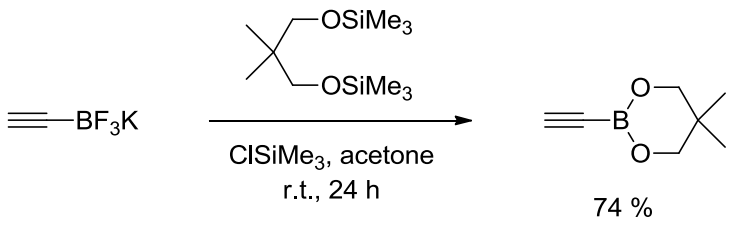
Scheme 6 – Synthesis of Alkynylboronates

Other synthetic approaches to alkynylboronates have also been devised. Vaultier developed an efficient route to alkynylboronates from alkynyldiaminoboranes by a synthetic sequence involving formation of the alkynyldiaminoboranes from the terminal alkyne, followed by replacement of the amine groups with various bis-silyl ethers (Scheme 7).[18]



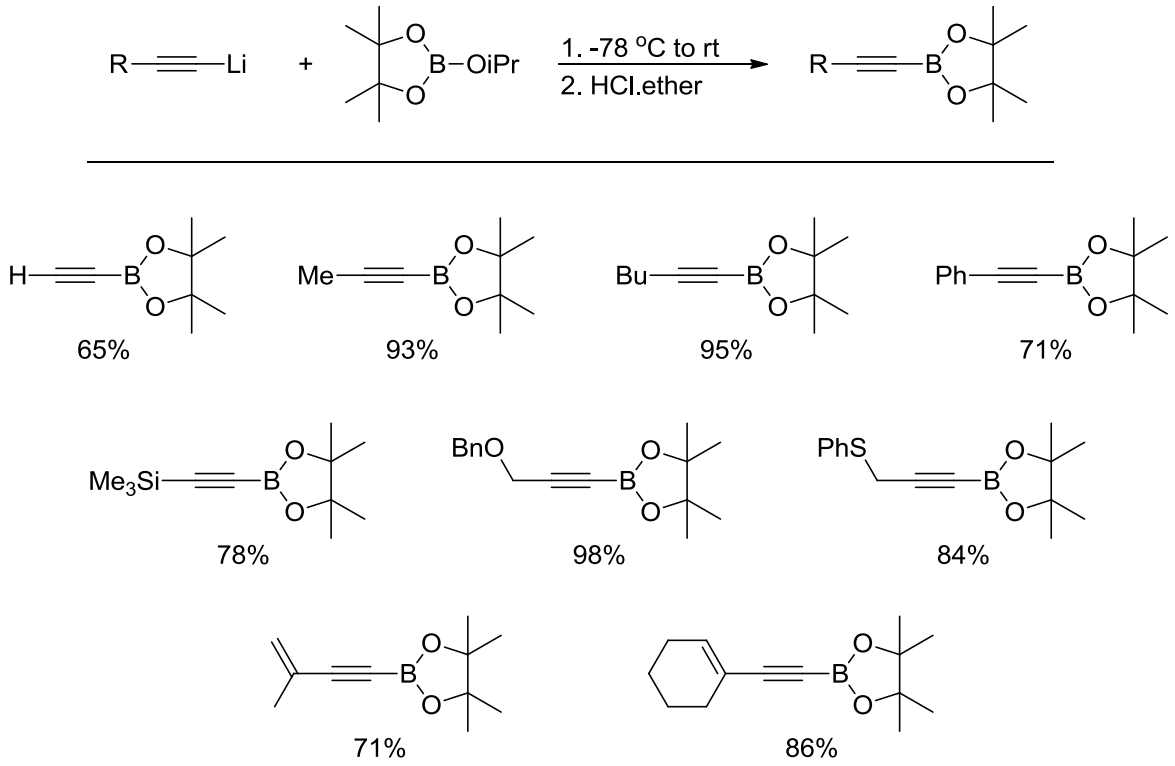
Scheme 7 – Synthesis of Alkynylboronates from Alkynyldiaminoboranes

Recently, Yamamoto reported that alkynylboronates can also be synthesised, in moderate yields but in high purity, from alkynyltrifluoroborates.[19] This protocol involves the synthesis of the alkynyltrifluoroborate from the terminal acetylene, followed by addition of a bis-silyl ether and $ClSiMe_3$ (Scheme 8).



Scheme 8 – Synthesis of Alkynylboronates from Alkynyltrifluoroborates

Previous work in the Harrity group has led to the synthesis of a wide range of alkynylboronates, each of these formed using Brown's method, outlined earlier. A summary of the substrates formed is shown in Scheme 9 below.



Scheme 9 – Alkynylboronates Synthesised in the Harrity group

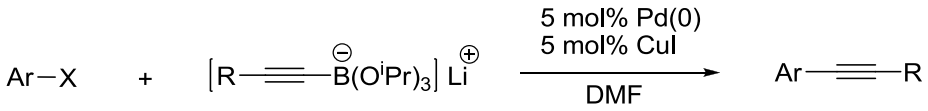
1.1.3 Cross-Coupling Reactions of Alkynylboronates

The carbon–carbon bond forming metal mediated cross-coupling reaction between organoboron compounds and organohalides has been widely examined in the literature, and employed in the formation of an extremely large variety of organic

compounds. One of the most attractive cross-coupling reactions is that of an alkynylmetal species with organohalides, as it is usually difficult to introduce alkyne groups into complex organic molecules, due to the harsh conditions required. The Sonogashira reaction, involving the palladium catalysed coupling of a terminal alkyne with an organohalide, is a good example of a well developed and useful route for the addition of an alkyne, and is widely used throughout both industry and academia. However, there are limitations in the Sonogashira reaction, mainly due to the need for a copper co-catalyst in the reaction. Specifically, the alkynylcopper intermediate can undergo competitive homo-coupling (Glaser reaction), forming unwanted side products. Therefore, a more selective activated alkyne species would be a useful solution to this problem.

It was reported by Negishi in 1978 that lithium 1-hexynyl(tributyl)borate readily undergoes palladium catalysed coupling with iodobenzene.[20] This discovery followed on from reports by three separate groups in 1975, who individually documented that aryl-substituted acetylenes could be synthesised by reaction of 1-alkynes with aryl halides in the presence of a palladium catalyst and a base.[21] Negishi's discovery added to what was a rapidly growing list of possible partners for metal catalysed cross-couplings.

Based on the increased thermal stability and reactivity of lithium 1-alkynyl(triisopropoxy)borates, Oh believed that these could prove to be even more effective alkynyl transfer reagents than those used by Negishi. Indeed, Oh showed that alkynylboronate species do undergo efficient palladium mediated cross-coupling reactions under mild conditions (Scheme 10).[22]



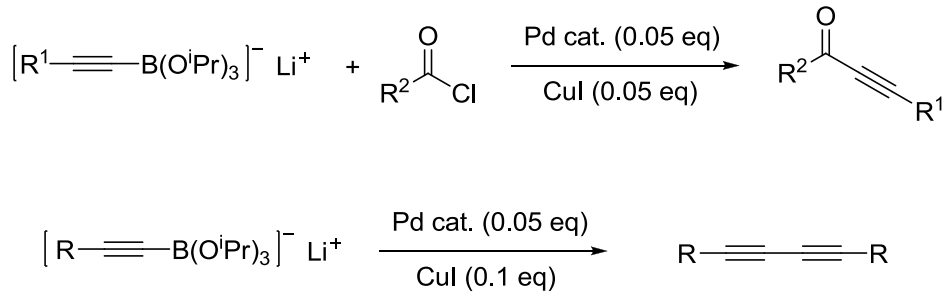
Scheme 10 – Suzuki-Miyaura Couplings of Alkynylboronates

Oh found that this reaction could be used to couple alkynes to a wide variety of aromatic species. He found the reaction to be compatible with electron rich and electron poor aromatics, and sterically hindered aromatics. Moreover, both aryl bromides and iodides could be used as the coupling partners. In all of Oh's

examples, it was found that no dimerisation occurred; the cross-coupling was selective for the desired products in each case. The yields for the reactions were always improved by addition of CuI, although the precise role of the copper species was not delineated.

Further studies by Oh demonstrated the utility of this novel method for the introduction of alkynes. In 2004 it was shown that both conjugated ynones and 1,3-diynes could be synthesised using this methodology (Scheme 11). Ynones can be synthesised by coupling of an alkynylboronate salt with an acid chloride.[23] The reaction requires either a Pd(0) or Pd(II) catalyst and a CuI additive. The highest yields (91%) were obtained when the reaction was conducted for 10 h in acetonitrile, with $PdCl_2(PPh_3)_2$ as the catalyst. Interestingly, the basic nature of the starting ate complex means that no additional base is required. Oh demonstrated that this reaction could be used to form a wide variety of functionalised conjugated ynones, by variation of the substituents on both the alkynylboronate salt and the acid chloride coupling partners.

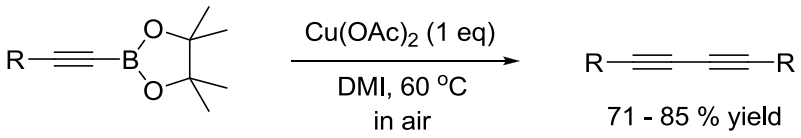
It was shown that synthesis of 1,3-diynes can be efficiently achieved by homocoupling of alkynylboronate salts (Scheme 11).[24] This methodology also gave the highest yields when using Pd(II) catalysts, and interestingly does not require either a base or a co-oxidant. Again, Oh demonstrated that a wide variety of alkynylboronate salts can be used in this methodology, allowing access to a large array of symmetrical 1,3-diynes.



Scheme 11 – Synthesis of Ynones and 1,3-Diynes

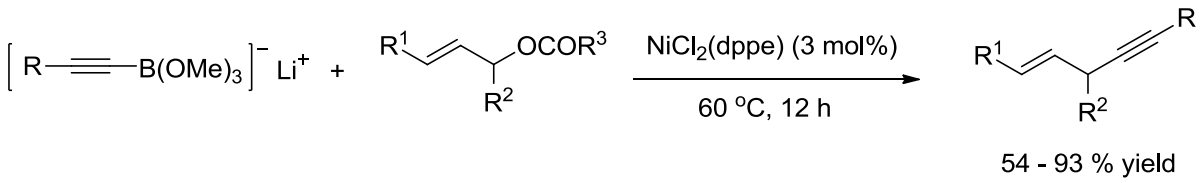
Subsequent work by Nishihara on the synthesis of symmetrical 1,3-diynes showed that the homocoupling could be achieved using stoichiometric amounts of a copper

salt as the catalyst, if the neutral alkynylboronate species was used as the substrate (Scheme 12).[25] Highest yields were achieved using $Cu(OAc)_2$, aprotic polar solvents (e.g. DMI), and by performing the reaction at 60 ^oC. An interesting discovery was that the coupling did not proceed if the reaction was conducted under inert atmosphere, suggesting the need for molecular oxygen as an oxidant. This methodology was used to obtain high yields of a wide variety of symmetrical 1,3-diynes.



Scheme 12 – Synthesis of Diynes via Alkynylboronate Homocoupling

Nickel can also be used to catalyse the coupling reactions of alkynylborates. In 2000, Deng demonstrated that efficient cross-coupling of alkynylboronates with 1,3-disubstituted allyl carbonates can be achieved using 3 mol% of $NiCl_2$(dppe) (Scheme 13).[26] A number of palladium and nickel catalysts were tested, but the nickel catalyst, with dppe as ligand, was found to give the highest yields of product (54 – 93%). This method was shown to be applicable to the coupling of a variety of different alkynylboronates and allyl carbonates, with the reactions proceeding with complete regioselectivity in each case.



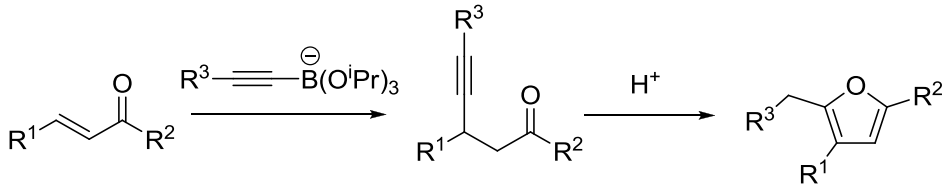
Scheme 13 – Nickel Catalysed Coupling of Alkynylborates with Allyl Carbonates

Recent work performed by Colobert has further expanded on the utility of alkynylboronates in coupling reactions, by demonstrating that these alkynylating agents can be generated in situ from acetylenic compounds.[27]

Alkynylboronate species can clearly undergo coupling reactions with a wide variety of partners, leading to a number of useful applications of this methodology. This allows for the synthesis of a wide variety of useful alkyne containing compounds from inexpensive and easily handled starting materials, demonstrating the synthetic power of alkynylboronate cross couplings.

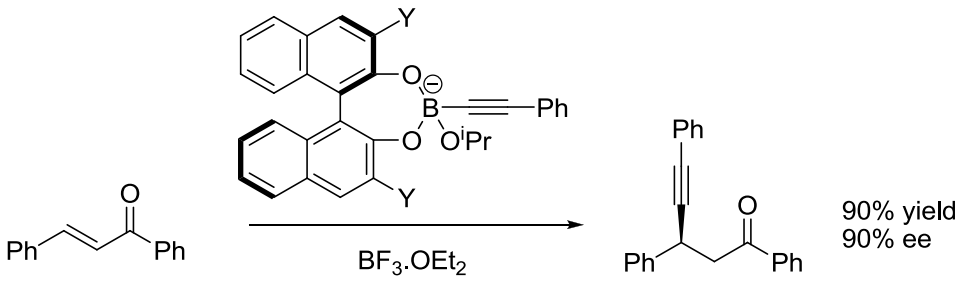
1.1.4 Conjugate Addition Reactions of Alkynylboronates

In 1992 Suzuki reported that alkynylborane species could react with α,β unsaturated ketones, via conjugate addition.[28] This discovery was significant, as alkynes are usually unable to perform conjugate addition to unsaturated carbonyl moieties using standard reagents, for example via alkynylcuprates. Chong *et al.* then found that the same reaction could be performed with air stable alkynylboronate species.[29] It was shown that addition of an alkynylboronate to an α,β-unsaturated ketone, followed by acid catalysed cyclisation of the resulting γ-alkynyl ketone, allows the formation of selectively functionalised furans (Scheme 14).



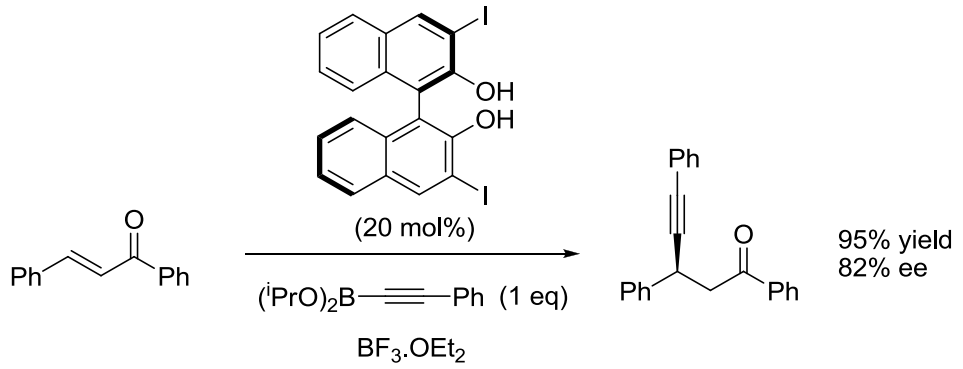
Scheme 14 – Conjugate Addition of Alkynylboronates

During the course of this study, Chong discovered that the addition step is extremely robust, and tolerates a variety of groups on the alkynylboronate. This led Chong to perform further studies on this reaction, in order to assess the scope and the mechanism of the conjugate addition process. Chong next decided to see if the stereochemistry of the conjugate addition could be controlled.[30] He found that by using an alkynylboronate with a BINOL group in place of isopropanol groups, it is possible to control the enantioselectivity of the alkyne addition, thus furnishing products with high levels of enantiocontrol (Scheme 15).



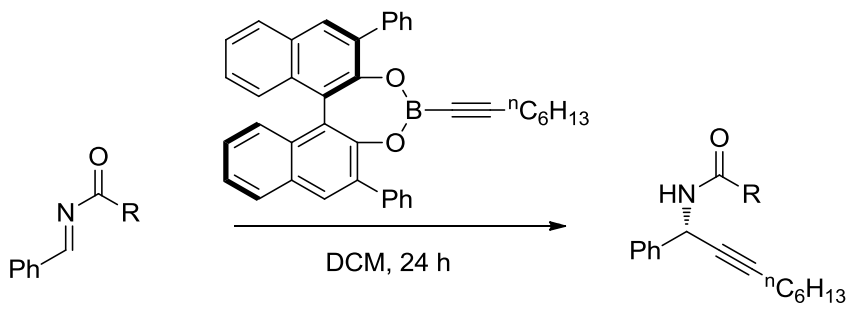
Scheme 15 – Asymmetric Alkynylboronate Conjugate Addition

Chong showed that this methodology could be applied to a variety of different enones and alkynes, and that this technique represents the first general example of the enantioselective alkynylation of enones. More recently, Chong has shown that this reaction can be performed using catalytic amounts of the expensive chiral BINOL ligand, by forming the chiral boronates in situ from the pre-formed alkynylboronate isopropyl esters (Scheme 16).[31]



Scheme 16 – Catalytic Asymmetric Alkynylboronate Conjugate Addition

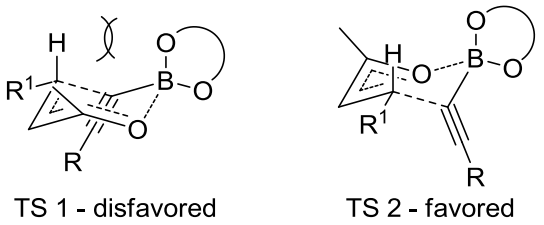
Chong has also used this chemistry in order to accomplish the asymmetric synthesis of propargylamines.[32] This was achieved by alkylation of *N*-acylbenzaldimines using BINOL modified alkynylboronates (Scheme 17). Using this powerful methodology, Chong was able to perform the first enantioselective total synthesis of (-)-*N*-acetylcolchinol.



R	yield / %	ee
Ph	82	80
OBn	90	40
CH_3	75	92

Scheme 17 – Conjugate Addition to Imines

Chong postulated that the asymmetric addition of the alkynylboronate was due to coordination of the carbonyl oxygen to the boron of the alkynylboronate, and of the γ-carbon of the enone to the α-carbon of the alkynylboronate, forming a six-membered transition state (Scheme 18). Therefore the addition occurs via the transition state that best accommodates the chiral environment of the ligand whilst minimising steric interactions (TS 2 in Scheme 18).

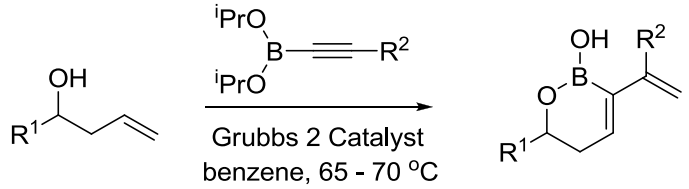


Scheme 18 – Possible Transition States for the Conjugate Addition of Alkynylboronates

Recently, Goodman has performed studies towards providing a rationale for the observed selectivities in Chong's directed conjugate additions.[33] Goodman's studies support Chong's theories on the proposed transition states for the reaction, and also highlight the key role that BINOL plays in the system. Chong found that the addition will not proceed as efficiently if alkynylboronates other than BINOL substituted derivatives are used. Goodman showed that this is due to the finely balanced reactivities required for the catalytic cycle to proceed without the production of side-products, for example from the cycloaddition of the alkynylboronate with the enone. It appears that only BINOL induces the correct level of Lewis acidity in the boron of the alkynylboronate for the reaction to proceed.

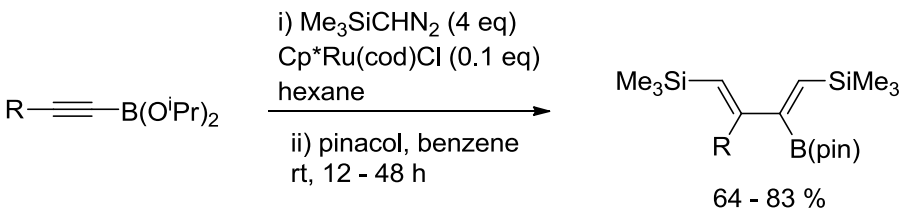
1.1.5 Further Applications of Alkynylboronates

There have been many examples in the recent literature that further demonstrate the versatile nature of alkynylboronate reagents. For example, Schreiber found that cyclic dialkenylboronic esters can be synthesised by transesterification of an alkynylboronic ester and a homoallylic alcohol, followed by trapping of the resulting mixed organoboronic ester using ring-closing ene-yne metathesis (Scheme 19).[34] The resulting cyclic organoboron species can then undergo oxidative cleavage, yielding substituted enones. They can also be efficiently transformed into other molecules with completely different skeleta, for example treatment with trioxane provides a diastereoselective route to allenes. This study demonstrates the usefulness of alkynylboronate species in powerful synthetic methodologies, in this case in the context of diversity-orientated synthesis.



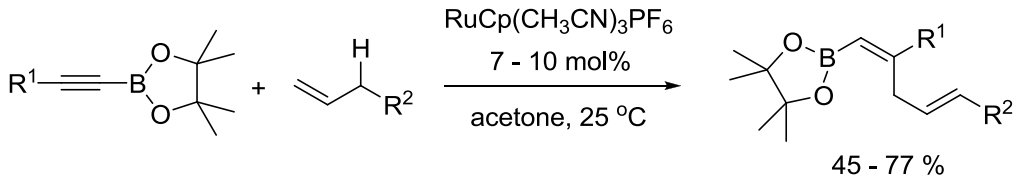
Scheme 19 – Ene-yne Metathesis of Alkynylboronates

Another example of the use of alkynylboronates in new chemical methodologies involving ruthenium catalysis has been developed by Shirakawa.[35] Ruthenium catalysed double addition of trimethylsilyldiazomethane to alkynylboronates allows for the formation of functionalised 1,3-butadienes (Scheme 20). A wide variety of functionalised alkynylboronates were found to be able acceptors of the double addition by the carbene, allowing for the formation of various 1,3-butadienes in good yields in all demonstrated cases.



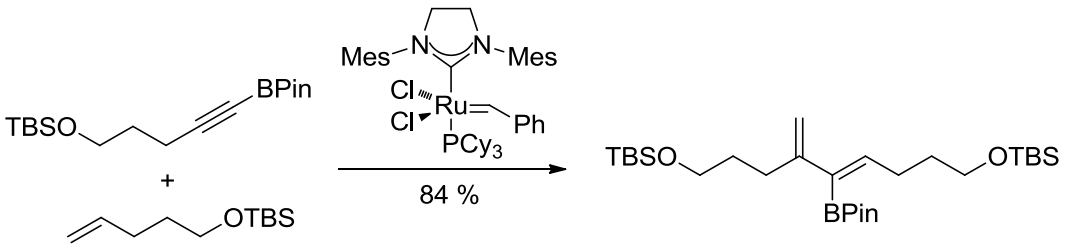
Scheme 20 - Ruthenium Catalysed Addition of Trimethylsilyldiazomethane to Alkynylboronates

Alkynylboronates can also undergo ruthenium catalysed Alder-ene reactions. Lee demonstrated that this transformation can be utilised to perform the synthesis of a variety of disubstituted vinyl boronates (Scheme 21).[36] It was found that while in some cases the reaction proceeds stereoselectively and in high yields, the efficiency of the reaction tends to depend heavily on the functionality of the alkene moiety, and appears to be independent of the functionality of the alkynylboronate.



Scheme 21 – Ruthenium Catalysed Alder-ene Reactions of Alkynylboronates

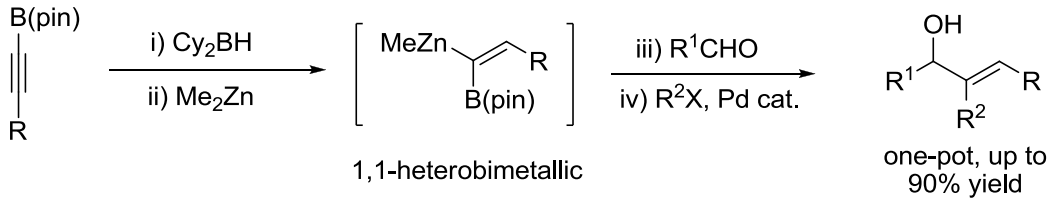
A more recent study by Lee showed that alkynylboronates can also be used to synthesise vinyl boronates containing 1,3-dienes regio- and stereoselectively via enyne cross-metathesis (Scheme 22).[37] The reaction is catalysed by Grubbs' second generation catalyst. The transformation proceeds in high yields and regioselectivities, irrespective of the substituents on the alkyne and alkene, however the substituents do affect the *E/Z*-selectivity of the reactions.



Scheme 22 – Synthesis of 1,3-Diene Containing Vinyl Boronates

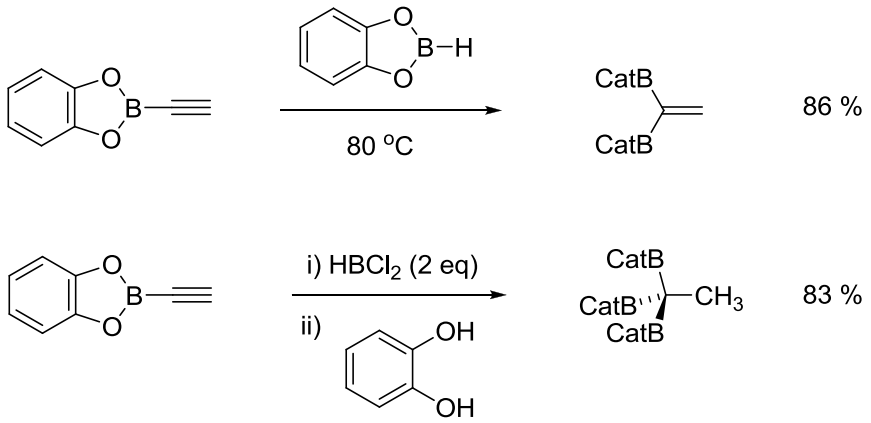
Recent work by Walsh has demonstrated how alkynylboronates can provide a practical synthesis of synthetically versatile 1-alkenyl-1,1-heterobimetallics via hydroboration of an alkynylboronate, followed by transmetallation with an organozinc reagent.[38] These intermediates were used *in situ*, allowing the efficient formation of a variety of useful compounds in one pot. For example, treatment with

an aldehyde followed by cross-coupling of the boron group allows the formation of functionalised allylic alcohols (Scheme 23).



Scheme 23 - Synthesis of 1-Alkenyl-1,1-heterobimetallics from Alkynylboronates

One final example of the varied chemistry that can be performed using alkynylboronates is the hydroboration of catechol alkynylboronate by catechol borane.[39] This was reported by Siebert in 2001, and allows the synthesis of 1,1-bisborylethene in good yields (Scheme 24). The hydroboration occurs regioselectively in each case, with the cis-addition products being favoured. If $HBCl_2$ is used as the hydroboration agent instead, double addition occurs, and the synthesis of 1,1,1-triborylethane can be achieved. Again, these products are formed regioselectively, with little of the 1,2-addition product obtained.



Scheme 24 – Hydroboration of an Alkynylboronate

1.1.6 [4+2] Diels-Alder Cycloaddition Reactions

Cycloaddition reactions are one of the most useful tools available to a synthetic organic chemist. Potentially, cycloaddition reactions can form organic compounds with high levels of regio- and diastereoselectivity. There are many different types of

cycloaddition reactions, but undoubtedly one of the most useful is the [4+2] Diels-Alder cycloaddition. These occur between a conjugated diene, and a dienophile. The dienophile is traditionally an alkene (Figure 4).[40]

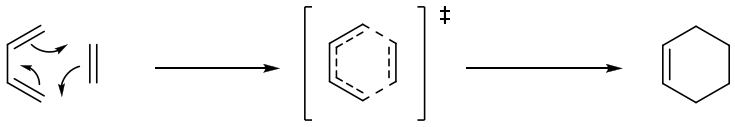


Figure 4 – A General Diels-Alder Cycloaddition

The success of the cycloaddition between a particular diene and dienophile depends largely on the matching of the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the two substrates (Figure 5). A normal Diels-Alder reaction occurs between the HOMO of an electron rich diene, and the LUMO of an electron poor dienophile. Thus the diene is acting as a nucleophile, and the dienophile as an electrophile. These types of cycloadditions are termed Normal-Electron-Demand (NED).

The inverse of this situation can occur if the diene is in conjugation with an electron withdrawing group. This electron poor diene will react, via its LUMO, with the HOMO of an electron rich dienophile. Therefore, in this situation, the diene is acting as the electrophile, and the dienophile as the nucleophile. These types of cycloadditions are termed Inverse-Electron-Demand (IED).

IED cycloadditions were first shown to exist by Sauer and Wiest in 1962.[41] They showed that it was possible to isolate a cycloadduct when the diene exists as the electrophilic component, and the dienophile exists as the nucleophilic component.

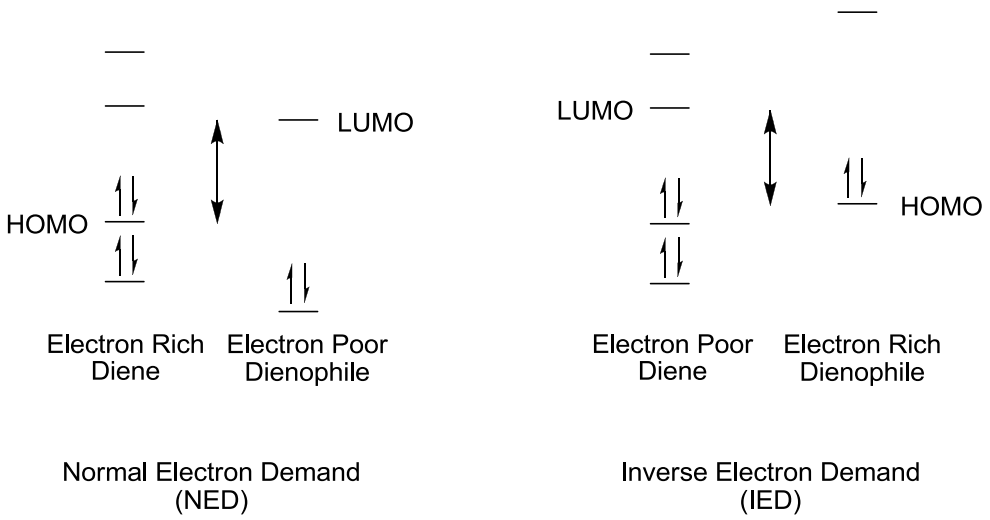
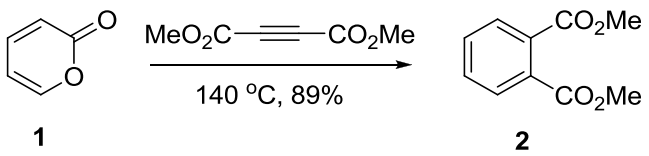


Figure 5 – Comparison of HOMO-LUMO Matching for NED and IED Cycloadditions

1.1.7 Cycloadditions Involving 2-Pyrones

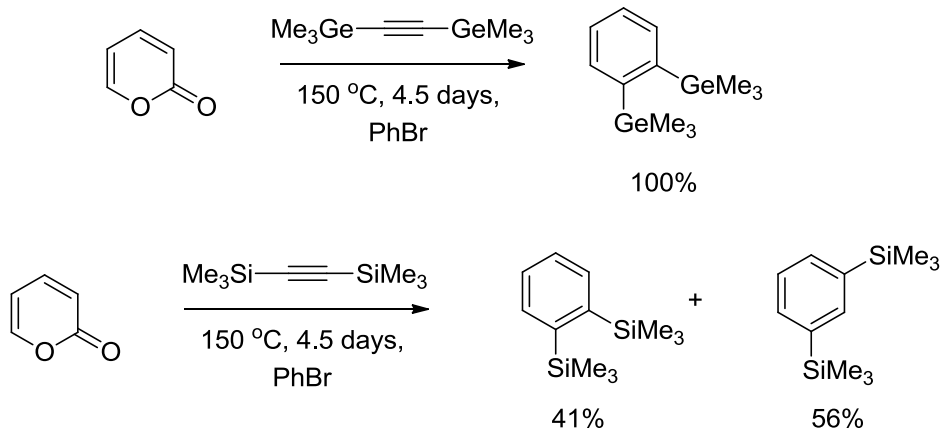
2-Pyrones were first proposed as possible dienes for [4+2] cycloaddition reactions by Diels and Alder in 1931.[42] Further work by Alder showed that a variety of 2-pyrones could undergo cycloaddition reactions with DMAD to form functionalised benzenes in high yields.[43] Scheme 25 shows the cycloaddition between 2-pyrone **1** and DMAD to form the substituted benzene **2.**



Scheme 25 – Cycloaddition of Parent 2-Pyrone

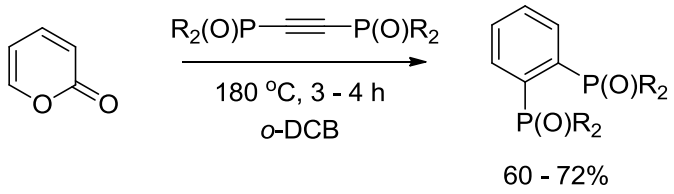
The cycloaddition of 2-pyrones with functionalised alkynes, followed by retro-cycloaddition to release CO_2, has since become well precedented, and has been used in the synthesis of a large number of benzene based systems. For example, disilyl and digermanium substituted benzenes can be formed via cycloaddition of 2-pyrones with appropriately functionalised alkynes (Scheme 26).[44] Interestingly, when disilylacetylene was used the 1,3-substituted products were obtained, alongside the

expected 1,2 products. Further investigation showed that this was due to an acid catalysed rearrangement of the initially formed 1,2-disilyl benzene.



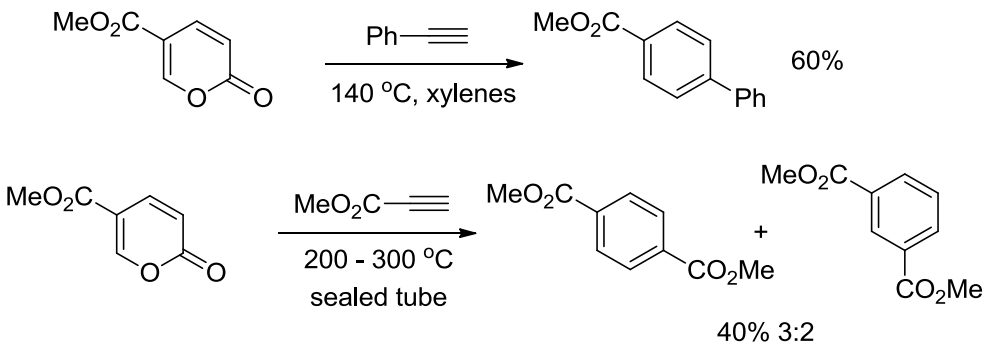
Scheme 26 – 2-Pyrone Cycloadditions with Disilyl and Digermanium Alkynes

Similarly, Kyba has demonstrated the formation of 1,2-diphosphorylbenzenes from 2-pyrone cycloaddition with 1,2-diphosphorylacetylene.[45] On reduction to the corresponding phosphines, this method provides a versatile route to chelating phosphine ligands for use as ligands in combination with transition metals (Scheme 27).



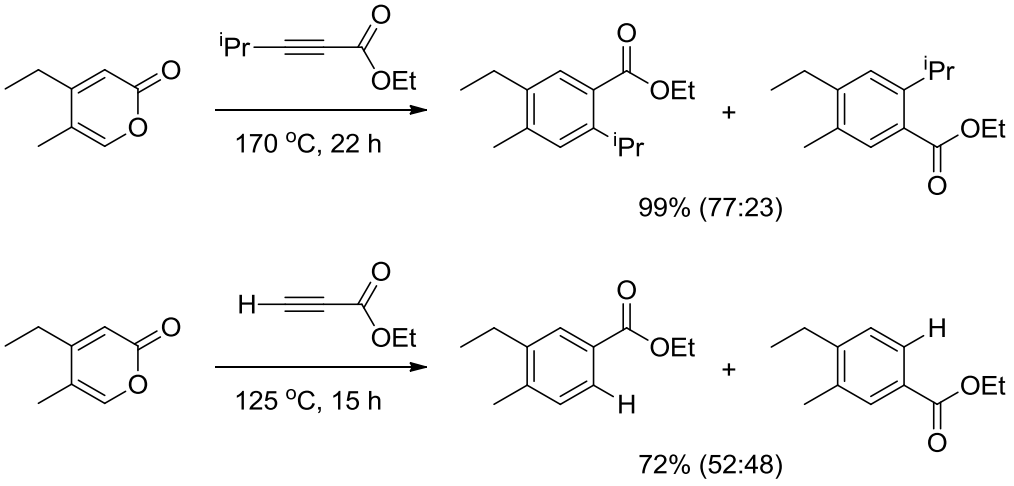
Scheme 27 - 2-Pyrone Cycloaddition with 1,2-Diphosphorylacetylene

Each of the cycloadditions previously described demonstrate the use of symmetrical alkynes in 2-pyrone cycloaddition reactions. If a non-symmetrical alkyne is used, issues arise due to the potential formation of regioisomeric products. Stille was the first to study 2-pyrone cycloadditions with non-symmetrical alkynes.[46] It was discovered that phenylacetylene reacts with methyl coumalate to give a single regioisomer in good yield; however the use of methyl propiolate gave a mixture of regioisomers in lower yield (Scheme 28).



Scheme 28 – 2-Pyrone Cycloadditions with Unsymmetrical Alkynes

In 1988, Dieter conducted a study on the regioselectivity in the cycloadditions between electronically and sterically unbiased 2-pyrones and electronically biased alkynes (Scheme 29).[47] It was discovered that internal alkynes tend to react with higher regioselectivity than the corresponding terminal acetylenes. However, the regiochemical insertion pattern in each case remained consistent.



Scheme 29 – Cycloaddition of 2-Pyrones with Electronically Biased Alkynes

Dieter explained this observation using Frontier Molecular Orbital theory (FMO). The presence of the electron withdrawing carbonyl group in the 2-pyrone ring means that carbon 2 in the 2-pyrone is relatively electron rich compared to carbon 5. This leads to more favourable interactions in the transition state; 2-pyrone carbon 2 with carbon b in the alkyne, and 2-pyrone carbon 5 with alkyne carbon a (Figure 6). FMO theory also predicts larger differences in orbital coefficients for the acetylenic

carbons in internal alkynes, compared with terminal acetylenes, leading to greater cycloaddition regioselectivities.

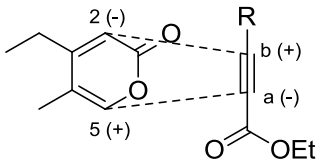
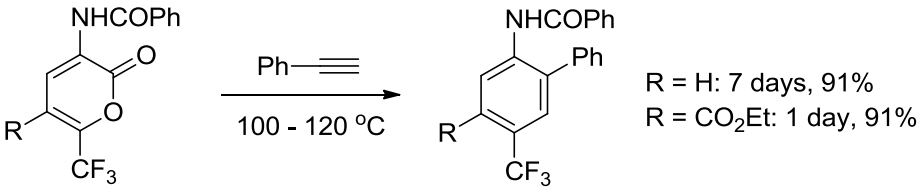


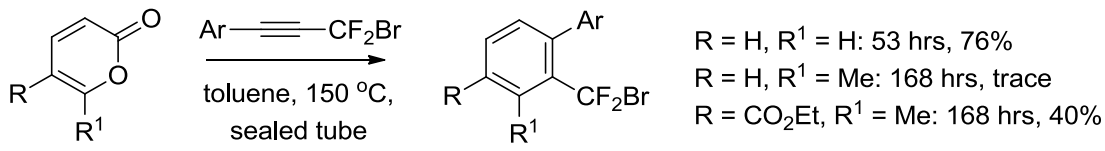
Figure 6 – Predicting Regioselectivities in 2-Pyrone Cycloadditions

Recent work by Haufe has utilised 2-pyrone cycloadditions for the formation of polyfluorinated alkylbenzenes (Scheme 30).[48] Only one regioisomer is produced from the reaction, however harsh conditions are required for good yields. Temperatures greater than 100 ^{o}C, and long reaction times are required, with a number examples only showing complete conversion after 7 days. The reaction efficiency can be improved by incorporation of an electron withdrawing group into the 5-position of the 2-pyrone ring. A high yield of product was obtained after only 1 day when an ester group was incorporated.



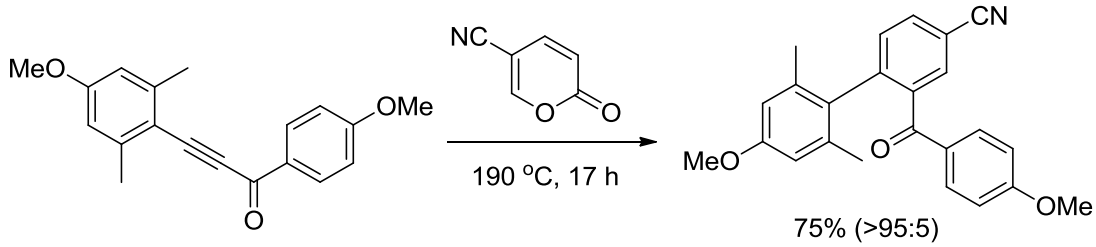
Scheme 30 – Cycloadditions of Fluorinated 2-Pyrones

More recently, Haufe has developed a more versatile route to halogenated methylbenzene substrates, by performing the cycloadditions of 2-pyrones with 1-(3-bromo-3,3-difluoroprop-1-ynyl)benzenes (Scheme 31).[49] Similar to the previous studies, the functionalised 2-pyrones reacted with greater efficiency when an electron withdrawing group was incorporated in the 5-position.



Scheme 31 – 2-Pyrone Cycloadditions with Fluorinated Alkynes

The versatility of 2-pyrone cycloadditions has seen them become a much used tool in organic synthesis. For example, Redden's recent synthesis of nonsteroidal phenanthrene ligands for the estrogen receptor involves the high yielding [4+2] cycloaddition of 5-cyano-2-pyrone (Scheme 32).[50]



Scheme 32 – A Cycloaddition of 5-Cyano-2-pyrone

Unlike most dienes, 2-pyrone is electron deficient. This is due to the presence of the electron withdrawing carbonyl group in conjugation with the diene. This means that most 2-pyrones react more readily with electron rich dienophiles, and so undergo IED cycloadditions. Previous work suggests that incorporation of an electron withdrawing group in the 2-pyrone enhances reactivity and leads to improved yields of cycloaddition product. Along with the examples previously discussed, this effect can be demonstrated by performing cycloadditions of different 2-pyrones (**3, 4** and **5**) with stannyl acetylenes (Figure 7).

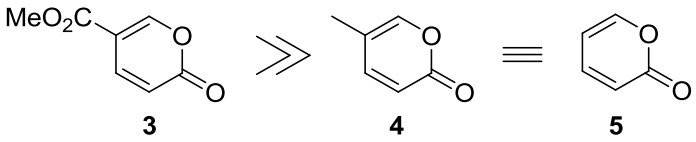
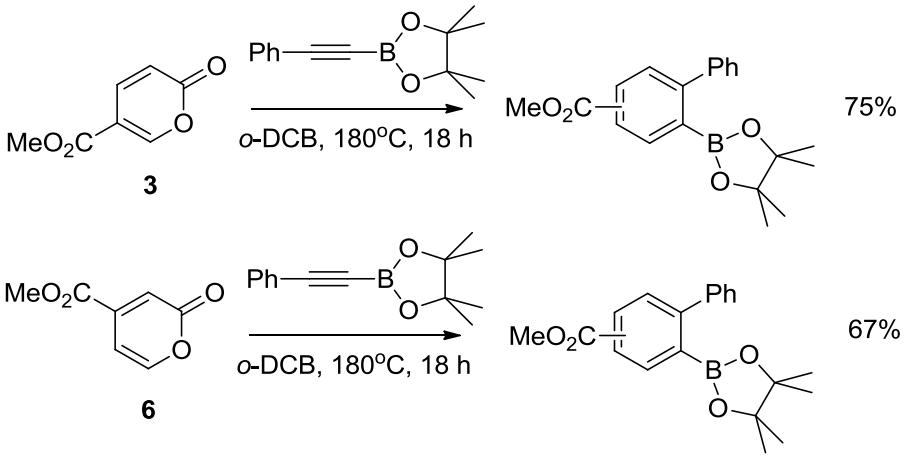


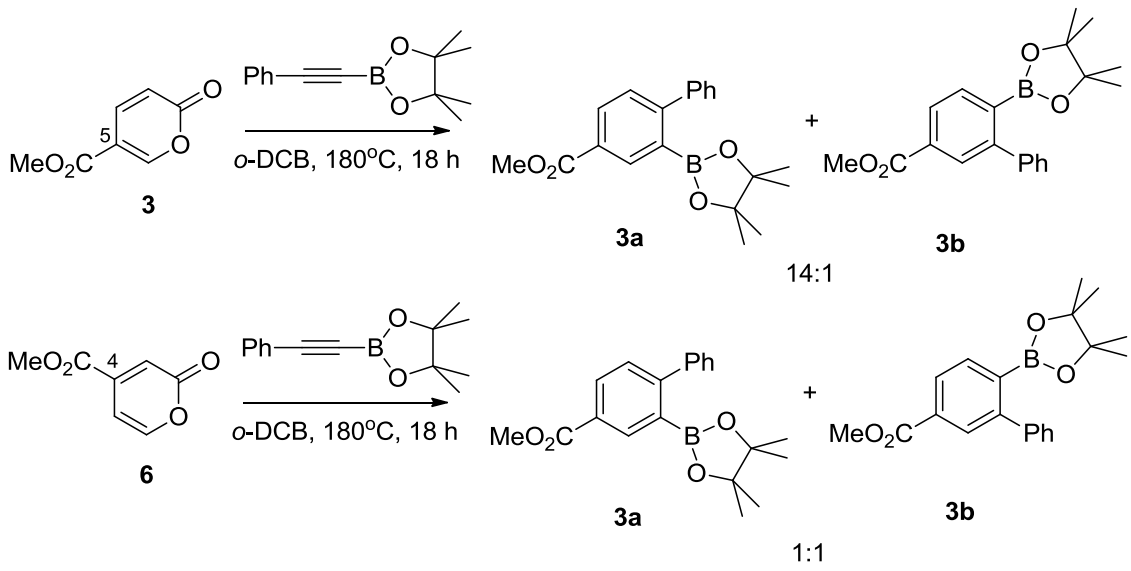
Figure 7 – Order of 2-Pyrone Reactivities Towards Cycloaddition with Stannyl Acetylenes

Previous work in the Harrity group has shown that varying the position of the electron withdrawing group on the 2-pyrone can affect the yield of the cycloaddition reactions. As shown in Scheme 33, it was found that the 2-pyrone undergoes slightly smoother cycloaddition if the electron withdrawing group is placed in a position where it can conjugate with the enol ester moiety on the 2-pyrone, shown here by the relative efficiencies of the cycloadditions of compounds **3** and **6**.[11]



Scheme 33 - Yields of Cycloadditions of 2-Pyrones Containing an Ester Functionalisation

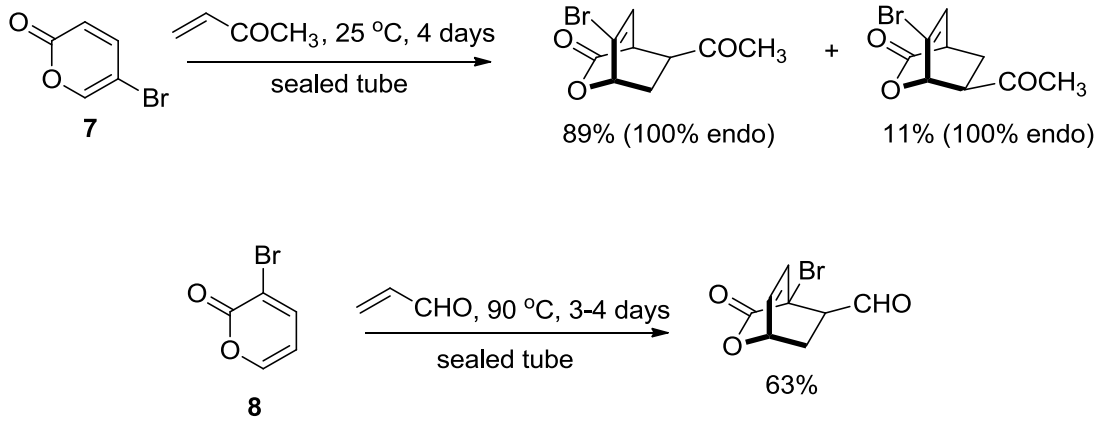
Altering the position of the electron withdrawing group can also affect the regioselectivity of these cycloadditions. For example, it was found that in the reaction of a phenyl-substituted alkynylboronate with a 2-pyrone bearing the methyl ester group in position 5 (compound **3**) regioisomer **3a** is preferred. If the group is in position 4 (compound **6**) the reaction produces an equal amount of the regioisomers **3a** and **3b** (Scheme 34).[11]



Scheme 34 - Regioselectivities of Cycloadditions of 2-Pyrones Containing an Ester Functionalisation

From this previous study it is clear that by placing an electron withdrawing group in various positions on the 2-pyrone, both cycloaddition yields and regioselectivities can be, to an extent, controlled. It would appear from this work that if the electron withdrawing group is in the 5-position, optimum yields and regioselectivities for the cycloaddition reactions can be obtained.

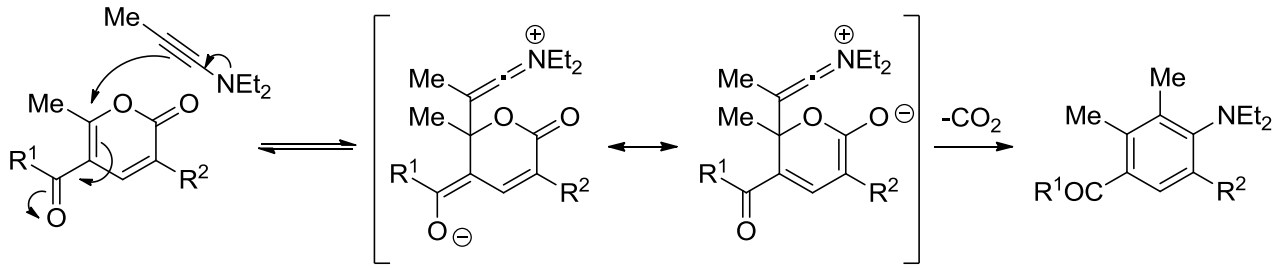
Studying the effect of addition of a species that can be both electron withdrawing and donating to the 5-position of the 2-pyrone would be interesting. Indeed, bromide can behave in such a way. Afarinkia and Posner, who have studied the cycloaddition reactions of bromo-2-pyrones extensively, have examined the effect of incorporating bromide at various positions on 2-pyrones.[51] They discovered that by placing bromide at the 5-position on the 2-pyrone (**7**), they could obtain greater yields and regioselectivities in cycloadditions than when bromide is placed at alternative positions on the 2-pyrone.[52] This is shown by comparing the yields obtained when using compound **7** versus **8** (Scheme 35). This observation is analogous to the results obtained by placing an ester group on the 2-pyrone. Therefore this suggests that, in this example, bromide is removing electron density from the 2-pyrone ring.



Scheme 35 – Cycloadditions of 3- and 5-Bromo-2-pyrones

Studies performed on the cycloaddition reactions of 2-pyrones all suggest that yields and regioselectivities can be improved by addition of an electron withdrawing group to the 2-pyrone. These studies have also shown that if the electron withdrawing group is placed on the 5-position of the 2-pyrone, optimal yields and regioselectivities are obtained.

A detailed study on the regioselectivity of 2-pyrone cycloadditions has recently been undertaken by Stefane.[53] Using a highly electronically biased dienophile, *N*,*N*-diethylpropynamine, Stefane has demonstrated, through experimental evidence and DFT calculations, that the IED cycloaddition of 2-pyrones can proceed in a stepwise manner (Scheme 36). In an extreme sense, this involves nucleophilic attack of the electron rich alkyne on the electron deficient 2-pyrone, followed by formation of the second C-C bond and subsequent benzene formation via elimination of CO_2.



Scheme 36 – Cycloaddition of 2-Pyrone with *N*,*N*-Diethylpropynamine

With respect to 2-pyrone cycloadditions with alkynylboronates, the presence of the electron withdrawing carbonyl group in the 2-pyrone ring means that the carbon α to the enol ether moiety is relatively electron poor compared to the carbon α to the carbonyl. By a similar analysis, and assuming a vacant p-orbital at boron, one can envisage a positive charge on the alkyne β-carbon atom. Such electrostatic interactions between the diene and the alkyne means that cycloadditions of these substrates could potentially be performed with a high degree of regiochemical control, i.e. the reaction should proceed via formation of a C-C bond between the most electron deficient carbon on the 2-pyrone, and the most electron rich carbon on the alkyne (Figure 6).

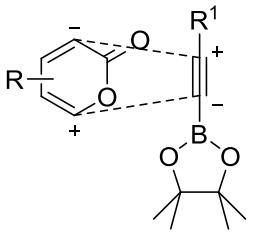


Figure 6 – Potential Regiocontrol in 2-pyrone Cycloadditions

The electron withdrawing/donating effects of substituents can be quantified using the Hammett constants, σ_m and σ_p. The Swain and Lupton equation also defines two further values; *R*, associated with resonance effects, and *F*, associated with field effects. These values can be used to predict the electronic effect a substituent will have on a reaction. The values for a wide range of substituents have been collated by Hansch.[54]

Previous work in the Harrity group has shown that regioselective cycloadditions are indeed possible. Varying the nature and position of the electron withdrawing group on the 2-pyrone ring would be interesting, in order to determine the effect these groups can have on altering this regioselectivity.

1.2 Aims

2-Pyrones have been shown to react smoothly with various alkynes and alkynylboronates in [4+2] cycloaddition reactions. It has been shown previously that the cycloaddition reactions can be optimised through the addition of an electron withdrawing species to the 2-pyrone ring.

The initial aims for this project were to synthesise 2-pyrones incorporating various electron withdrawing groups, then to examine the effect that the different groups had on the efficiency and regioselectivity of cycloadditions with alkynylboronates. Initially, we decided to use readily available halo-2-pyrones, and to study their cycloaddition with phenyl-, trimethylsilyl- and *n*-butyl-substituted alkynylboronates.

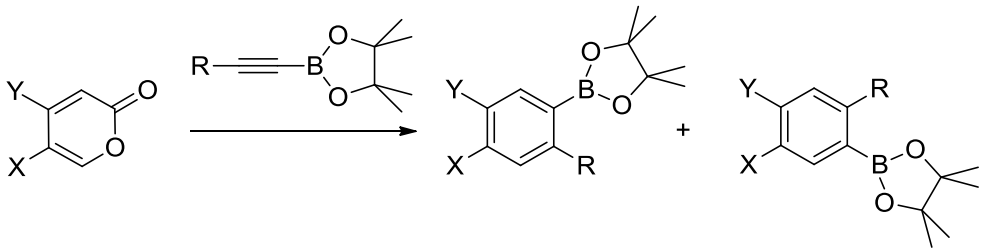
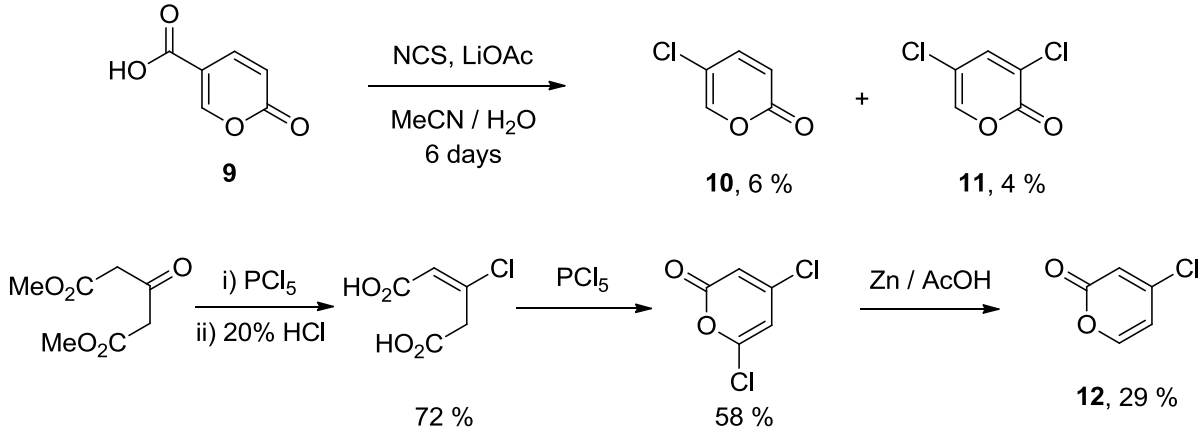


Figure 8 - Cycloadditions of 2-Pyrones with Alkynyl Boronic Esters

1.3 Results and Discussion

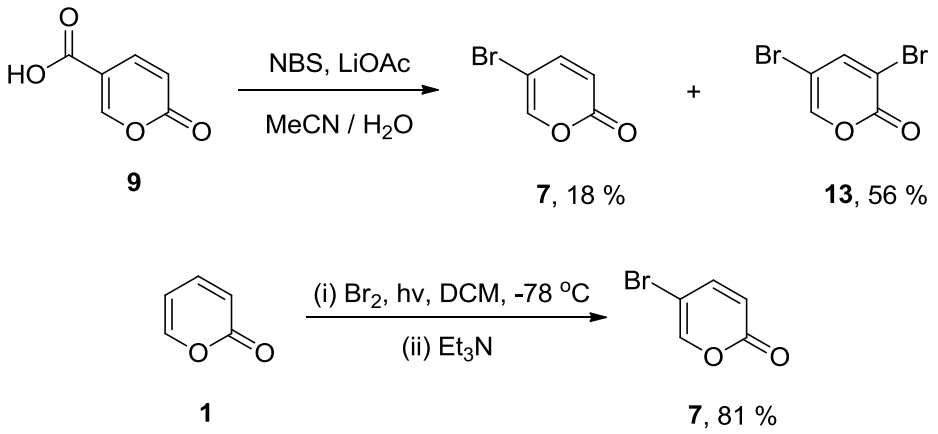
1.3.1 Synthesis and Cycloadditions of Halo-2-pyrones

In order to assess the effect of the halide substitution pattern of 2-pyrones on the cycloadditions with alkynylboronates, a number of functionalized 2-pyrones first needed to be synthesised. The isomeric 2-pyrones 5-chloro-2-pyrone **10** and 4-chloro-2-pyrone **11** were examined first. These were readily prepared by previously published methods (Scheme 37).[55] In our hands, the chlorination of coumalic acid for formation of 5-chloro-2-pyrone **10** and 2,5-dichloro-2-pyrone **11** was achieved in low yields, similar to those reported. This method was however found to be sufficient to form enough 2-pyrone with which to perform cycloaddition studies, as the low cost of the required reagents allowed us to perform the reaction on large scale.



Scheme 37 - Synthesis of Chloro-2-pyrones

To widen our study of the cycloadditions of halo-2-pyrones with alkynylboronates, 5-bromo-2-pyrone **7** was also synthesised.[56] This was initially accomplished via a Hünsdiecker reaction, similar to the one used to perform the chlorination of coumalic acid. Due to the modest yield of this reaction for the desired 2-pyrone, it was decided that an alternative route should be used. In the event, radical bromination of the parent 2-pyrone **1** followed by elimination with triethylamine afforded the desired compound in better yield (Scheme 38).

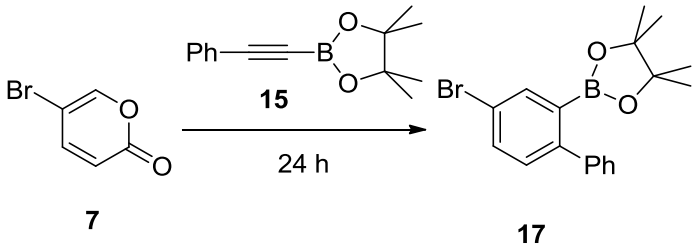


Scheme 38 - Synthesis of Bromo-2-pyrones

The alkynylboronates used as cycloaddition partners in this study were synthesised using the previously mentioned method developed by Brown.[17] For this study, it was decided that the trimethylsilyl- (**14**), phenyl- (**15**) and *n*-butyl- (**16**) substituted alkynylboronates would be most suitable, as these should provide differing electronic and steric effects.

With the desired halo-2-pyrones and alkyne partners in hand, attention was turned to the cycloaddition reactions. To optimise the conditions for the cycloadditions, phenyl substituted alkyne **15** was used as the dienophile, with 5-bromo-2-pyrone **7** as the diene. Firstly, the reaction solvent was assessed. It was envisaged that both boiling point and solubilising potential of the solvent could affect the reaction, although at the elevated temperatures required for cycloaddition, the latter was considered less important. Table 1 outlines the experiments performed to assess the effect of temperature on the cycloaddition reaction. From these results, it is clear that if the temperature of the reaction is too low (less than 140 ^{o}C) then the reaction does not proceed smoothly, and so less product is formed. This was shown by the low yield found when the reaction was conducted in toluene at 95 ^{o}C (entry 1). It was also found that the product appears to degrade if the reaction temperature is greater than 160 ^{o}C (entries 4 and 5). Therefore it was envisaged that refluxing in either mesitylene (boiling point = 155 ^{o}C) or xylenes (boiling point = 140 ^{o}C) would represent ideal conditions with which to perform the cycloaddition reactions. The conversions quoted in Table 2 were recorded after each reaction had been conducted at the stated temperature for 24 h. The yields were obtained by spiking the dried

sample of each of the crude reaction mixtures with a known amount of 1,2-dichloroethane, then analysing this mixture by ^{1}H NMR spectroscopy. The amount of product present in the crude reaction mixture could be found by comparing the integrals of the product peaks to those of the dichloroethane peak. In the event, a poor yield of desired product was obtained in all cases when the reaction was performed at (or near) reflux over 24 h.

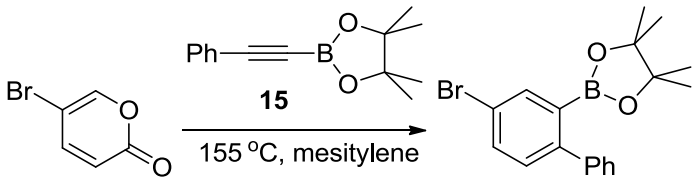


7 **17**

Entry	Solvent	Temperature / ^{o}C	Conversion / %
1	Toluene	95	4
2	Xylenes	140	21
3	Mesitylene	155	9
4	*o*-DCB	195	1
5	Nitrobenzene	210	-

Table 1 - Solvent Screen of Bromo-2-pyrone Cycloadditions

A further consideration in the optimisation of the cycloadditions was the reaction time. Table 2 shows data gathered for reactions performed in mesitylene over differing lengths of time. From this data it can be seen that if the reaction time is too long, the product will degrade, which is shown by the lower product yields obtained in reactions conducted over 16 h.

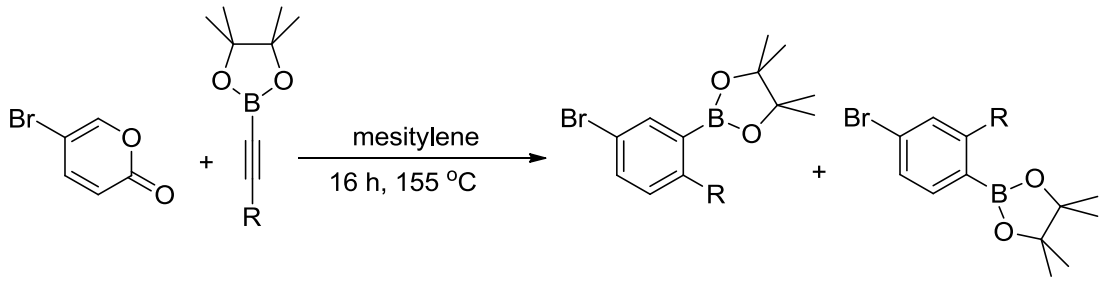


7 **17**

Reaction Time / h	Yield **17** /%
8	39
16	46
24	36
48	9
72	9

Table 2 – Screen of Reaction Times for Bromo-2-pyrone cycloadditions

With an initial screen of conditions in hand, other alkynylboronates were studied. The results are shown in Table 3. It is clear that using a trimethylsilyl-substituted alkyne gives the best yield (80%), whilst the phenyl-substituted alkyne gives the best regioselectivity (only one regioisomer detected). We propose that the trimethylsilyl alkyne is most efficient due to the fact that these cycloadditions are all inverse electron demand, hence, the trimethylsilyl group leads to a relatively electron rich alkyne because of its low electronegativity.



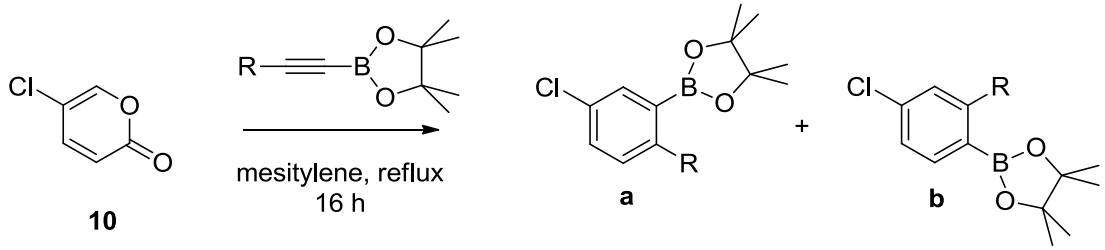
7 **a** **b**

Entry	R	Yield/%	a : b
1	Ph	**17**; 46	>98:2
2	TMS	**18**; 80	3:2[a]
3	^{n}Bu	**19**; 44	3:2[a]

[a] Identity of the major regioisomer not confirmed

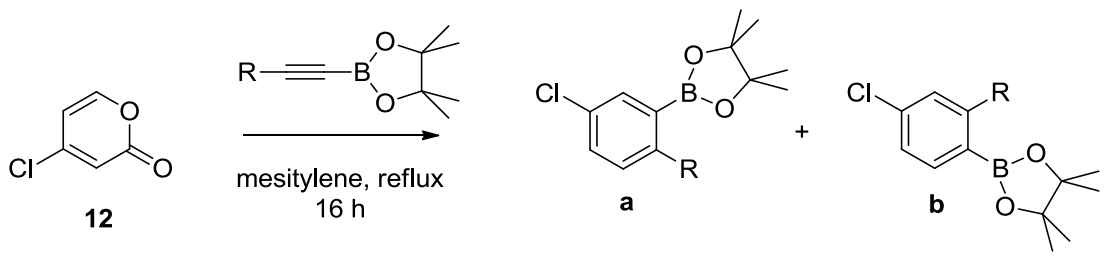
Table 3 – Cycloadditions of 5-Bromo-2-pyrone

With these results in hand, attention was turned to the chloro-substituted 2-pyrones, **10** and **12**. In a similar to manner to the observations made with the bromo-2-pyrones, the chloro-2-pyrones provided a far higher yield when reacted with the trimethylsilyl-substituted alkyne **14**. The identity of the major regioisomer obtained from the cycloaddition of **10** with **14** was confirmed by transformation to the corresponding 3- and 4-chloro-phenols (Appendix, page 149). The highest regioselectivities were again achieved when using phenylalkynylboronate as the dienophile. Unfortunately, the *n*-butyl substituted alkyne displayed poor reactivity, and no product was obtained from either reaction (Table 4 and Table 5).



Entry	R	Yield/%	a : b
1	Ph	**20**; 21	>98:2
2	TMS	**21**; 70	4:3
3	^{n}Bu	0	-

Table 4 – Cycloadditions of 5-Chloro-2-pyrone

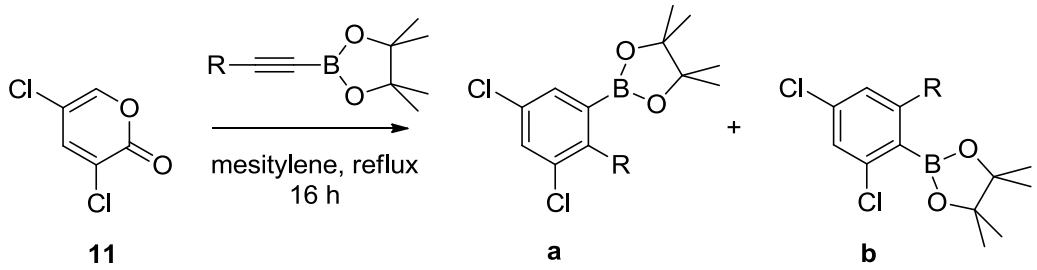


Entry	R	Yield/%	a ; b
1	Ph	**20**; 25	<2:98
2	TMS	**21**; 70	3:5
3	^{n}Bu	0	-

Table 5 – Cycloadditions of 4-Chloro-2-pyrone

Interestingly, the position of the chlorine atom on the 2-pyrone ring appeared to have little effect on the outcome of the cycloaddition reactions. In both cases, high regioselectivities were obtained upon cycloaddition with aryl-substituted alkyne, affording the two different regioisomeric products in moderate but similar yields. This observation is in stark contrast to the cycloadditions of methyl ester substituted 2-pyrones, reported previously in our group, which show a sharp drop in regioselectivity when the ester is incorporated at the 4-position on the ring. This is presumably due to the greater mesomeric effect of the ester withdrawing electron density from the 3-carbon on the ring, which supports the notion that the regioselectivity of these cycloaddition reactions is controlled mainly by electronic effects.

Having previously obtained large amounts of the dichloro-substituted 2-pyrone **11**, the cycloaddition reactions of this diene were also examined (Table 6). Again, this 2-pyrone displays high yields but no regioselectivity when reacted with silyl alkyne, but low yields and high regioselectivity when reacted with phenyl alkyne. Unfortunately, the *n*-butyl substituted alkyne again displayed poor reactivity, and no product was obtained from the reaction.



11 **a** **b**

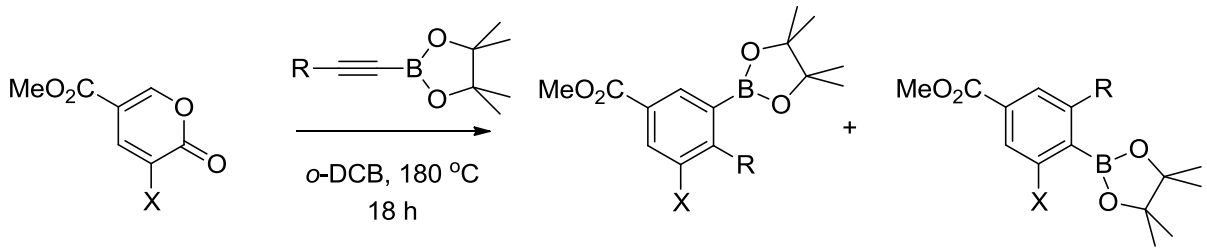
Entry	R	Yield/%	a : b
1	Ph	**22**; 32	<98:2
2	TMS	**23**; 70	1:1
3	^{n}Bu	0	-

Table 6 – Cycloadditions of 2,5-Dichloro-2-pyrone

1.3.2 Synthesis and Cycloadditions of Cyano-2-pyrones

From these results it was clear that halo-substituted 2-pyrones are generally poorly reactive towards alkynylboronates, unless the alkyne is activated by a

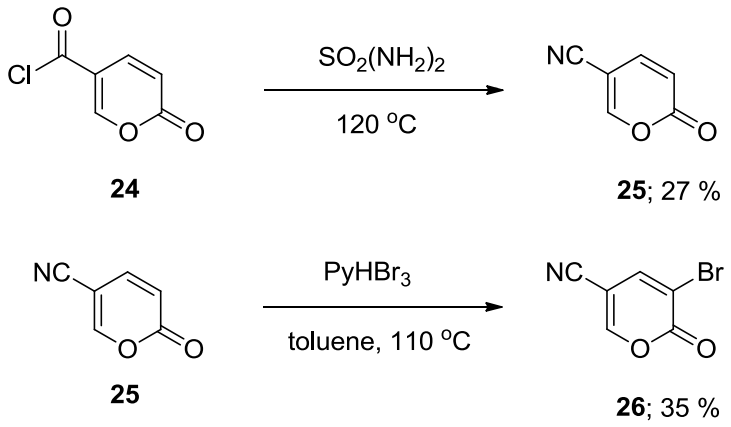
trimethylsilyl-substituent. However, previous work in the group had shown that when a more electron withdrawing substituent is used on the 2-pyrone, the cycloadditions proceed more generally with far greater efficiency (Table 7).[13]



X	R	Yield/% (a:b)
H	Ph	75 (14:1)
H	TMS	100 (1:1)
H	^{n}Bu	80 (3:1)
Br	Ph	77 (>95:5)
Br	TMS	77 (3:2)
Br	^{n}Bu	82 (10:1)

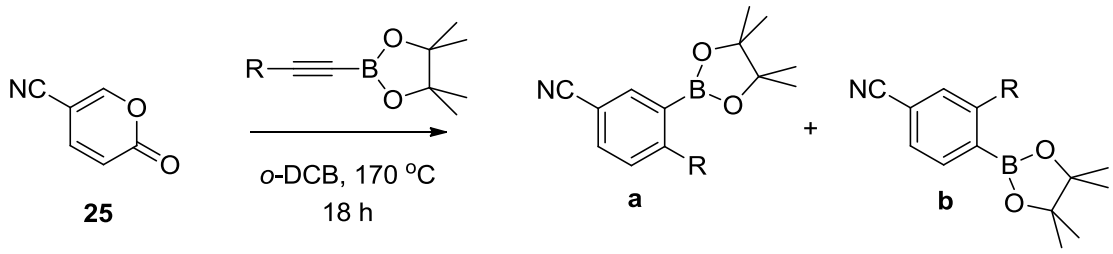
Table 7 – Previously Published Cycloadditions of Ester Functionalised 2-Pyrones[13]

Therefore, the effect of incorporating an alternative electron withdrawing substituent was examined. It has been previously reported that the 5-cyano-2-pyrone substrates are readily available by treating acyl chloride **24** with sulfamide. The acyl chloride is in turn easily prepared by treating coumalic acid with thionyl chloride.[57] This allowed for the formation of the cyano-substituted 2-pyrone **24** in moderate yields, but in large quantities (Scheme 39). The obtained 5-cyano-2-pyrone can then be brominated readily using pyridinium tribromide, affording the desired 3-bromo-5-cyano-2-pyrone **26** in modest yields, but again in large quantities.



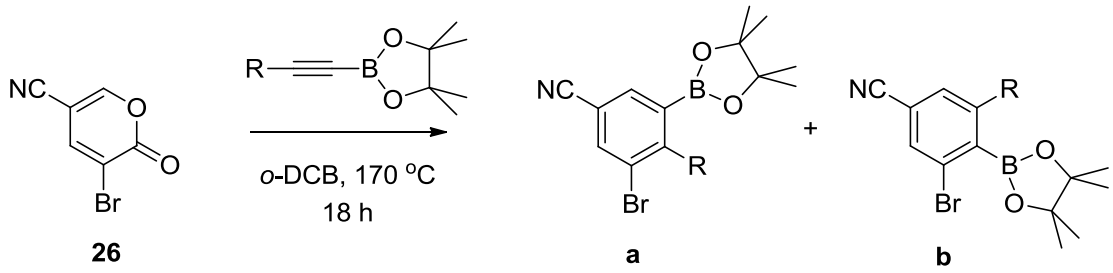
Scheme 39 - Synthesis of Cyano-2-pyrones

With these new, electron deficient, 2-pyrones in hand attention was turned to their cycloaddition reactions. Pleasingly, 2-pyrones **25** and **26** displayed far greater reactivity than the previously used halo-2-pyrones, with good to high yields being obtained for all of the three alkyne partners used. Specifically, we were delighted to find that the bromo-substituted 2-pyrone **26** reacts with phenyl alkynylboronate to form compound **30a** selectively in 94% yield. As with the halo-2-pyrones, reaction with phenyl-substituted alkyne displayed high levels of regioselectivity, whereas reaction with alkyl-substituted alkyne displayed a poorer level of regioselectivity. Unfortunately, silyl alkynylboronate displayed no regioselectivity upon cycloaddition (Table 8 and Table 9). It was found that cyano-2-pyrones are less subject to degradation at higher temperatures than halo-2-pyrones; therefore reactions were performed in *o*-dichlorobenzene at 170 ^{o}C for 18 h in order to maximize the product yields.



Entry	R	Yield/%	a : b
1	Ph	**27**; 76	>98:2
2	TMS	**28**; 99	1:1
3	^{n}Bu	**29**; 53	5:1

Table 8 – Cycloadditions of 5-Cyano-2-pyrone



Entry	R	Yield/%	a : b
1	Ph	**30**; 94	>98:2
2	TMS	**31**; 96	1:1
3	^{n}Bu	**32**; 65	11:1

Table 9 – Cycloadditions of 3-Bromo-5-cyano-2-pyrone

1.3.3 – Assignment of Cycloadduct Regiochemistry

The assignment of the major regioisomers from 2-pyrone cycloadditions with phenyl alkynylboronate was carried out by nOe spectroscopy. For the cyano-substituted cycloadduct, **27a**, on irradiation of the aromatic proton at 8.02 ppm, a nOe enhancement was observed with the protons on the pinacol group of the boronic ester (Figure 9). On irradiation of the pinacol protons, a nOe enhancement was observed with both the proton at 8.02 ppm, and the protons on the phenyl ring. Therefore, we can conclude that the boronic ester group is

situated between the aromatic proton at 8.02 ppm, and the phenyl group, i.e.; *meta*- to the cyano group. Similar analyses were performed on each of the substrates shown below, allowing us to confirm the identity of the regioisomer obtained in each case. The regiochemistry of the dichloro-substituted cycloadduct **22a** was inferred from the regiochemistry of the analogous dibromo-substituted cycloadduct, which has been previously synthesised and charachterised.[12] The nOe spectra for compounds **27a**, **30a**, **20a** and **20b** can be found in the Appendix, pages 150 – 160.

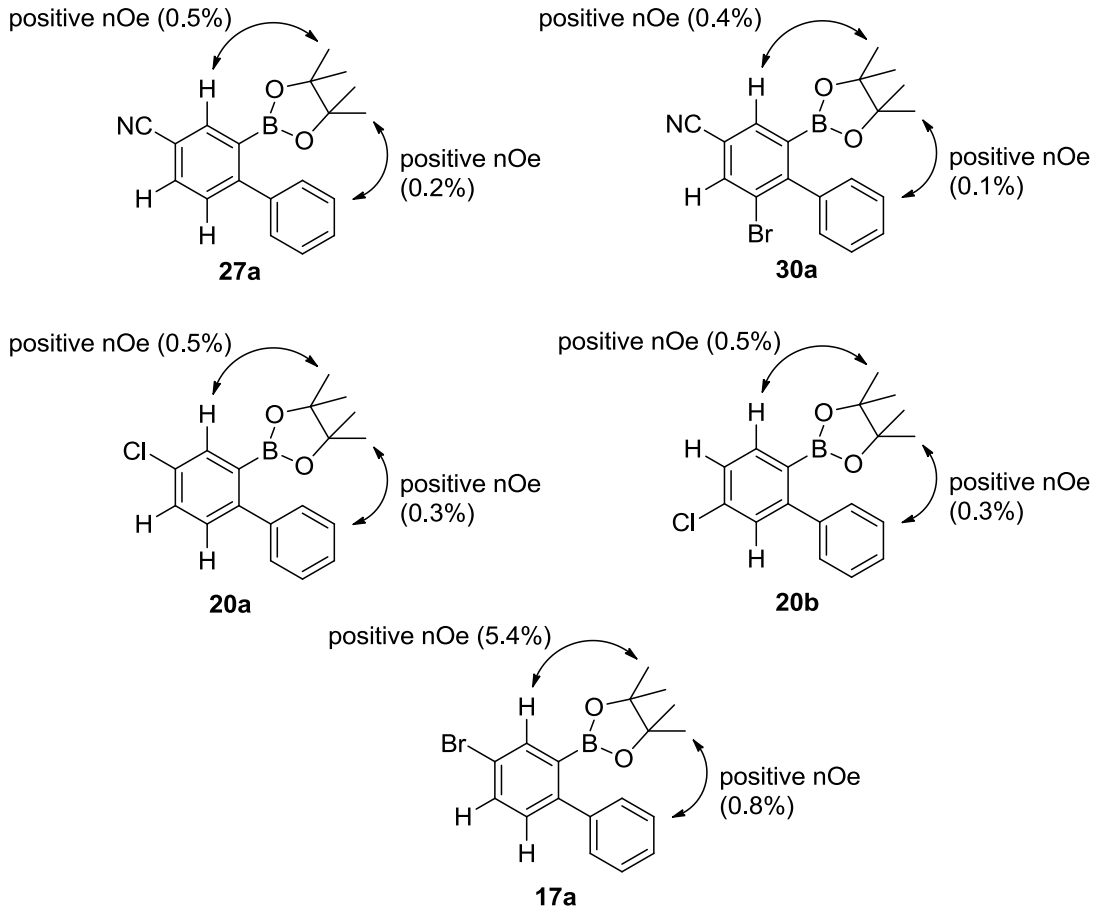


Figure 9 – nOe Studies on Aromatic Boronic Esters

From these studies we have made the following general conclusions:

- Aryl alkynylboronates undergo highly selective cycloaddition reactions with 2-pyrones, but with varying yields.

- Silyl alkynylboronates undergo high yielding cycloaddition reactions with 2-pyrones but with little to no regioselectivity.

These trends are summarised in Table 10 below:

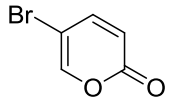
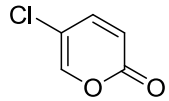
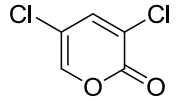
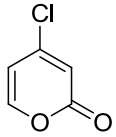
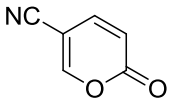
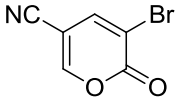
Pyranone	Alkynylboronate	Yield / %	Ratio **a** : **b**
	Ph	46	> 98:2
	TMS	80	3:2
	^{n}Bu	44	3:2
	Ph	21	> 98:2
	TMS	70	1:1
	^{n}Bu	-	-
	Ph	32	> 98:2
	TMS	71	1:1
	^{n}Bu	-	-
	Ph	25	> 98:2
	TMS	70	1:1
	^{n}Bu	-	-
	Ph	76	> 98:2
	TMS	99	1:1
	^{n}Bu	53	5:1
	Ph	94	> 98:2
	TMS	96	1:1
	^{n}Bu	65	11:1

Table 10 – Cycloadditions of 2-Pyrones with Alkynylboronates

1.3.4 Quantum Mechanical Studies on Alkynylboronate Cycloadditions

In an effort to further understand these results, quantum mechanical studies were performed in order to view the lowest energy transition states for the cycloaddition between 2-pyrones and the phenyl- and silyl-substituted alkynes. These studies were performed by Andrew Leach, of AstraZeneca®. Remarkably, in each case studied, the cycloadditions appear to proceed through an asynchronous transition state, whereby the bond between the alkyne and C_5 of the 2-pyrone forms slightly faster than the bond between the alkyne and 2-pyrone C_2. As outlined in Figure 10 below, this is highlighted in each case by the fact that the C_a-C_5 distance is always shorter than C_b-C_2. This is in line with previously reported results, which suggest that 2-pyrones can undergo cycloadditions via asynchronous transition states.[53]

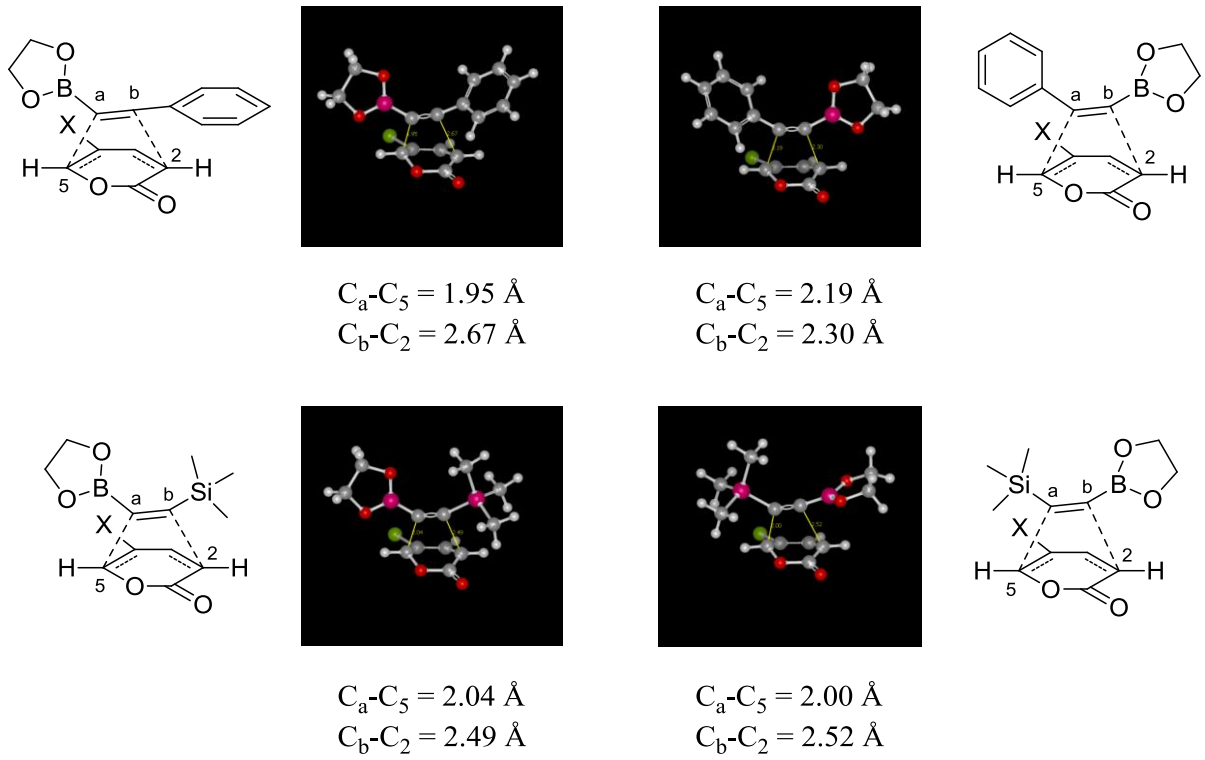


Figure 10 - 2-Pyrone – Alkyne Bond Lengths in Cycloaddition Transition States

Interestingly, the lowest energy transition state for the cycloaddition of the phenyl alkynylboronate predicts the same regioselectivity as seen experimentally. In this system, the two alkyne carbons appear to be orientated in line with the adjacent phenyl ring, suggesting electron delocalisation between the two π systems. In

contrast, the opposite regioisomer provides a higher energy transition state, and does not show this linear relationship (Figure 11). Due to the asynchronous nature of the cycloaddition, a partial positive charge will build up on one of the alkyne carbons. As seen in each of the below transition states, the positive charge can be stabilised by the phenyl group by delocalisation if aligned parallel with the pyrone ring. This leads to a lower energy transition state, and hence explains why the preferred regioisomer is both predicted theoretically and observed experimentally.

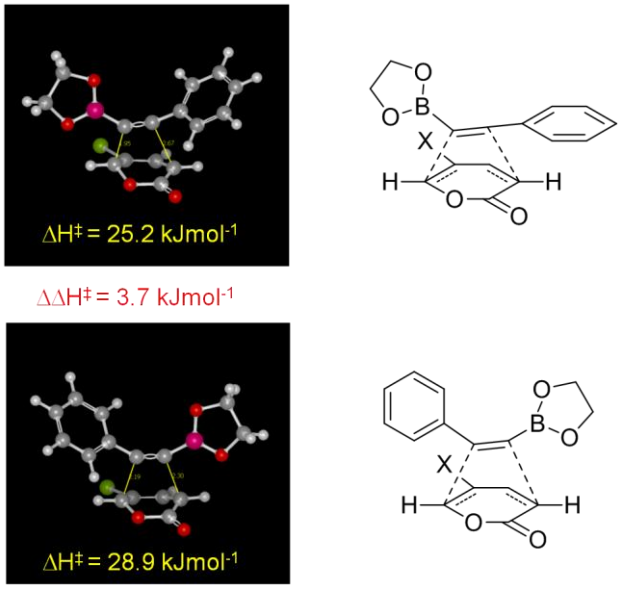


Figure 11 - Energy Difference between Regioisomeric Transition States - Arylalkynylboronate

If the silyl substituted alkynylboronate is instead used in the calculations, a different picture is seen (Figure 12). A smaller energy difference can now be seen between the transition states for the two possible regioisomers, suggesting that the reaction will proceed with little regioselectivity. This is indeed the case, as the silyl alkynylboronate was found to be essentially non-regioselective in the cycloadditions with every 2-pyrone used. This is unsurprising, as conjugative stabilisation of the forming partial positive charge on the alkynylboronate is not possible using either the attached silyl or boronic ester groups. In addition, one can consider the relative nucleophilicity of C_a/C_b. Interestingly, the field effect values *F* given by the Swain-Lupton equation are very similar for both the Si- and B-based substituents (Me_3Si;

+0.01 and $(HO)_2B$; -0.03 with Ph; +0.12), providing another plausible rationale for the observed regiochemical insertion patterns.[54]

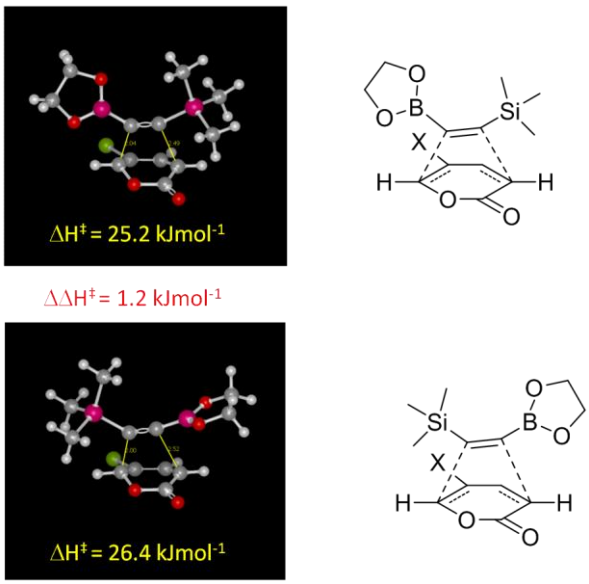
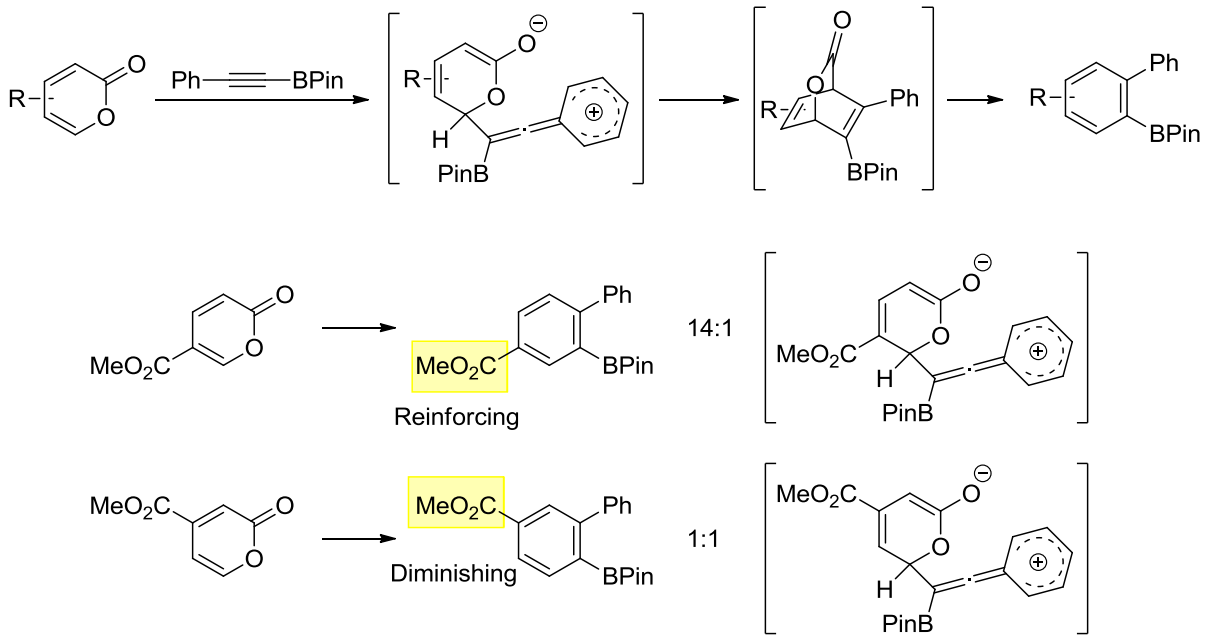


Figure 12 - Energy Difference between Regioisomeric Transition States – Silylalkynylboronate

From these studies, it is possible to put forward an explanation for the results previously reported in the group. As outlined earlier, methylcoumalate undergoes an essentially regioselective cycloaddition with phenyl alkynylboronate; however the regioisomeric 2-pyrone undergoes cycloaddition non-regioselectively under the same conditions. We now believe that this is due to the asynchronous nature of the cycloaddition reactions. Scheme 40 below depicts an extreme view of the 2-pyrone cycloadditions, where the reaction proceeds in a stepwise manner. If the ester is incorporated into the 5-position of the 2-pyrone, a reinforcing effect can be expected, due to resonance stabilisation of the newly formed negative charge by the ester group. This will encourage addition to the 2-pyrone in the 6-position. However, if 2-pyrone regioisomer with the ester in the 4-position is employed, a competing interaction will occur as the ester substituent will now encourage addition to the opposite side of the ring. This explains why such differing results can be obtained by altering the pattern of functionality on the 2-pyrone ring.



Scheme 40 – Asynchronous Cycloadditions of Ester-Substituted 2-Pyrones

These studies have allowed us to propose some guidelines that may allow us to rationalise the regiochemistry of alkynylboronate/2-pyrone cycloadditions. It appears that resonance stabilisation of the asynchronous transition state is important in determining alkyne insertion patterns, both with respect to the diene and dienophile partners. Indeed, it is clear that there is little difference in the regioselectivity of the cycloaddition between 4-chloro-2-pyrone **12** and 5-chloro-2-pyrone **10**, and this may be due to the fact that the chloride group is not strongly electron withdrawing and hence the 2-pyrone ring is the dominant factor in determining the regiochemical outcome of the reaction.

While these studies have allowed us to develop a clearer picture of the first part of the cycloaddition reaction, when the 2-pyrone and alkynylboronate first combine, we are yet to develop a complete picture of the entire process. Currently, studies are underway in order to allow us to examine the second part of the cycloaddition, the retro Diels-Alder reaction, which leads to product formation.

1.4 Conclusions

In conclusion, we have found that higher yields for the reactions of 2-pyrones with alkynylboronates can be obtained when the silyl-substituted alkynylboronate is used in these cycloadditions. The highest regioselectivities can be obtained with the phenyl substituted dienophile, where typically only one regioisomer is formed.

It was also discovered that 2-pyrones that have electron withdrawing groups incorporated, such as the cyano-substituted substrates, provide cycloadducts in higher yields. Halogens were shown to be essentially electron neutral functional groups on 2-pyrone rings, as no enhancement or diminishment of either yields or regioselectivities were observed for these substrates.

Through theoretical studies on the cycloaddition transition states, we have discovered that 2-pyrone reactions with alkynylboronates proceed via asynchronous transition states. This accounts for the differences in regiochemical outcomes for phenyl and silyl substituted alkynylboronates, and also explains the previously reported poor regioselectivity for cycloadditions of 2-pyrones functionalized in the 4-position with a strongly electron withdrawing group.

1.5 Further Work

The yields and regioselectivities of the 2-pyrone cycloadditions with alkynylboronates appear to vary greatly depending on the electronic nature of both cycloaddition partners. From the results we have obtained, and from the conclusions we have made from theoretical studies, it would be expected that varying the alkynylboronate functionality should affect the cycloaddition outcome. For example, functionalizing the alkyne with a strongly electron withdrawing or donating group should drastically alter the cycloaddition regioselectivities.

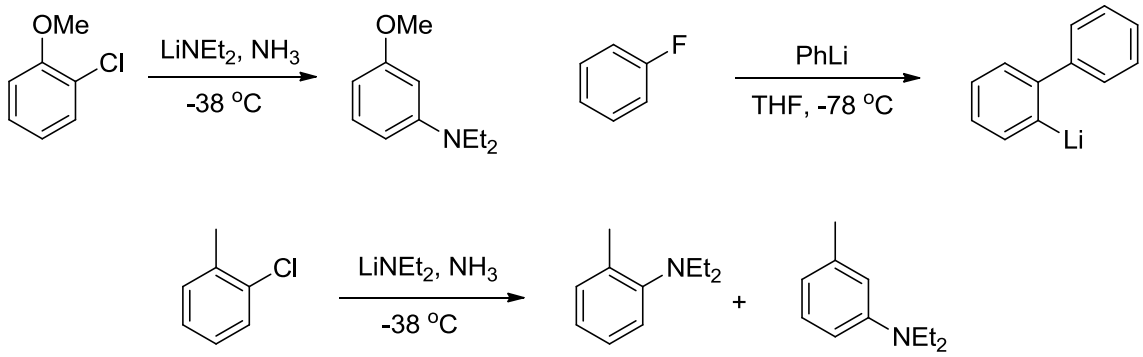
2-Pyrones clearly provide interesting results when utilized in [4+2] Diels-Alder reactions. Further work needs to be done in order to clarify whether these reactions generally proceed via synchronous or asynchronous transition states. A clearer picture on this issue could provide the opportunity to develop regioselective cycloadditions, using a range of usually non-selective dienophiles.

Chapter Two - 2-Pyrone Cycloadditions as a Route to Benzyne Precursors

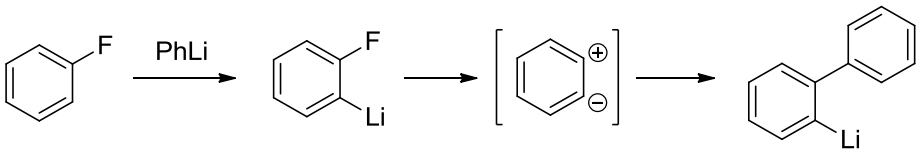
2.1 Introduction

2.1.1 Benzyne Precursors

Benzyne intermediates have been reported in the literature for over 60 years. During the 1940's and 1950's, numerous reports appeared demonstrating the unpredictable behaviour of halobenzenes with strongly basic reagents (Scheme 41).[58-60] In 1942, Wittig proposed an explanation for these observations, hypothesising the intermediacy of a zwitterionic intermediate generated by aryl deprotonation *ortho* to halogen (Scheme 42). However, this theory did not explain why reactions were not observed at other positions on the aromatic ring, as each proton should be similarly basic.



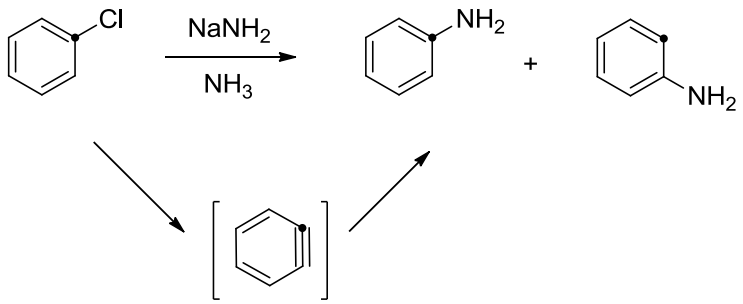
Scheme 41 – Amination of Halobenzenes Using Strongly Basic Reagents



Scheme 42 – Wittig's Proposed Theory of a Zwitterionic Intermediate

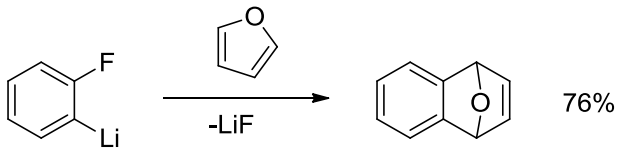
In 1953, Roberts performed an amination reaction using ^{14}C labelled chlorobenzene. Surprisingly, he discovered that a 1:1 ratio of regioisomers was produced, with the

^{14}C label incorporated into the carbon directly attached to nitrogen, and also *ortho* to the nitrogen (Scheme 43). From these results, Roberts proposed an addition-elimination mechanism involving *"at least transitory existence of an electrically neutral "**benzyne**" intermediate"*.[60]



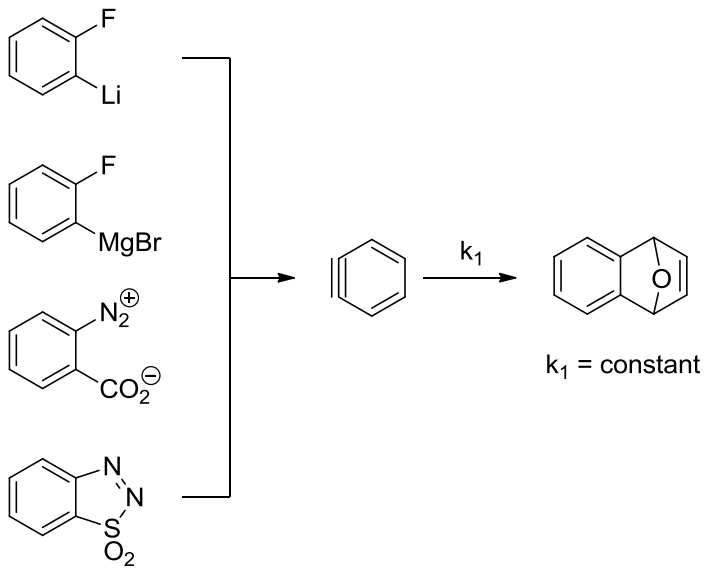
Scheme 43 – Roberts' Amination of Labelled Chlorobenzene

Only two years after Roberts proposed the idea of benzyne intermediates, Wittig discovered that benzynes can be used in Diels-Alder cycloadditions, as dienophiles. By forming a benzyne intermediate *in situ*, cycloaddition was achieved using furan as the diene partner (Scheme 44).[61]



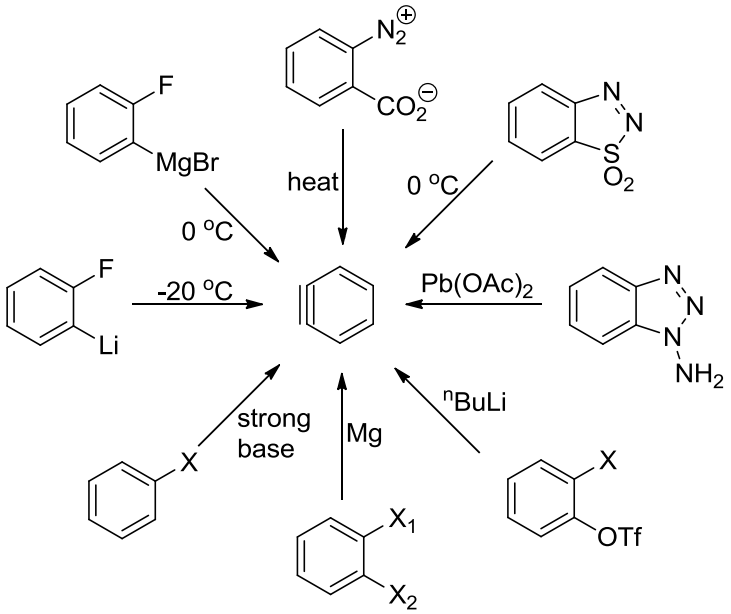
Scheme 44 – Diels-Alder Cycloaddition of Benzyne

Further to these discoveries, Huisgen then found that arynes can be generated from a variety of precursors, with each precursor providing identical reactivities in cycloaddition reactions (Scheme 45).[62]



Scheme 45 – Cycloaddition of Various Benzyne Precursors

Since Huisgen's report on alternative benzyne precursors, numerous other substrates have been found to perform as benzyne precursors. Each of the compounds outlined in Scheme 46 below provide benzynes *in situ* with similar reactivities.[63-66]



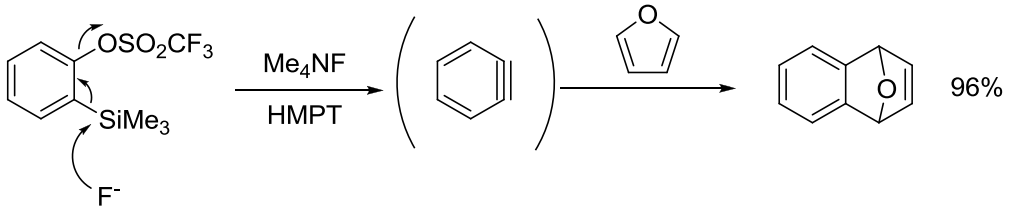
Scheme 46 – Alternative Benzyne Precursors

Whilst each of the above aryne precursors provide benzyne intermediates, and their subsequent products, in good yields and with good reproducibility, there are issues

associated with each method. For example, formation of benzynes from halobenzenes requires strongly basic organometallic reagents, which are incompatible with a number of functional groups. Also, the diazo-carboxylate species requires heating for benzyne formation, which raises safety issues on larger scale, due to the explosive nature of diazo compounds. These limitations provided the impetus for the development of a milder method of benzyne formation.

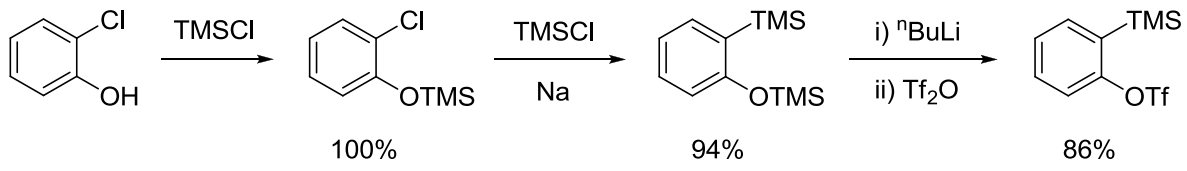
2.1.2 Synthesis of *Ortho*-Silyl Aryl Sulfonylates

In 1983, Kobayashi reported the first mild, in situ generation of benzynes. His method involved the novel use of an *o*-trimethylsilyl phenyl triflate, alongside a fluoride source. The utility of the benzyne precursors was demonstrated by trapping with furans, allowing for product formation in high yields at room temperature using various fluoride sources (Scheme 47).[67]



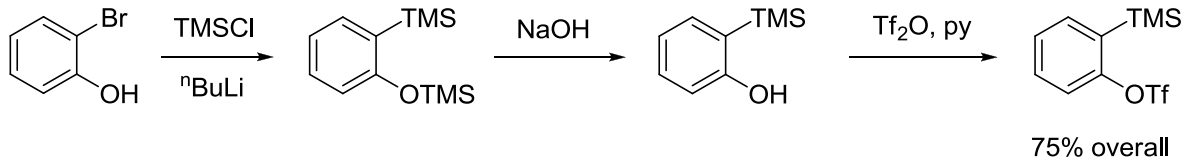
Scheme 47 - Kobayashi's Mild Method for Benzyne Formation

The initial synthesis of *o*-trimethylsilyl phenyl triflate, proposed by Kobayashi, involves a four step synthetic route (Scheme 48). This proceeds in good yields, however the overall reaction time is significant (80 h), and the synthesis requires use of a number of reagents which may be incompatible with functionalised derivatives (sodium, *n*-butyllithium).[67]

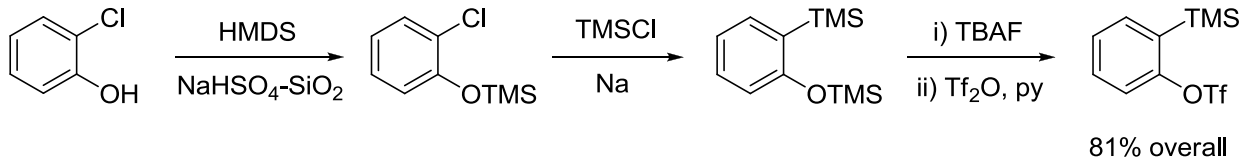


Scheme 48 - Kobayashi's Synthesis of *o*-Trimethylsilyl Phenyl Triflate

In recent years, a number of alternative routes have been proposed. It was reported in 2007 that the key *o*-silyl-phenol silyl ether can be prepared in good yield in one step from 2-bromophenol (Scheme 49), however again this route requires the use of *n*-butyllithium, providing the potential for incompatibility issues.[68] More recently, Brimble proposed a synthesis of the benzyne precursor in far shorter reaction times; however the same compatibility issues remain (Scheme 50).[69]



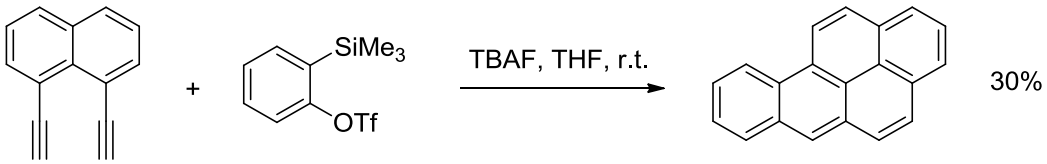
Scheme 49 - Chen's Synthesis of *o*-Trimethylsilyl Phenyl Triflate



Scheme 50 - Brimble's Synthesis of *o*-Trimethylsilyl Phenyl Triflate

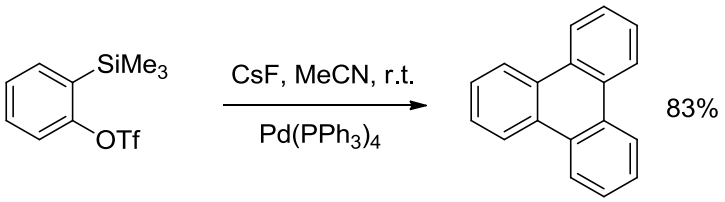
2.1.3 *Ortho*-Silyl Aryl Sulfonylates as Benzyne Precursors

Despite the mild conditions required for the formation of benzynes from *o*-trimethylsilyl phenyl triflates, it was not until 1997 that the first examples of their use became widely reported. Guitian demonstrated the synthesis of benzopyrene, via reaction of benzyne with 1,8-diethynylnaphthalene (Scheme 51).[70] The reaction occurs via a dehydro Diels-Alder reaction (DDAR) between *in situ* formed benzyne and one enyne fragment, followed by a radical Myers cyclisation between the intermediate strained allene formed, and the second enyne. Either intermolecular hydrogen abstraction or intramolecular hydrogen migration affords the final product.



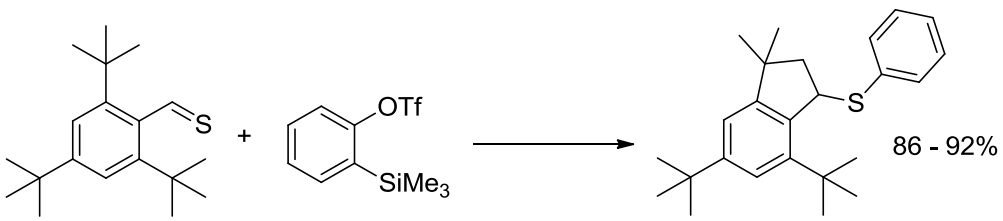
Scheme 51 - Benzyne Mediated Synthesis of Benzopyrene

Later work by Guitian has shown that *o*-trimethylsilyl phenyl triflates can be readily used in palladium catalysed cyclotrimerisation reactions, allowing for the mild synthesis of triphenylenes (Scheme 52).[71]



Scheme 52 - Palladium Catalysed Cyclotrimerisation of Benzynes

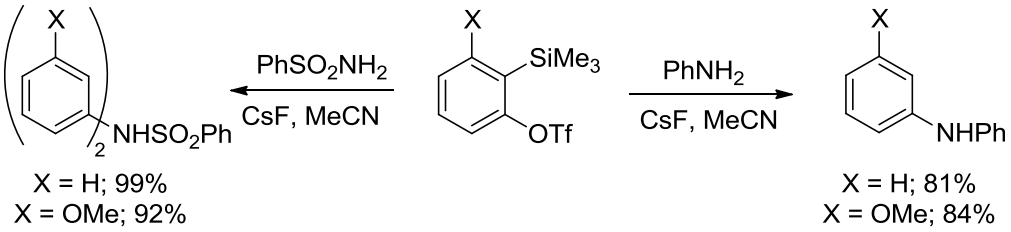
Okuma observed that on reaction of benzynes with thioaldehydes, the expected [2+2] product does not form. Instead benzyne adds to the thioaldehyde, producing a diradical, which then appears to undergo hydrogen atom abstraction, finally followed by internal combination to produce the products shown in Scheme 53.[72]



Scheme 53 - Unexpected Reaction of Benzynes with Thioaldehydes

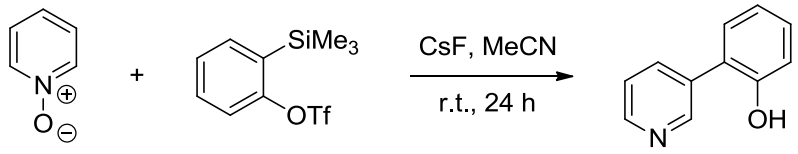
Over the past decade, Larock has reported numerous examples where *ortho*-silyl aryl sulfonylates have been utilised to form useful compounds under mild conditions, via *in situ* generated benzynes. His first published example demonstrated the facile *N*-arylation of amines and sulphonamides.[73] By reacting benzyne formed in situ from *ortho*-silyl phenyl sulfonylate with a variety of amines and sulphonamides, *N*-

arylation can be achieved under mild conditions, and without the need for metal catalysts. Interestingly, when a non-symmetrical methoxy-substituted benzyne is used, reactions proceed with high regioselectivity. The amine attacks the least sterically hindered and more electrophilic position which is *meta*- to the methoxy group (Scheme 54).



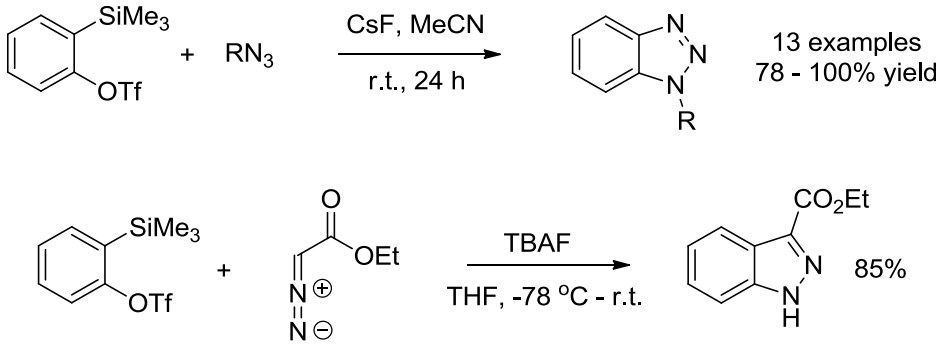
Scheme 54 - Mild Method for *N*-Arylation of Amines and Sulphonamides

Larock has also demonstrated the ability for benzynes to take part in [3+2] cycloadditions, utilising 1,3-dipoles. For example, the synthesis of 3-(2-hydroxyaryl)pyridines can be achieved by reacting *ortho*-silyl phenyl sulfonylates with caesium fluoride and pyridine *N*-oxides (Scheme 55).[74] Previous studies towards this reaction showed that classical methods of benzyne formation provided mixtures of regioisomers, due to the harsh conditions required. The mild conditions utilised by Larock allowed for a regioselective synthesis, which proceeds via a [3+2] cycloaddition reaction, followed by rearrangement to the desired products.



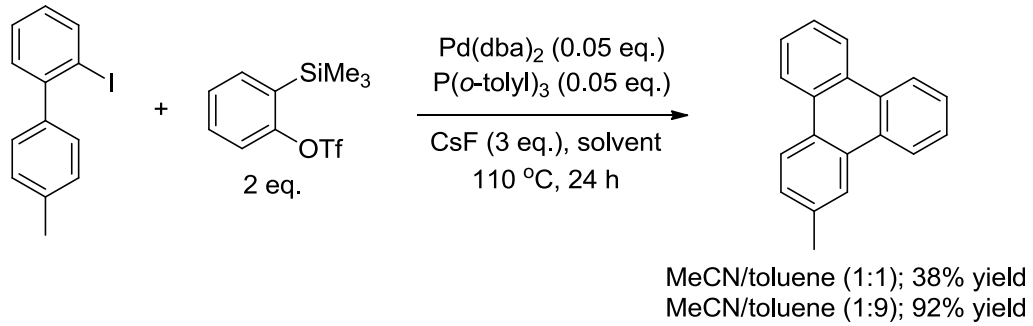
Scheme 55 - Regioselective [3+2] Cycloaddition of Benzynes with Pyridine *N*-Oxides

In an extension of this method, benzotriazoles and indazoles are formed via the reaction of benzynes with either azido or diazo compounds.[75,76] This has allowed for the synthesis of a wide range of these valuable heterocycles in moderate to excellent yields (Scheme 56). In the case of indazoles, the reactions needed to be performed at low temperatures, using TBAF in THF, in order to avoid the formation of *N*-arylated by-products.



Scheme 56 - [3+2] Cycloaddition Routes to Benzotriazoles and Indazoles

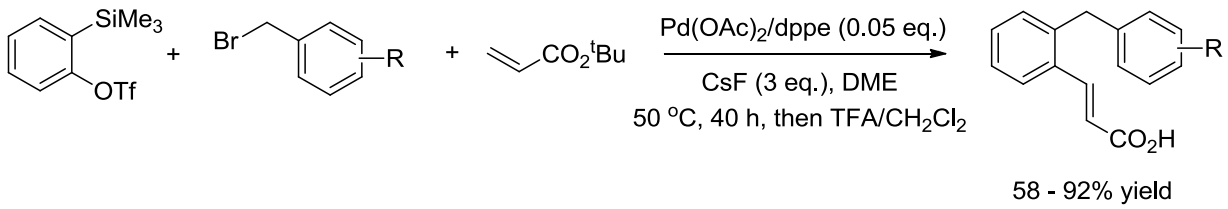
As described previously, benzynes can readily undergo cyclotrimerisation under palladium catalysis. Therefore, it might be expected that the Pd-catalyzed annulation of arynes by aromatic and vinylic halides would be difficult, due to competing cyclotrimerisation. However, Larock has demonstrated that this reaction can be performed efficiently using *ortho*-silyl phenyl sulfonylates (Scheme 57).[77] Again, the mild conditions employed are key to the success of this reaction, as the generation of benzyne can be carefully controlled by altering reaction conditions, in this case by simply using a solvent system of acetonitrile/toluene (1:9). The solvent effect seen here is due to the poor solubility of caesium fluoride in organic solvents, which is why acetonitrile is usually used. By increasing the amount of toluene, the amount of caesium fluoride in solution is reduced, allowing for slow benzyne generation, reducing the amount of side products obtained.



Scheme 57 - Palladium Catalysed Annulation of Arynes

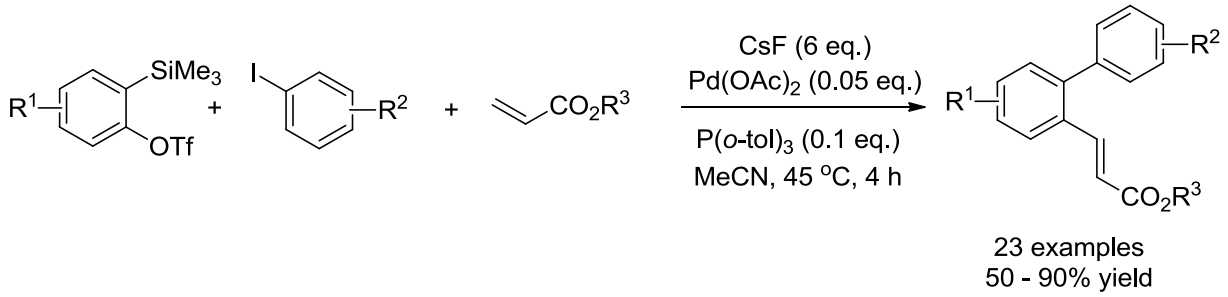
Similarly, Greaney has extended this chemistry by demonstrating a three component palladium catalysed coupling reaction (Scheme 59).[78] This allows for a domino

intramolecular carbopalladation reaction between *in situ* formed benzynes, acrylates and benzyl halides. In order to reduce the amount of side products formed, the formation of benzyne was slowed by using dimethoxyethane, a solvent in which caesium fluoride is only partial soluble.



Scheme 58 – A Domino Intramolecular Carbopalladation using Benzynes

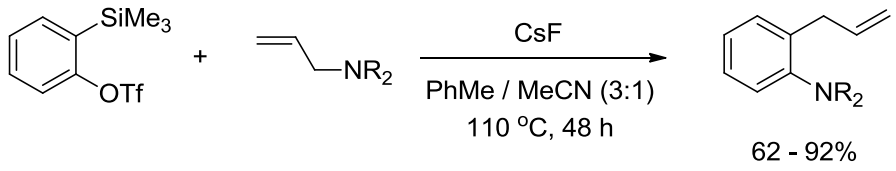
Greaney has also shown that this methodology can be extended to aryl halides, allowing for a three component Heck coupling of benzynes (Scheme 59).[79] In order to avoid the competing direct Heck reaction between aryl iodide and acrylate components, the reaction stoichiometry proved to be crucial to reaction success. Optimal yields were obtained using 2 eq. benzyne precursor, 1 eq. acrylate and 1.5 eq. aryl iodide.



Scheme 59 - Three Component Coupling of Benzynes, Aryl Iodides and Acrylates

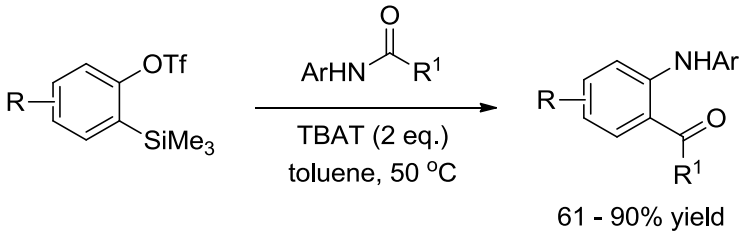
Greaney has also demonstrated that *in situ* formed benzyne can be used in sigmatropic rearrangements, such as the aza-Claisen reaction.[80] The benzyne aza-Claisen reaction, between benzynes formed *in situ* from *ortho*-silyl aryl sulfonylates, and tertiary allyl amines, allows for formation of aniline products in high yields,

without the need for a metal catalyst or stoichiometric amounts of Lewis acid (Scheme 60).



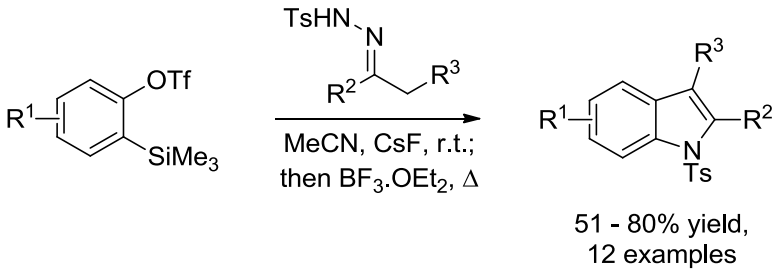
Scheme 60 - The Benzyne Aza-Claisen Reaction

Insertions into amide bonds can also be achieved using benzynes.[81] Greaney has shown recently that this can be done using benzynes formed *in situ* from *ortho*-silyl aryl sulfonylates (Scheme 61). A variety of substrates were used, however in all cases the amide needed to be *N*-arylated.



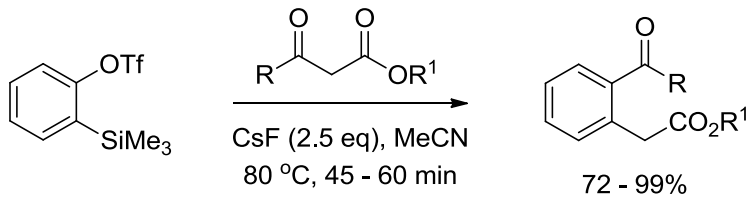
Scheme 61 – Benzene Insertion into the Amide Bond

Greaney has recently developed the benzyne Fischer-Indole reaction, affording a variety of indoles in high yields.[82] The reaction proceeds via initial arylation of hydrazones containing an electron withdrawing group, followed by Fischer cyclisation promoted by raising reaction temperature and adding $BF_3.OEt_2$ (Scheme 62).



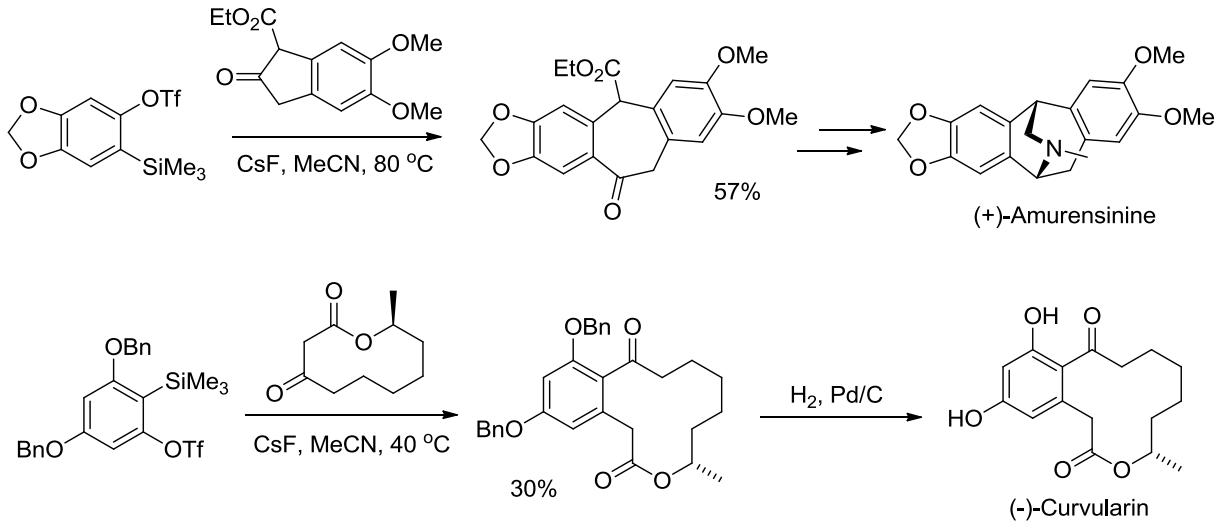
Scheme 62 – The Benzyne Fischer-Indole Reaction

Stoltz has also documented a number of useful reactions utilising benzynes. In 2005, he reported that the direct acyl-alkylation of benzynes can be achieved by reacting *in situ* formed benzynes with β-ketoesters (Scheme 63).[83] This demonstrated the first example of mild aryne insertion into a carbon-carbon bond.



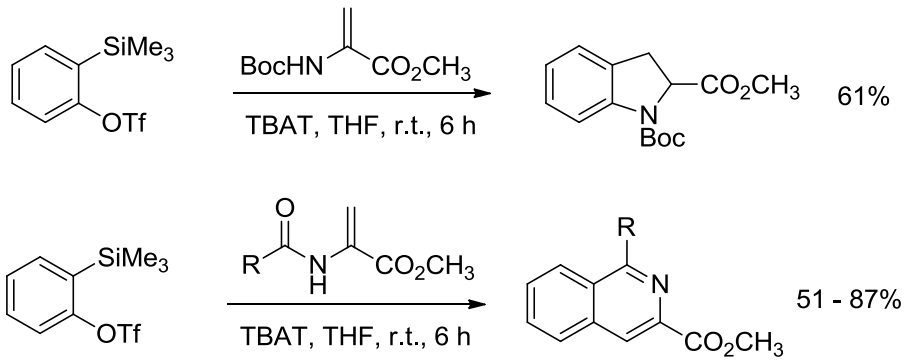
Scheme 63 – Direct Acyl-Alkylation of Benzynes

The direct acyl-alkylation of benzynes has since been shown by Stoltz to be a powerful tool in organic synthesis. He has recently used this technique in the enantioselective syntheses of both (+)-amurensinine and (-)-curvularin, demonstrating the utility of this reaction in forming complex natural products (Scheme 64).[84,85]



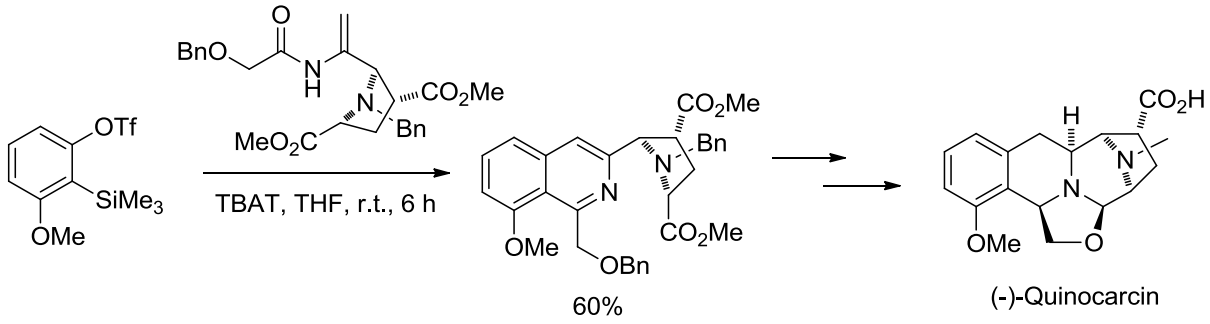
Scheme 64 – Enantioselective Synthesis of (+)-Amurensinine and (-)-Curvularin

Stoltz has also shown that benzynes can be used for the synthesis of indolines and isoquinolines.[86] By utilising either enecarbamates or enamides, products can be formed in high yields under mild conditions (Scheme 65).



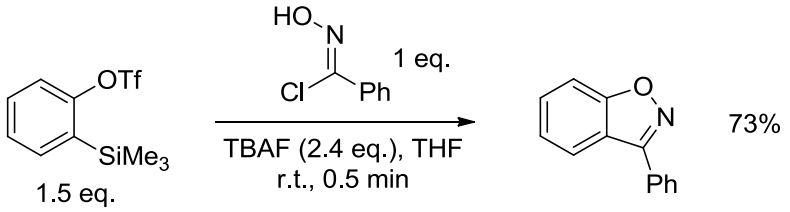
Scheme 65 – Synthesis of Indolines and Isoquinolines from Benzynes

Utilising this technique, Stoltz has subsequently demonstrated the concise asymmetric total synthesis of (-)-quinocarcin (Scheme 66).[87]

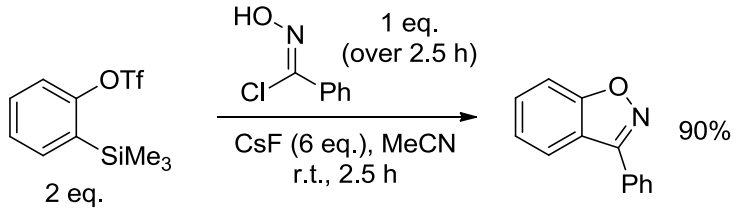


Scheme 66 – Total Synthesis of (-)-Quinocarcin

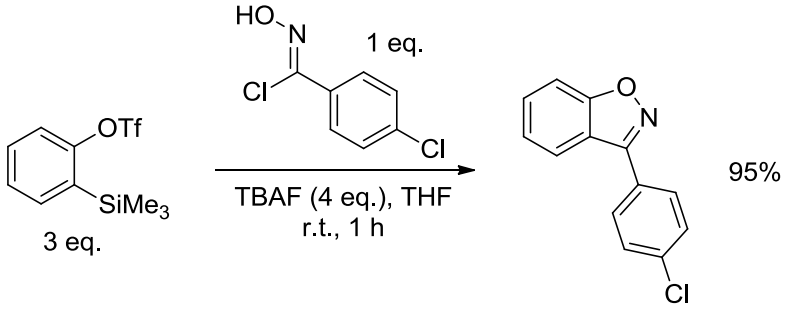
Benzynes formed *in situ* can also be used in cycloadditions with nitrile oxides, for the synthesis of benzisoxazoles. In 2010, Moses, Larock and Browne independently reported that this reaction proceeds smoothly using *ortho*-silyl aryl triflates as the benzyne precursor, with nitrile oxides formed *in situ* from chloro-oximes.[88-90] The fluoride source used to form the benzyne precursor also acts as a base to form the required nitrile oxides. Moses and Browne reported that using TBAF in THF at room temperature, products form in excellent yields in less than one hour (Scheme 67 and Scheme 69). Larock reported that caesium fluoride can also be used to initiate the reaction, although slow addition of the chloro-oxime was required in this case (Scheme 68).



Scheme 67 – Moses' Conditions for Benisoxazole Formation



Scheme 68 – Larock's Conditions for Benzisoxazole Formation



Scheme 69 – Browne's Conditions for Benzisoxazole Formation

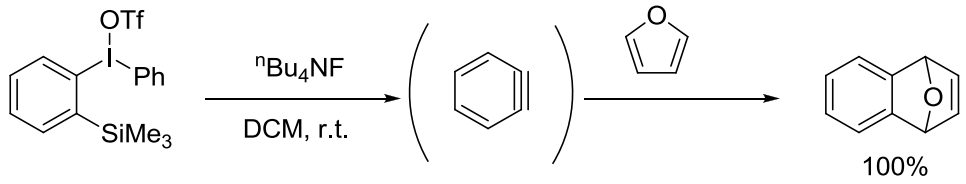
Despite the large variety of chemistry that has been developed using *ortho*-silyl aryl sulfonylates, the scope of substrates that can be employed is rather limited. As can be seen in the majority of examples previously described, non-symmetrical benzyne precursors are seldom used, mainly due to the poor regioselectivities obtained. Only benzynes that contain groups providing a large electronic or steric bias, such as the previously described examples utilising the *ortho*-methoxy group, provide products with good selectivity.

Substrate scope is also limited by functional group incompatibilities during the synthesis of precursors, as described previously. As such, functional groups which are sensitive to organolithium reagents, such as esters, nitriles and halides are

difficult to incorporate into *ortho*-silyl aryl sulfonylates. Therefore, milder methods for their synthesis are required.

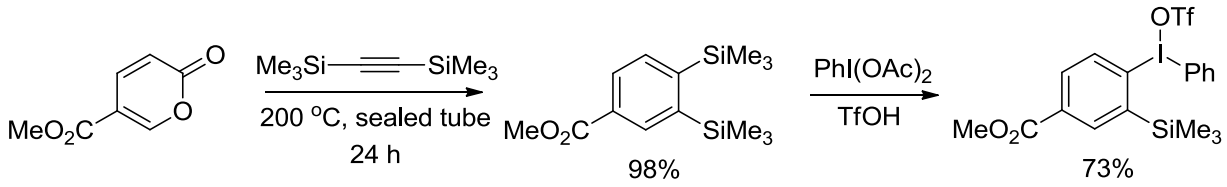
2.1.4 Alternatives to *Ortho*-Silyl Aryl Sulfonylates for Benzyne Precursors

An alternative precursor to benzyne intermediates was proposed by Kitamura.[91] It was found that treatment of phenyl[2-(trimethylsilyl)phenyl]iodonium triflate with a fluoride source allows for the in situ formation of benzynes, in much the same way as for *ortho*-silyl aryl sulfonylates (Scheme 70).



Scheme 70 - Hypervalent Iodine Species as Benzyne Precursors

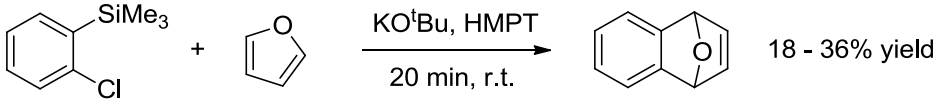
Kitamura then expanded on this concept by demonstrating an efficient formation of the required hypervalent iodine species, utilising 2-pyrone cycloadditions (Scheme 71).[92] This method has allowed for the incorporation of an ester group into the benzyne precursor, which would currently be unachievable using classical methods for benzyne formation.



Scheme 71 - A 2-Pyrone Cycloaddition Route to a Phenyl[2-(trimethylsilyl)phenyl]iodonium triflate

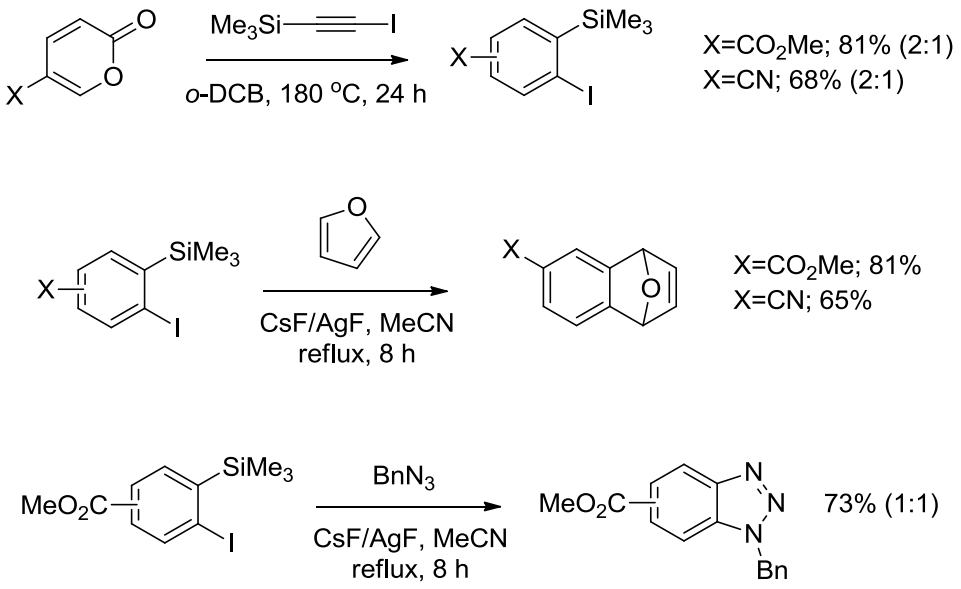
Previous reports have also suggested that *o*-trimethylsilylhalobenzenes could be used as alternative benzyne precursors. Cunico discovered in 1973 that treatment of 2-(chloro)trimethylsilylbenzene with potassium *t*-butoxide, then trapping of the formed

benzyne with furan, affords product in variable yields, depending on order of reactant addition.[93] Similar results were also obtained using bromo- and iodo-substrates (Scheme 72). Despite the mild conditions required for this method of benzyne formation, the low and variable yields of desired benzyne adducts has meant that this chemistry has not been thoroughly explored since.



Scheme 72 - *o*-Trimethylsilylhalobenzenes as Benzyne Precursors

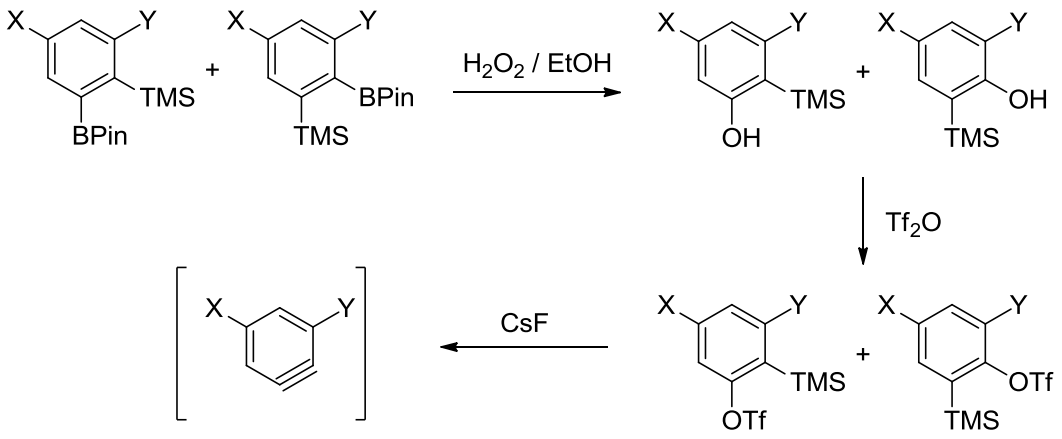
Recent work in the Harrity group has demonstrated that this method for benzyne formation can be improved using mild fluoride sources.[94] As shown in Scheme 73, 2-(iodo)trimethylsilylbenzenes can be formed in high yields via the cycloaddition of functionalised 2-pyrones with trimethylsilyl iodoacetylene. The cycloadducts obtained are then treated with caesium fluoride and silver fluoride in order to form benzynes *in situ*. Subsequent trapping experiments were performed using furans, benzylazide and cyclones, each affording products in excellent yields.



Scheme 73 – Synthesis and Subsequent Benzyne Formation of *o*-Trimethylsilyliodobenzenes

2.2 Aims

Having demonstrated the utility of 2-pyrone cycloadditions for the formation of aromatic boronic esters, attention was then turned to the further functionalisation of the cycloadducts. It was clear that the aromatic products formed using aryl alkynylboronates would provide a useful route to regiodefined multi-aryl motifs, via coupling reactions. However, it was decided that the silyl-substituted products could provide us with a more interesting opportunity for further functionalisation. It is known that aromatic boronic esters can be readily transformed into phenols via simple oxidation using hydrogen peroxide.[95] By sulfonylation of the *o*-silyl phenols formed from this oxidation, it was thought that the widely used benzyne precursors, *o*-silylaryl triflates, could be formed (Scheme 74). This would provide us with a novel method for allowing both regioisomers to converge to a single intermediate; as the benzyne formed after fluoride initiated elimination would be identical in each case.

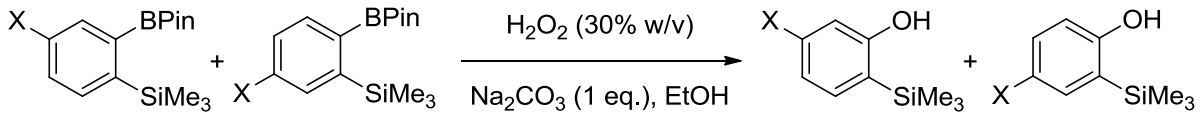


Scheme 74 - 2-Pyrone Cycloadditions as a Route to Benzyne Precursors

2.3 Results and Discussion

2.3.1 Synthesis of Benzyne Precursors

Having obtained a variety of benzene boronic ester substrates via 2-pyrone cycloadditions, attention was turned to the oxidation of these substrates to the corresponding *ortho*-silyl phenols. This was done using conditions previously developed in the Harrity group.[95] Pleasingly, each of the previously synthesised aromatic boronic esters underwent smooth oxidation to provide the desired phenols within 4 h at room temperature, with no detected loss of the *ortho*-trimethylsilyl group (Table 11). The compounds shown below were isolated as a mixture of the two possible regioisomers. In cases where the ratio of regioisomers was not 1:1, the identity of the major regioisomer was not confirmed, except for compounds **33a** and **33b**. In this case **33a** was confirmed as the major regioisomer, via desilylation to the corresponding *para*- and *meta*-chloro-phenol substrates (Appendix, page 149). Purification of each of these compounds was pleasingly simple, with only a short filtration through a silica plug required in order to remove pinacol related by-products.



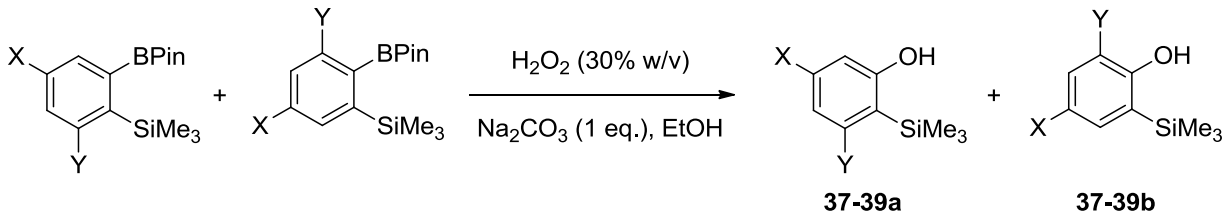
33-36a **33-36b**

X	Products	Yield / %	Ratio **a**:**b**
Cl	**33a,b**	75	5:3
Br	**34a,b**	75	3:2[a]
CN	**35a,b**	71	1:1
CO_2Me	**36a,b**	70	3:2[a]

[a]Identity of the major regioisomer not confirmed

Table 11 – Oxidation of Benzene Boronic Esters

Using these conditions, we were pleased to find that more functionalised aromatic boronic esters can also be smoothly oxidized to the corresponding *ortho*-silyl phenols. In fact, these substrates underwent oxidation in higher yields, with greater than 80% of the desired products obtained in each case (Table 12).



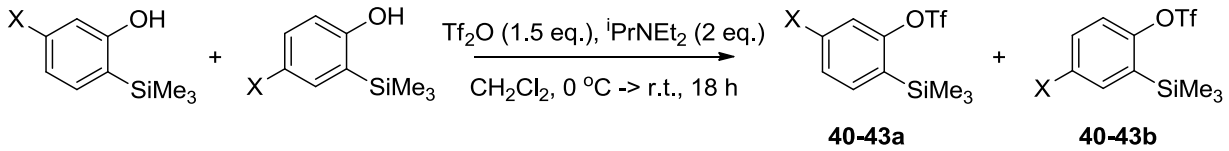
37-39a **37-39b**

X	Y	Products	Yield / %	Ratio **a**:**b**
Cl	Cl	**37a,b**	95	1:1
CN	Br	**38a,b**	84	3:2[a]
CO_2Me	Br	**39a,b**	81	3:2[a]

[a]Identity of the major regioisomer not confirmed

Table 12 – Oxidation of Tetrasubstituted Benzene Boronic Esters

With the required phenol products in hand, attention was turned to optimizing the sulfonylation reactions. After trying various conditions it was discovered that Danishefsky's method for the sulfonylation of *ortho*-silyl phenols to *ortho*-silylaryl triflates was the most effective.[96] This involved dissolving the substrate in dichloromethane at 0 ^{o}C under nitrogen, before adding 2 eq. of Hünig's base, followed by dropwise addition of 1.5 eq. of freshly distilled trifluoromethanesulfonic anhydride. It was found that the reaction also occurs if triethylamine is used as base; however purification of the products proved to be easier when Hünig's base was employed. It was also found that the reaction will occur if the trifluoromethanesulfonic anhydride used is not first distilled, although lower yields were obtained in such cases. Using these conditions the previously obtained *ortho*-silyl phenols shown in Table 13 below were sulfonylated in almost quantitative yield.



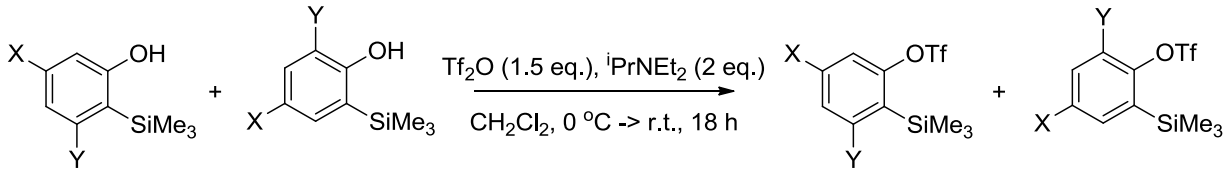
40-43a **40-43b**

X	Products	Yield / %	Ratio **a**:**b**
Cl	**40a,b**	94	5:3
Br	**41a,b**	100	3:2[a]
CN	**42a,b**	100	1:1
CO_2Me	**43a,b**	98	3:2[a]

[a]Identity of the major regioisomer not confirmed

Table 13 – Sulfonylation of *ortho*-Silyl Phenols

The sulfonylation of the phenol substrates containing *ortho*-functionalisation was also found to be successful using these conditions. However, this proved to be less efficient than when the less sterically hindered phenols were used, with slightly lower yields of benzyne precursors obtained (Table 14).



44-46a **44-46b**

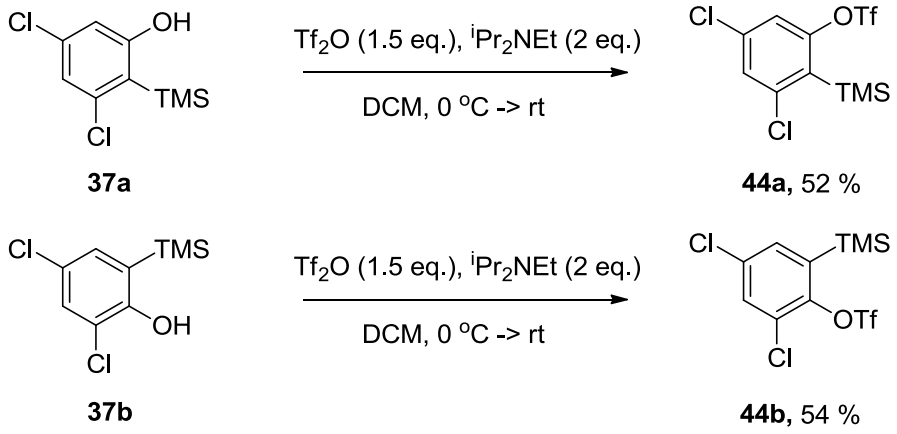
X	Y	Products	Yield / %	Ratio **a**:**b**
Cl	Cl	**44a,b**	53	1:1
CN	Br	**45a,b**	60	1:1
CO_2Me	Br	**46a,b**	76	3:2[a]

[a]Identity of the major regioisomer not confirmed

Table 14 – Sulfonylation of Tetrasubstituted Phenols

From these experiments, it is clear that the reaction is more efficient when the 1,2,4-trisubstituted *ortho*-silyl phenols are used, with almost quantitative yields

being obtained in each case. In principle, the reduced yields observed in the case of the tetrasubstituted aromatics could be due to steric hindrance from the *ortho*-halo substituent slowing down the sulfonylation of one of the two regioisomers. In order to examine this, the two isomers of the dichloro *ortho*-silyl phenol **37a,b** were separated by column chromatography, then each subjected to the sulfonylation reaction conditions. In the event, little difference in efficiency was detected, suggesting that the *ortho*-chloro substituent on phenol **37a,b** is not responsible for the retardation of this particular reaction (Scheme 75).

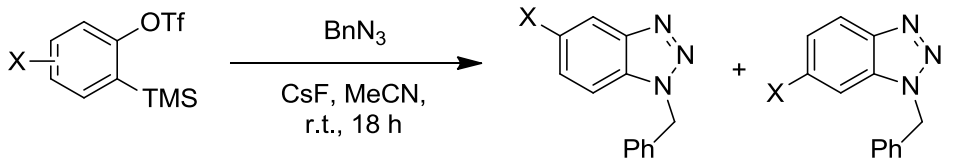


Scheme 75 - Sulfonylation of Separated Regioisomeric Aromatic Boronic Esters

2.3.2 – Benzyne Trapping Experiments

To demonstrate the utility of these compounds for further functionalisations, a selection of the *ortho*-silyl aryltriflates were taken forward to some representative benzyne trapping reactions. In this context, benzyl azide has been employed as partner for benzyne click reactions, as reported by Larock and co-workers.[75] In applying this technique to our more functionalized analogues, we were pleased to find that each of the benzyne precursors examined reacted cleanly to give good yields of the required benzotriazole products (Table 15). Unfortunately, in each case little or no regioselectivity was observed. The benzyne precursors used in these reactions contained a mixture of regioisomers in each case, with the ratio of each shown in parentheses. Studies were not performed using different ratios of these regioisomers, therefore it is unclear at this time as to whether the different isomers provide different reactivities. Although there are no examples of benzyne precursors similar to the substrates

shown below, Larock has shown that dihalo-substituted benzynes undergo benzotriazole formation with efficiency comparable to our examples (56% yield).[75]



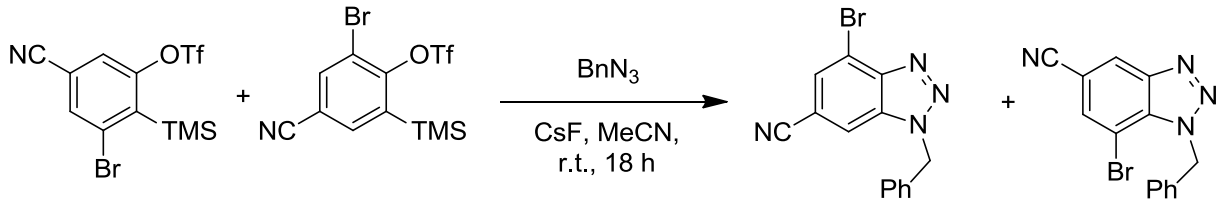
47-49a **47-49b**

X	Products	Yield / %	Ratio **a**:**b**
CN (1:1)	**47a,b**	65	2:1[a]
CO_2Me (3:2)	**48a,b**	67	1:1
Br (3:2)	**49a,b**	70	2:1[a]

[a]Identity of the major regioisomer not confirmed

Table 15 – Benzotriazole Formation Using Benzynes

It was hoped that by using a benzyne precursor containing an *ortho*-bromo substituent, a more regioselective reaction would occur, due to the possibility of a steric clash between the *ortho*-bromide and the benzyl group of the reacting azide. This was indeed shown to be the case, as compound **45a,b** provided the desired benzotriazoles **50a,b** in 4:1 ratio (Scheme 76). Unfortunately, this reaction was found to be disappointingly sluggish, with only a 30% yield of product obtained.



50a **50b**

30%, 4:1

Scheme 76 - Benzotriazole Formation Using *ortho*-Bromo Substituted Benzynes

The major regioisomers shown above were confirmed by performing nOe studies on **50a,b**. On irradiation of the major benzyl peak in the ^1H NMR spectrum, a nOe enhancement was observed with one of the aromatic protons, suggesting that they are in close proximity. On irradiation of the minor benzyl peak, no such

enhancement was observed (Figure 13). Therefore, our assumption that the regioselectivity of the reaction is controlled by steric effects appears to be true, as the major regioisomer obtained is the compound with the benzyl group positioned away from the *ortho*-bromo substituent.

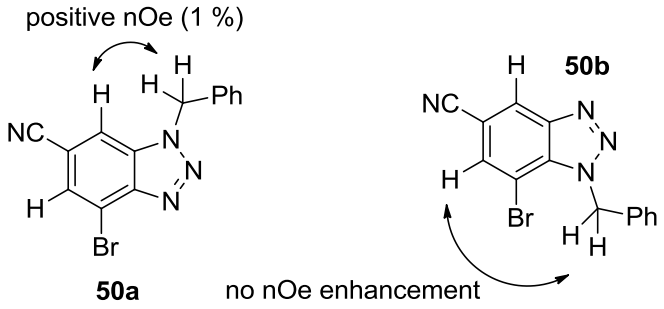
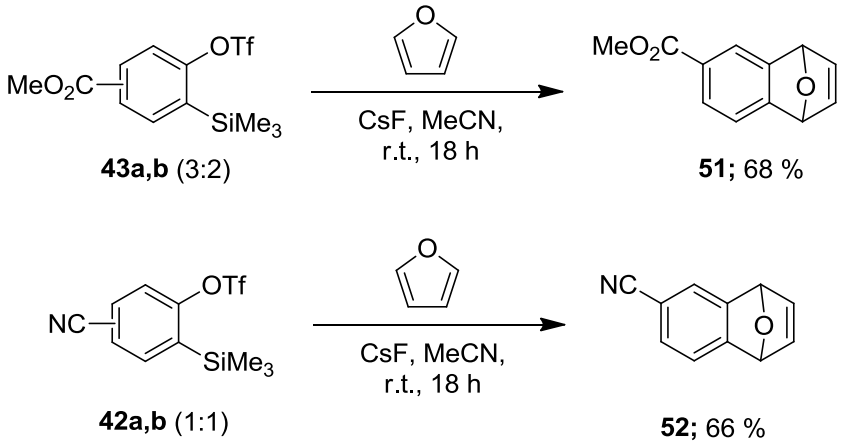


Figure 13 - nOe Experiment for Determination of Regioisomers

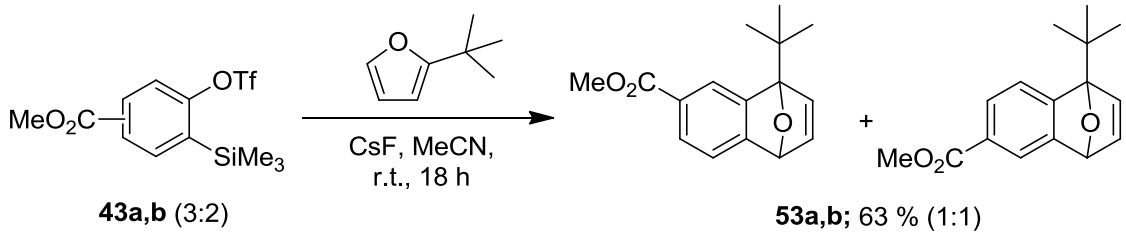
To further the functionalisation of benzyne precursors, compounds **42** and **43** were reacted in [4+2] cycloadditions with furans. When the symmetrical parent furan was used alongside precursors **42** and **43**, a single product was cleanly formed in good yields (Scheme 77). Therefore, from the mixture of regioisomers obtained from alkynylboronate cycloadditions, in three steps we have been able to form a single product in high overall yield.



Scheme 77 – Reaction of Benzynes with Symmetrical Furans

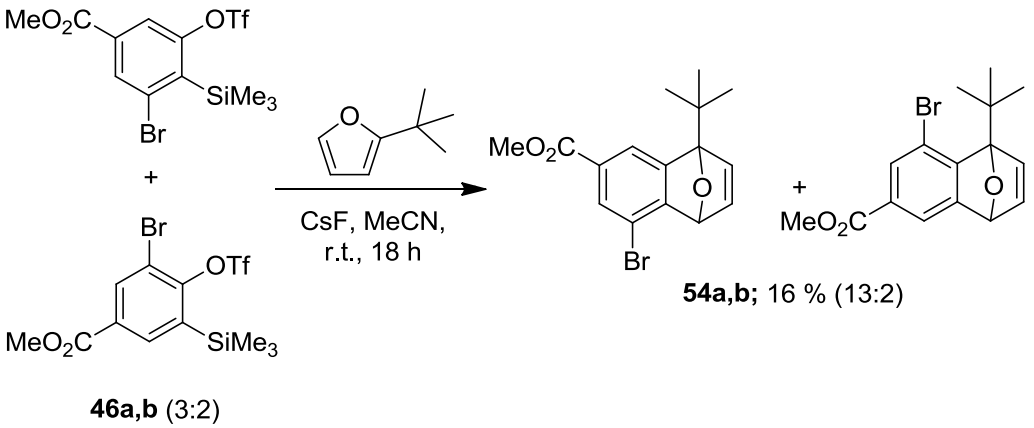
In order to demonstrate [4+2] cycloadditions of the *in situ* formed benzynes with a non-symmetrical diene, the ester substituted precursor was reacted with *tert*-

butyl-substituted furan. Pleasingly, this cycloaddition also proceeded smoothly, with a high yield obtained of the desired cycloadduct (Scheme 78). However, disappointingly this reaction produced a mixture of regioisomers, with the products forming in a 1:1 ratio.



Scheme 78 - Reaction of Benzyne with a Non-Symmetrical Furan

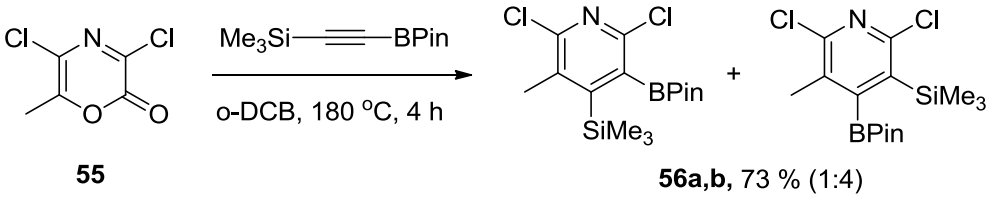
In order to again attempt to affect a more regioselective cycloaddition, the *ortho*-bromo substituted precursor was used alongside *tert*-butyl furan. As with the previously described click chemistry using benzyl azides, modest regioselectivities were obtained, but the reaction proceeded in poor yield. The identity of the major regioisomer was not confirmed; however we assumed that steric interactions between the *ortho*-bromo and *tert*-butyl substituents would lead to preferential formation of regioisomer **54a**, as shown in Scheme 79 below.



Scheme 79 – Cycloaddition of Bromo-Substituted Benzyne Precursor with a Non-Symmetrical Furan

2.33 – Synthesis of a Pyridyne Precursor

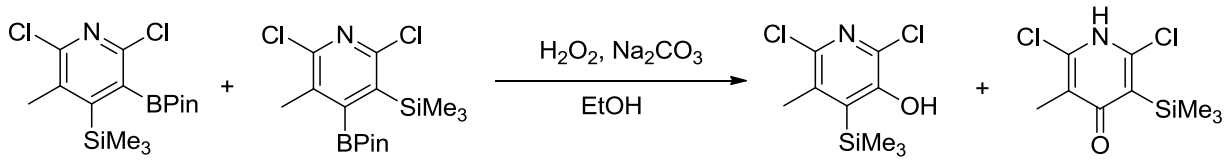
Having established the utility of 2-pyrones as precursors to benzyne substrates, attention was turned to the possibility of using oxazinones as precursors to pyridyne substrates. Previous work in our group has shown that oxazinones can be smoothly converted to pyridine boronic esters, via cycloaddition with alkynylboronates.[97] This was repeated successfully, affording the regioisomeric *ortho*-silyl cycloadducts **56a,b** in good yield (Scheme 80).



55 **56a,b,** 73 % (1:4)

Scheme 80 – An Oxazinone Cycloaddition with an Alkynylboronate

It is also known that these products can then be readily oxidized to form compounds **57a** and **57b** (Scheme 81). This was also found to be successful, using the conditions previously reported for the oxidation of benzene boronic esters. Interestingly, it was found that oxidation of boronic ester **56b** does not form the expected 4-hydroxy-pyridine, but instead forms the corresponding 4-pyridone.

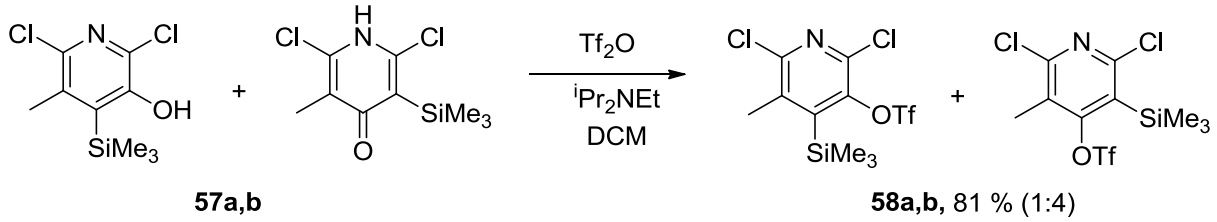


56a,b **57a,b,** 86 % (1:4)

Scheme 81 – Oxidation of Pyridine Boronic Esters

It was hoped that these products would undergo sulfonylation, using the same conditions shown previously, in order to form *ortho*-silyl pyridyltriflates. Pleasingly, the established sulfonylation conditions did prove successful for the formation of both **58a** and **58b**, affording the desired pyridyne precursors in excellent yield (Scheme 82). Overall, the synthetic sequence was found to be simple and high yielding, with no chromatography of the intermediates required.

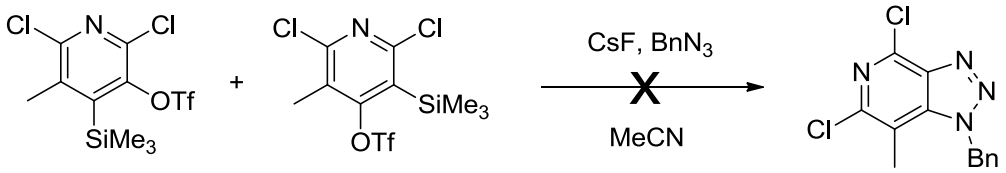
The overall yield of pyridine precursor was 51% over three steps from the starting oxazinone.



57a,b **58a,b,** 81 % (1:4)

Scheme 82 – Formation of a Pyridyne Precursor

Having obtained the desired potential pyridyne precursors, we attempted to use these in benzyne trapping experiments. Unfortunately these proved unsuccessful, with complex mixtures obtained in each case (Scheme 83).



60a,b

Scheme 83 – Attempted Pyridyne Trapping Experiment

2.4 Conclusions

2-Pyrone cycloadditions have been shown to be a viable route for the formation of the benzyne precursors, *ortho*-silylaryltriflates. Oxidation of the aromatic boronic ester products formed from 2-pyrone – alkynylboronate cycloadditions proceeds smoothly under standard conditions, with high yields of the desired *ortho*-silylphenols obtained.

The oxidised products undergo sulfonylation smoothly under mild conditions, allowing for the formation of *ortho*-silylaryltriflates. This has allowed for development of a mild route for the formation of these synthetically useful intermediates. The substrates formed contain functional groups that could not previously have been incorporated into benzyne precursors, such as esters and nitriles.

Subsequent benzyne trapping experiments have demonstrated the utility of these substrates, with good yields obtained for products from reaction of the *in situ* formed benzyne with both benzyl azide and furans. Low regioselectivities were observed when the reaction partner was unsymmetrical, however better regioselectivities can be seen when the benzyne precursor contains an *ortho*-bromo substituent.

2.5 Further Work

The method of benzyne precursor formation demonstrated here should be generally useful for the formation of a variety of previously unavailable substrates. 2-Pyrones are readily available with a range of functionalities, and theoretically each of these substrates could be converted into *ortho*-silylaryltriflates.

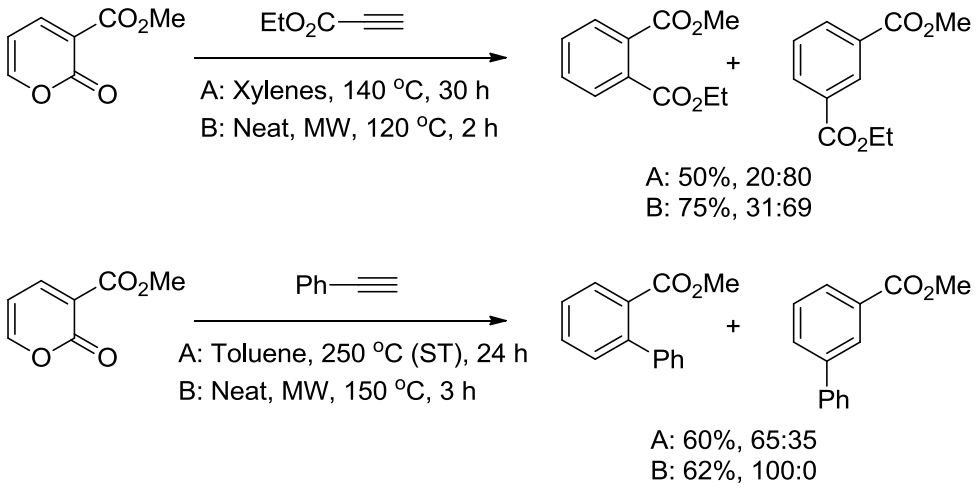
We envisage that this chemistry could now be used both academically and industrially as a mild and simple route for the formation of benzyne precursors.

Chapter Three – Directed Cycloadditions of 2-Pyrones

3.1 Introduction

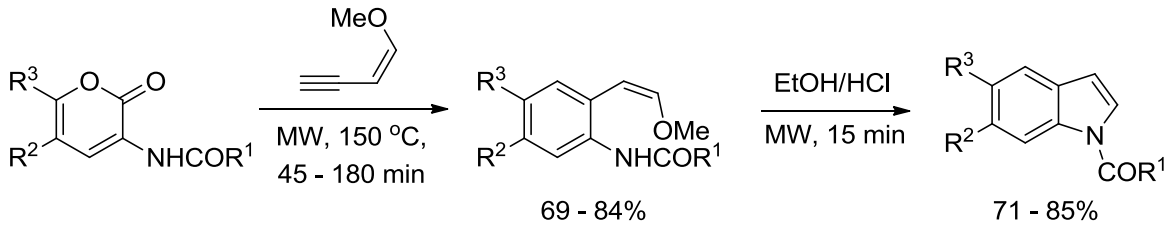
3.1.1 Mild Methods for 2-Pyrone Cycloadditions

Although there are a number of publications that demonstrate the formation of benzene substrates through 2-pyrone [4+2] cycloadditions, few include instances where the reaction occurs under mild conditions. Usually, high temperatures and long reaction times are required in order to perform the cycloaddition; although Loupy has reported improved results for the reaction of 3-carbomethoxy-2-pyrone with both ethyl propiolate and phenyl acetylene by using solvent-free microwave assisted conditions.[98] As outlined in Scheme 84 below, an improvement on the previously reported thermally promoted reactions was observed both in terms of the yields and regioselectivities of the cycloadditions.[99]



Scheme 84 – 2-Pyrone Cycloadditions Under Microwave Conditions

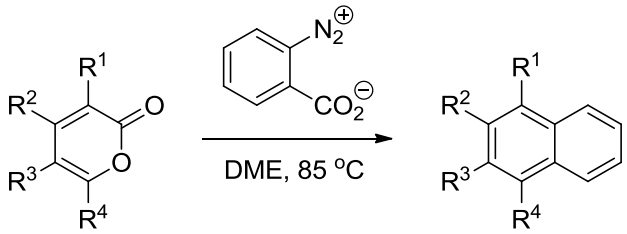
Recent work by Kocevar has also demonstrated a 2-pyrone cycloaddition that occurs in less than 3 h, by utilising microwave irradiation.[100] This has allowed for a simple and versatile route to a number of highly functionalised indoles, as outlined in Scheme 85 below.



Scheme 85 – A Microwave Assisted Formation of Indoles from 2-Pyrones

These methods allow for faster reactions, however high temperatures are still required. Alternative methods for milder 2-pyrone cycloadditions have been developed, involving the use of highly reactive electron rich dienophiles. For example, unfunctionalised 2-pyrone can undergo cycloaddition with benzyne under milder conditions, allowing for the formation of naphthalene.[101]

More recently, Guitian has demonstrated that functionalised 2-pyrones also undergo cycloaddition with benzyne, leading to the formation of a variety of functionalised naphthalenes in good yields at temperatures lower than 100 °C (Table 16).[102]

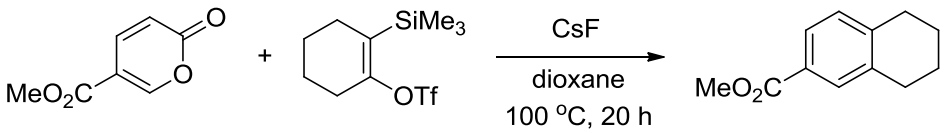


R^1	R^2	R^3	R^4	Yield / %
H	H	CO_2Me	H	80
Br	H	CO_2Me	H	93
H	OMe	H	Me	53

Table 16 - 2-Pyrone Cycloadditions of Benzyne

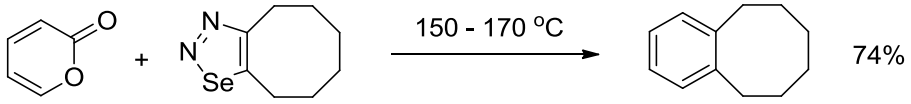
Further studies by Guitian have shown that 2-pyrones can also be used in cycloadditions with *in situ* generated cyclohexyne (Scheme 86).[103] This work represents the first instance of cyclohexyne generation using the milder conditions of fluoride induced elimination of trimethylsilyl and trifluoromethanesulfonate groups.

The reaction was not optimised for methyl coumalate, but high yields were obtained when highly functionalised 2-pyrones were used instead.



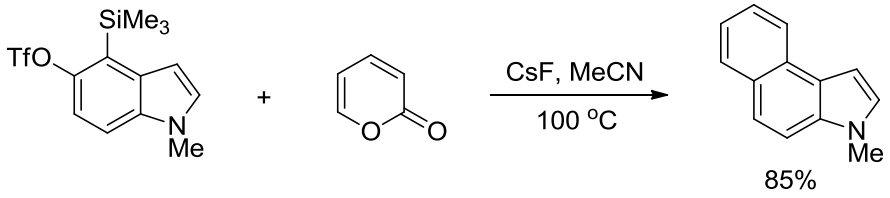
Scheme 86 – 2-Pyrone Cycloaddition with Cyclohexyne

Meier has shown that 2-pyrones can also undergo cycloaddition with larger ring-sized cycloalkynes, formed via thermal decomposition of 1,2,3-selenadiazoles (Scheme 87). The product forms in good yields, however high temperatures are still required for this reaction.[104]



Scheme 87 – 2-Pyrone Cycloaddition with Cyclooctyne

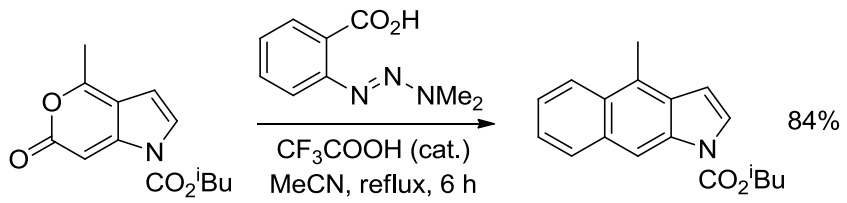
Alternative arynes have also been found to be suitable cycloaddition partners for the parent 2-pyrone. Garg has demonstrated the Diels-Alder reactions of *in situ* formed indolyne substrates with various dienes (Scheme 88).[105] Specifically, heating a mixture of caesium fluoride, indolyne precursor and 2-pyrone to 100 °C in acetonitrile smoothly promotes the cycloaddition to generate polycyclic products in high yields.



Scheme 88 – 2-Pyrone Cycloaddition with Indolyne

Complementary to the above example, benzofused indole substrates can also be made via cycloaddition of a pyranopyrrole substrate with benzyne. The reaction

proceeds smoothly, with a high yield of product obtained after 6 h at 80 ^{o}C (Scheme 89).[106]



Scheme 89 – Cycloaddition of Benzyne with Pyranopyrrole

It is clear that whilst 2-pyrone [4+2] cycloadditions with alkynes are an important tool in organic synthesis, there are a number of associated issues. Currently, there exists no method for performing 2-pyrone cycloadditions at ambient temperatures. In order to improve on the scope of 2-pyrone cycloadditions, and to make their use as a general method for the synthesis of functionalized benzene substrates more attractive to industry, a method for performing these reactions at ambient temperatures would be advantageous.

3.1.2 Alkynyltrifluoroborates

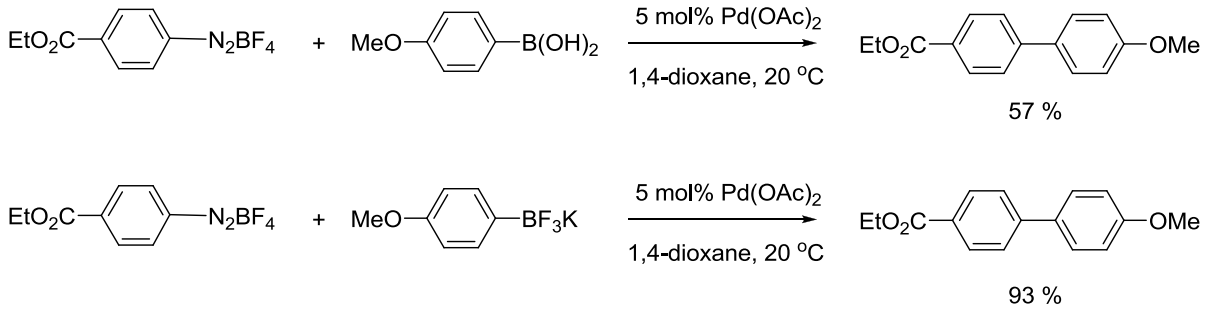
It is clear that organoboron species are extremely useful reagents, and that they can be employed in a wide range of organic transformations. However, boronic acids and boronic esters have a number of issues associated with their use. Boronic acids tend to be unstable compounds, and can be difficult to handle. Boronic esters are more stable, but still need to be stored under inert atmosphere and at low temperatures to avoid degradation. Boronic esters also usually require use of expensive diols in their synthesis, which are then difficult to remove in order to purify the required organoboronic ester. To this end, much attention has been focused recently into alternatives to boronic acids and esters.

Organotrifluoroborates were first synthesised by Vedejs *et al.* in 1995.[107] These new organoboron species have since been shown to be highly stable compounds which can be stored in air under ambient conditions without any noticeable degradation. As mentioned previously, this is in contrast to most other organoboron compounds,

which for the most part must be stored under inert atmosphere and at reduced temperatures.

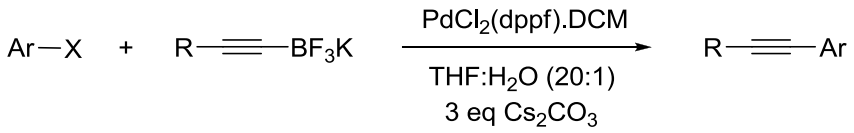
3.1.3 Coupling Reactions of Alkynyltrifluoroborates

As organotrifluoroborates were found to be more stable than organoboronates, yet retained similar reactivities, it was thought that organotrifluoroborates could be used as substitutes for organoboronates in a range of reactions. For example, work by Genêt demonstrated that these air stable substrates could not only be used as alternatives to organoboronates in Suzuki cross-coupling reactions, but in fact in many cases they performed better (Scheme 90).[108]



Scheme 90 – Varying Efficiencies of the Palladium Catalysed Coupling Reactions of Arylborates

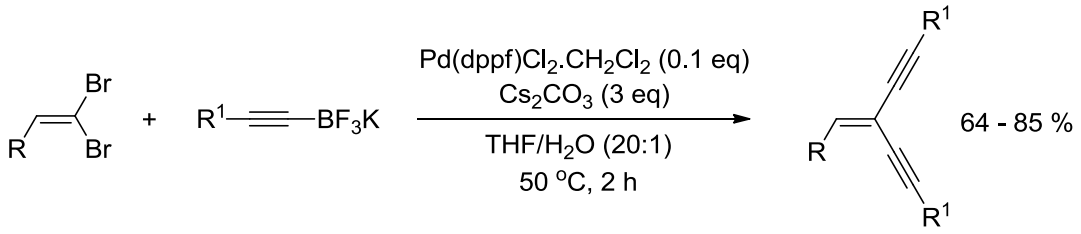
Genêt was also the first to successfully synthesise alkynyltrifluoroborates, using an analogous method to that employed in the synthesis of alkynylboronates.[109] Unlike the previously used aryl- and vinyltrifluoroborates, alkynyltrifluoroborates were found to be unsuccessful coupling partners for arenediazonium tetrafluoroborates. However, later work by Molander demonstrated that coupling could be achieved if aryl halides or triflates are used (Scheme 91).[110] Molander found that while a wide variety of Pd catalysts and solvents could be employed in the coupling, the reaction proceeds in highest yield (87 %) when $PdCl_2(dppf).CH_2Cl_2$ is used as catalyst, and a 20:1 mixture of THF:H_2O is used as solvent.



Scheme 91 – Palladium Catalysed Cross-coupling of Alkynyltrifluoroborates

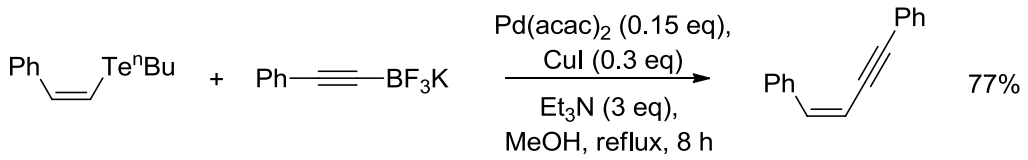
Recent work by Kabalka has shown that the Suzuki cross-coupling reactions of alkynyltrifluoroborates with aryltriflates can be significantly enhanced by performing reactions under microwave irradiation.[111] Using environmentally friendly conditions (^{i}PrOH-H_2O 2:1 was used as solvent) and extremely short reaction times (15 min in all examples), high yields (65 – 91%) of cross-coupled products were obtained.

Kabalka has also reported a convenient route to geminal enediynes via coupling of alkynyltrifluoroborates with readily accessible dibromoalkenes (Scheme 92).[112] Similar to the studies reported by Molander, $PdCl_2(dppf).CH_2Cl_2$ was found to be the most efficient catalyst for the coupling. The method was utilised to form a wide range of functionalised enediynes, all of which were obtained in high yields (64 – 85%).



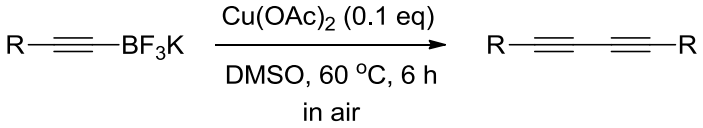
Scheme 92 – Formation of Enediynes via Cross-coupling Reactions

In recent years, many other examples of palladium catalysed cross-couplings using alkynyltrifluoroborates have been reported. An example of this is in the synthesis of 1,3-enynes via a Suzuki-type reaction of vinylic tellurides with potassium alkynyltrifluoroborate salts, reported by Stefani in 2005.[113] It was found that a variety of catalysts and coupling partners could be used in the reaction. Highest yields (77%) were obtained using $Pd(acac)_2$, CuI, and Et_3N in refluxing methanol for 8 h (Scheme 93).



Scheme 93 – Formation of 1,3-Enynes via Cross-coupling Reactions

Copper can also be used to catalyse cross-coupling reactions of alkynyltrifluoroborates. Paixao *et al.* have shown that heating alkynyltrifluoroborate salts in DMSO in the presence of a CuX_n catalyst results in high yields of the homo-coupled product.[114] This allows for the effective formation of symmetrical 1,3-diynes, without the need for a base or expensive palladium catalysts. A variety of substituted alkynes can be used in this methodology, resulting in a wide variety of possible coupled products. Highest yields were obtained when 0.1 equivalents of $Cu(OAc)_2$ was used as a catalyst (Scheme 94). All of the reactions were conducted in air, and it was assumed that molecular oxygen acts as an oxidant to reform the catalytically active copper species.

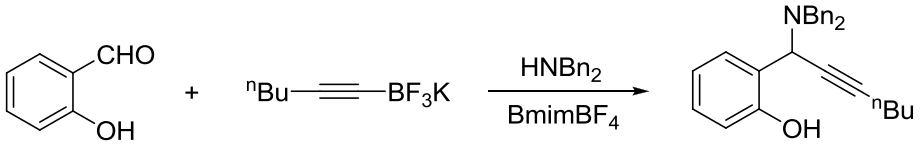


Scheme 94 – Copper Catalysed Homo-coupling of Alkynyltrifluoroborates

3.1.4 Further Applications of Alkynyltrifluoroborates

Alkynyltrifluoroborates have also been found to be capable of participating in a wide variety of chemical transformations other than coupling reactions. For example, Kabalka *et al* have discovered that alkynyltrifluoroborates are suitable reagents for carrying out imine addition reactions.[115] The increased stability of alkynyltrifluoroborate salts towards hydrolysis means that acids can be used to catalyse the reaction, this would be not be viable in the case of the readily hydrolysed alkynylboronates. Kabalka found that use of a stoichiometric amount of benzoic acid greatly increases the yields of the imine addition reactions (Table 17). It is presumed that the acid catalyses the condensation of the amine with the aldehyde

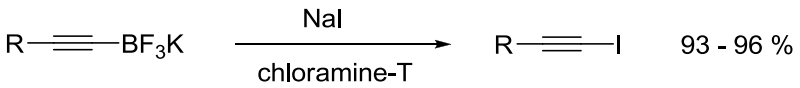
to form an iminium ion, which is reactive towards the alkynyltrifluoroborate. It was found in this study that the reactions proceed in the highest yields when ionic liquids are used as solvent, for example $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate).



Catalyst	Yield (%)
-	10
PhCOOH	81

Table 17 - Acid Catalysed Mannich Reaction of Alkynyltrifluoroborates

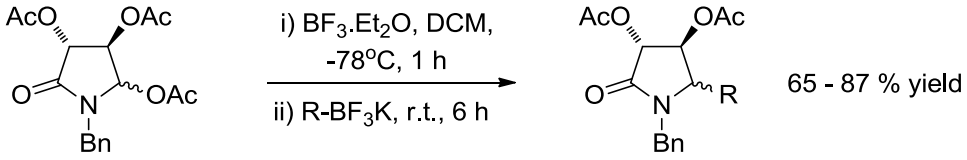
Kabalka also found that alkynyltrifluoroborates can be readily and efficiently transformed into synthetically useful iodoalkynes.[116] This can be achieved using sodium iodide and chloramine-T, and reacting in THF at room temperature for 20 min. High yields (>93%) were obtained in all cases (Scheme 95). Kabalka has also used this methodology for the formation of bromoalkynes.[117]



Scheme 95 – Synthesis of Iodoalkynes from Alkynyltrifluoroborates

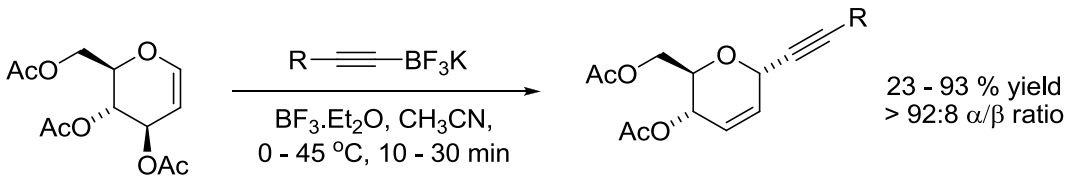
It has been shown that alkynyltrifluoroborates can undergo Lewis acid catalysed nucleophilic addition to chiral cyclic *N*-acyliminium ions, which allows for the stereoselective synthesis of functionalized *N*-heterocycles (Scheme 96).[118] It was found that the products were formed stereoselectively and in high yields when $BF_3.Et_2O$ was used as the Lewis acid promoter. Other Lewis acids examined were unable to give satisfactory yields or stereoselectivities. The study carried out by Vieira mainly utilised aryltrifluoroborates, however a selection of alkynyltrifluoroborates were also used. Again, these all gave *N*-heterocycles in good yields and stereoselectivities when $BF_3.Et_2O$ was used as the catalyst. The authors postulated that the reaction proceeds via the *in situ* formation of an

alkynyldifluoroborane species, which is facilitated by removal of a fluoride, using $BF_3.Et_2O$.[119] It is therefore believed that when organotrifluoroborates take part in Lewis acid catalysed nucleophilic additions, the resulting difluoro-species acts to remove the acetate group, and the resulting ate complex is then the active nucleophilic agent.



Scheme 96 – Nucleophilic Addition of Alkynyltrifluoroborates to *N*-Acyliminium Ions

A similar methodology has also been used recently to allow the highly stereoselective synthesis of α-*C*-glycosides.[120] This was carried out via the $BF_3.Et_2O$ mediated nucleophilic addition of alkynyltrifluoroborates to D-glucal (Scheme 97). This report showed similar findings to the previous report by Vieira, in that the additions were only found to proceed smoothly if $BF_3.Et_2O$ was used as the catalyst, supporting the theory that a $BF_3.Et_2O$ mediated fluoride abstraction is involved. A variety of alkynyltrifluoroborates were utilised in the study, with products generated in moderate to good yields and with high diastereoselectivities in each case.



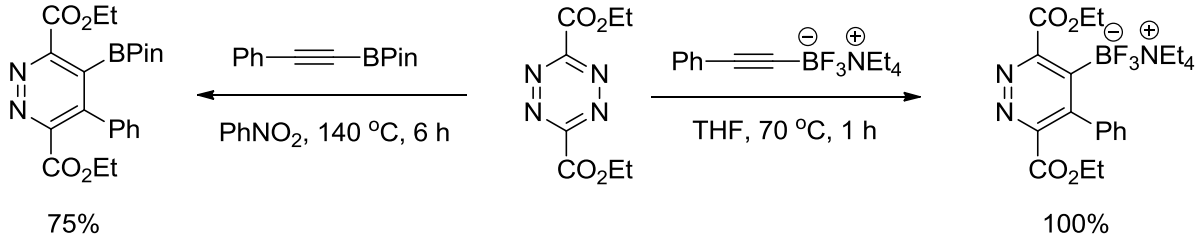
Scheme 97 – Nucleophilic Addition of Alkynyltrifluoroborates to D-Glucal

Further information on alkynyltrifluoroborates and various other organotrifluoroborates can be found in Genêt's extensive review.[121]

3.1.5 Directed Cycloadditions of Alkynyltrifluoroborates

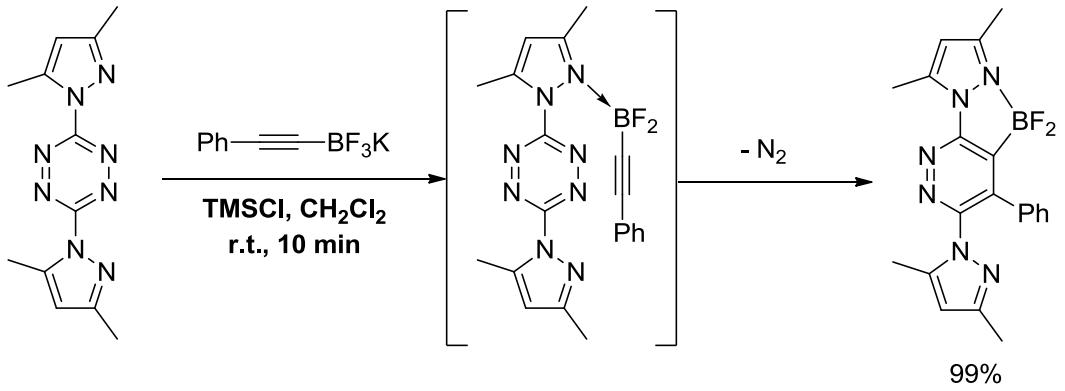
As described previously, much work has been done in the Harrity group on the formation of aromatic and heteroaromatic boronic esters via [4+2] cycloadditions of

alkynylboronates with various dienes.[7-15] During these studies, it was discovered that alkynyltrifluoroborates can also be used in these reactions, affording functionalised aromatic trifluoroborate salts.[10] Interestingly, the cycloaddition reaction of tetrazines with alkynyltrifluoroborates was found to be more efficient than when the corresponding alkynyl*boronates* were used. For example, it was found that the bis-ester-substituted tetrazine undergoes cycloaddition with phenyl alkynyltrifluoroborate quantitatively when the reaction is conducted at 70 ^{o}C for 1 h, whereas the reaction requires longer times and higher temperatures when phenyl alkynylboronate is used (Scheme 98).



Scheme 98 – Cycloaddition of Tetrazines with Alkynylboronates and Alkynyltrifluoroborates

It was also discovered that the cycloadditions of alkynyltrifluoroborates can be further improved by utilising the methodology of monodefluorination of alkynyltrifluoroborates by Lewis acids, which allows for *in situ* formation of alkynyldifluoroboranes. If a Lewis basic site is incorporated into the tetrazine, this can coordinate to the vacant *p*-orbital on the boron of the *in situ* formed alkynyldifluoroboranes. Therefore, the diene and dienophile are tethered together, which greatly enhances the cycloaddition rate. Reactions were found to be complete within 10 min at room temperature, a marked improvement on the [4+2] cycloadditions performed in the absence of Lewis acid (Scheme 99). It was also found that if a non-symmetrical tetrazine is used, the reaction is regioselective, with the regioselectivity being directed by the coordination to the alkynyldifluoroborane.



Scheme 99 – Directed Cycloaddition of Tetrazines

3.2 Aims

The cycloadditions of 2-pyrones with alkynylboronates have been demonstrated to be a simple method for forming useful aromatic products. Unfortunately, at present, the cycloadditions suffer from the drawbacks of needing high temperatures to proceed, and also exhibit variable scope with respect to regiocontrol. It was thought that both of these aspects of 2-pyrone cycloadditions could be improved by using the method previously developed in the group for improving the reactions of tetrazines. As outlined in Figure 14, it was envisaged that incorporation of a Lewis basic site adjacent to the CO_2 moiety of the ring would allow for this directed cycloaddition to occur. Therefore, we turned our attention to the synthesis of such substrates, and subsequent cycloadditions with *in situ* formed alkynyldifluoroboranes.

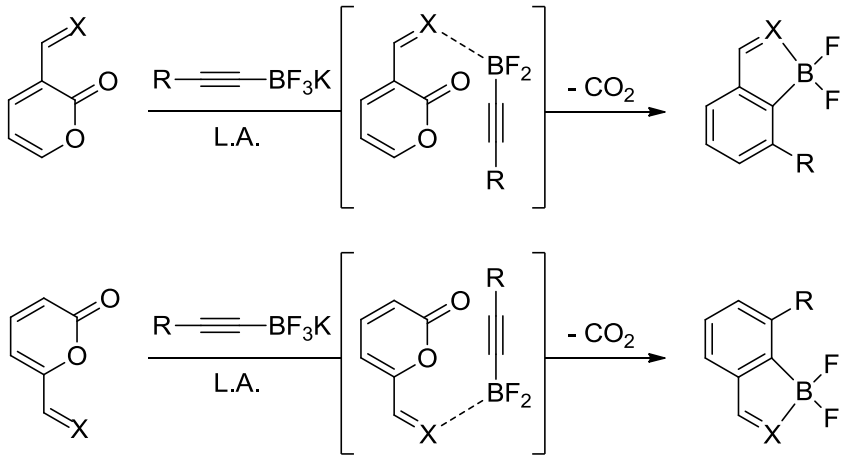
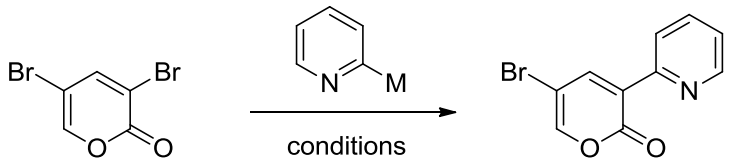


Figure 14 – Potential Directed 2-Pyrone Cycloadditions

3.3 Results and Discussion

3.3.1 Synthesis of Heterocyclic Substituted 2-Pyrones

In order to test our hypothesis, we first needed to find a reliable method for the synthesis of appropriately functionalized 2-pyrones. Initially, it was thought that this could be achieved by coupling pyridine to the previously described dibromo-2-pyrone **13**. Cho has demonstrated that regioselectivity in the Stille couplings of 3,5-dibromo-2-pyrone can be achieved by subtle changes in the reaction conditions.[122] In our hands, the reaction did allow for formation of 3-pyridyl-2-pyrone **59**, albeit in low yield (Table 18). Other coupling methods were also used, but unfortunately none were found to be successful.



13 **59**

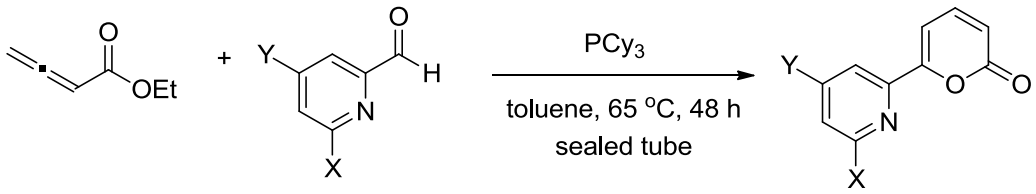
M	Catalyst	Conditions	Yield / %
$B(OMe)_2$	$Pd(PPh_3)_4$ (0.1 eq.)	Toluene, K_2CO_3, 18h	-
ZnCl	$Pd(PPh_3)_4$ (0.1 eq.)	THF, 18h	SM
$SnBu_3$	$Pd(PPh_3)_4$ (0.1 eq.)	CuI (0.1 eq.), toluene	50 – 60
$B(O^iPr)_3Li$	Pd_2dba_3 (0.01 eq.)	$P(O)Ph_2H$, KF, dioxane	-

Table 18 – Synthesis of 3-Pyridyl-2-pyrone

Due to the difficulties involved with both the synthesis of the requisite di-bromo-2-pyrone, and the subsequent coupling reactions, it was decided that an alternative route to a suitable 2-pyrone should be devised.

We expected that the regioisomeric 6-substituted pyridine 2-pyrone should also give the desired directing effect. Targeting these substrates would allow us to take advantage of a report by Kwon who showed that 6-substituted 2-pyrones can be formed in good and reproducible yields via a phosphine catalysed annulation

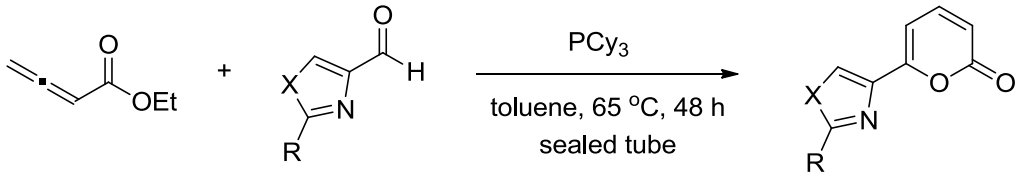
reaction of ethyl allenoate and a wide range of aldehydes.[123] This reaction was found to be successful and reproducible for the formation of 6-pyridyl-substituted 2-pyrones, providing the products in moderate to high yields (Table 19).



X	Y	Yield / %
H	H	**60**; 81
H	OMe	**61**; 30
Me	H	**62**; 83

Table 19 - Synthesis of 6-Pyridyl-2-pyrones

Utilising the conditions for 6-pyridyl-2-pyrone formation as above, the synthesis of 2-pyrones functionalised with 5-membered heterocycles was also achieved. Thiazole and methyl-oxazole containing 2-pyrones **63** and **64** were isolated in moderate yields under standard conditions (Table 20).



X	R	Yield / %
O	Me	**63**; 38
S	H	**64**; 36

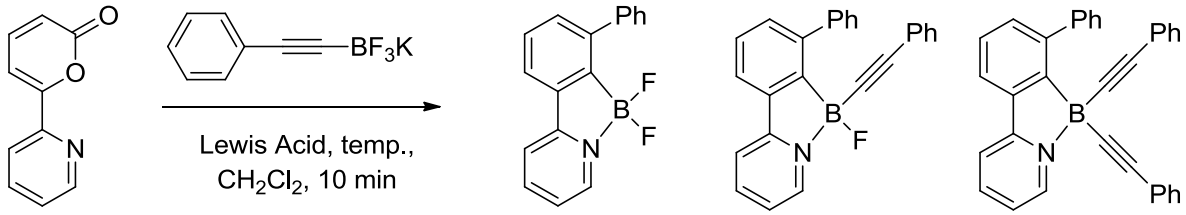
Table 20 – Synthesis of 6-Heteroaryl-2-pyrones

3.3.2 Optimisation of Cycloaddition Conditions

With a reproducible route to the required 2-pyrone substrates in hand, and the synthesis of a range of alkynyltrifluoroborates achieved, the cycloaddition reaction between pyridine substituted 2-pyrone **60** and phenyl alkynyltrifluoroborate was studied. Initial results proved promising, with moderate yields of the cycloadducts formed regioselectively at *room temperature within less than an hour*, a marked improvement on the previously reported conditions for cycloadditions of 2-pyrones. However, a number of issues arose from these initial experiments:

1. It was noted during our preliminary work that a large amount of starting material was being recovered as a precipitate from the reactions. Although the cause of this precipitation is unclear, it appears that a salt can be formed between the 2-pyrone and inorganic impurities resulting from salts remaining in the alkynyltrifluoroborates used. After a more rigorous purification of the alkyne partner, it was found that the reactions proceeded in far higher yields, with little amounts of starting material recovered. Using the purified alkyne, the optimal reaction conditions were found (Table 21).

2. Unlike the previously reported cycloadditions of tetrazines, it was noticed that three products were consistently obtained. These consisted of the expected difluoroborane cycloadduct product, alongside a mono- and di-alkynylated borane species.



60 **65a** **65b** **65c**

Entry	Lewis Acid (eq)	Alkyne (eq)	Temp / °C	Yield / %			RSM / %	Total Conversion / %
				65a	**65b**	**65c**		
1	TMSCl (3)	3	25	12	8	50	11	70
2	TMSCl (3)	3	40	17	21	36	6	74
3	$BF_3.OEt_2$ (3)	3	0	40	21	20	13	81
4	$BF_3.OEt_2$ (3)	3	25	75	10	10	0	95
5	**$BF_3.OEt_2$ (3)**	**3**	**40**	**82**	**5**	**5**	**0**	**92**
6	$BF_3.OEt_2$ (1)	1	40	62	0	0	30	62
7	$BF_3.OEt_2$ (2)	2	40	65	8	9	10	82
8	$BF_3.OEt_2$ (6)	6	40	42	10	20	0	72

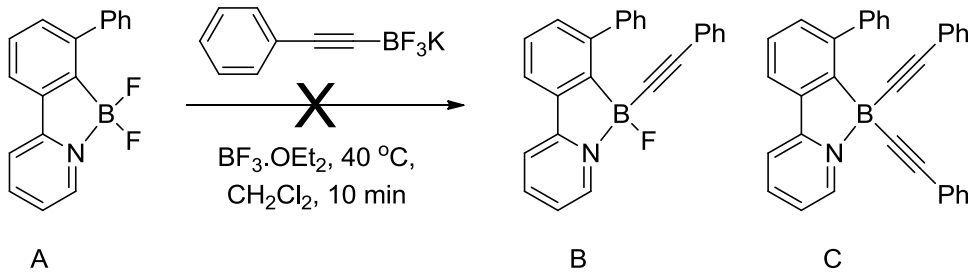
Table 21 – Optimisation of a Directed 2-Pyrone Cycloaddition

As Table 21 shows, TMSCl was used as Lewis acid in the first instance, as this was found to give the highest yields of product for the previously mentioned directed cycloadditions of tetrazines. Unfortunately, although the reaction proceeds, large amounts of by-products were observed at both room temperature and 40 °C (Entries 1 and 2). We therefore switched to using $BF_3.OEt_2$ as the Lewis acid and found that the reaction proceeds in good yield at room temperature. However, by increasing the temperature to 40 °C, formation of side products can be minimised (Entries 4 and 5). At lower temperatures the reaction was found to be sluggish, with lower product yields obtained, due to both incomplete reaction and a greater amount of side product formation (Entry 3). By using more equivalents of alkyne and Lewis acid, it appears that the reaction is also retarded, possibly due to degradation of starting materials

due to the large excess of Lewis acid present (Entry 8). The reaction can be run successfully using only one equivalent of alkynyltrifluoroborate, with no side products formed in this case (Entry 6). However, the reaction did not reach completion, and so it was decided that all future reactions should be run using the conditions outlined in Entry 5.

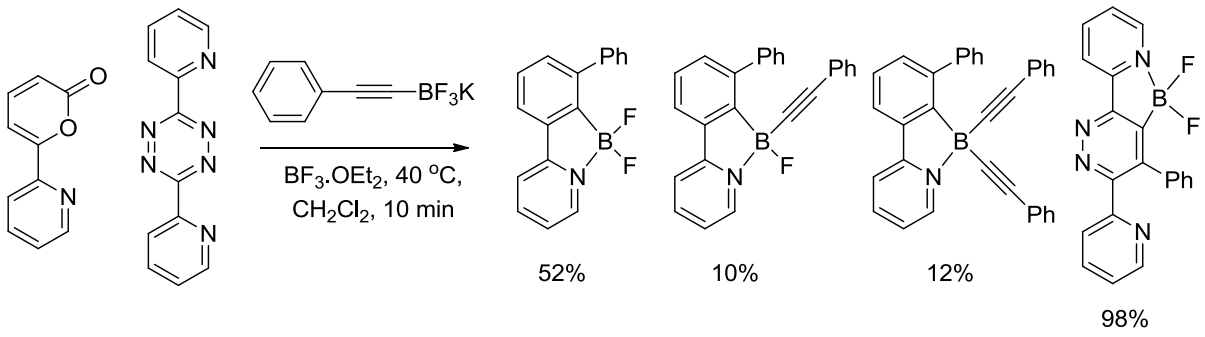
3.3.3 Examining the Mechanism of 6-Pyridyl-2-pyrone Cycloaddition

Attention was next turned to discovering the mechanism by which the unwanted alkynylborane cycloadducts were formed. Firstly, the difluoroborane cycloadducts were resubjected to the reaction conditions, in order to determine whether the alkynylation occurred before or after cycloaddition. Quantitative recovery of aryldifluoroborane was observed, suggesting that alkynylation occurs before the cycloaddition takes place (Scheme 100).



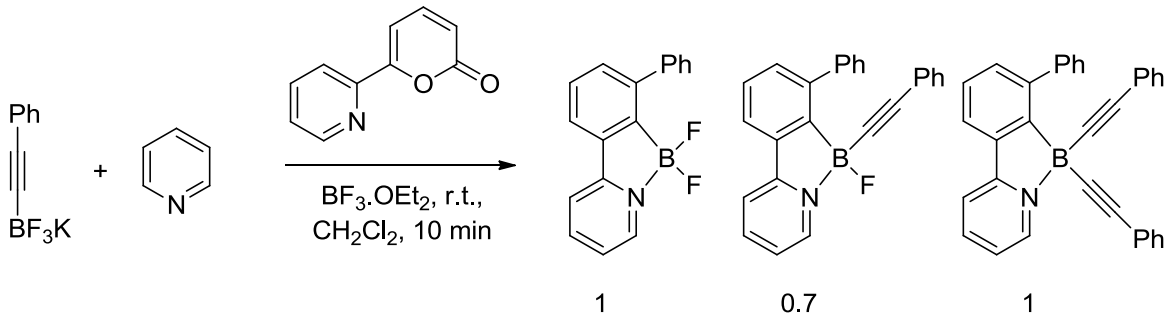
Scheme 100 - Attempted Synthesis of a Dialkynylborane from a Difluoroborane

We envisaged that the formation of trialkynylborane and dialkynylborane species could occur *in situ*, the cycloaddition of which would lead to the alkynylated borane species observed. In order to examine this, the reaction was conducted in the presence of a bis-pyridyl substituted tetrazine (Scheme 101). In the event, tetrazine was quantitatively converted to the corresponding pyridazine-difluoroborane cycloadduct, whilst alkyne incorporation was still observed on the benzene-difluoroborane products, suggesting that alkynylation does not take place in free solution but occurs on the 2-pyrone substrate.



Scheme 101 - Cycloaddition of 6-Pyridyl-2-pyrone Alongside a Tetrazine

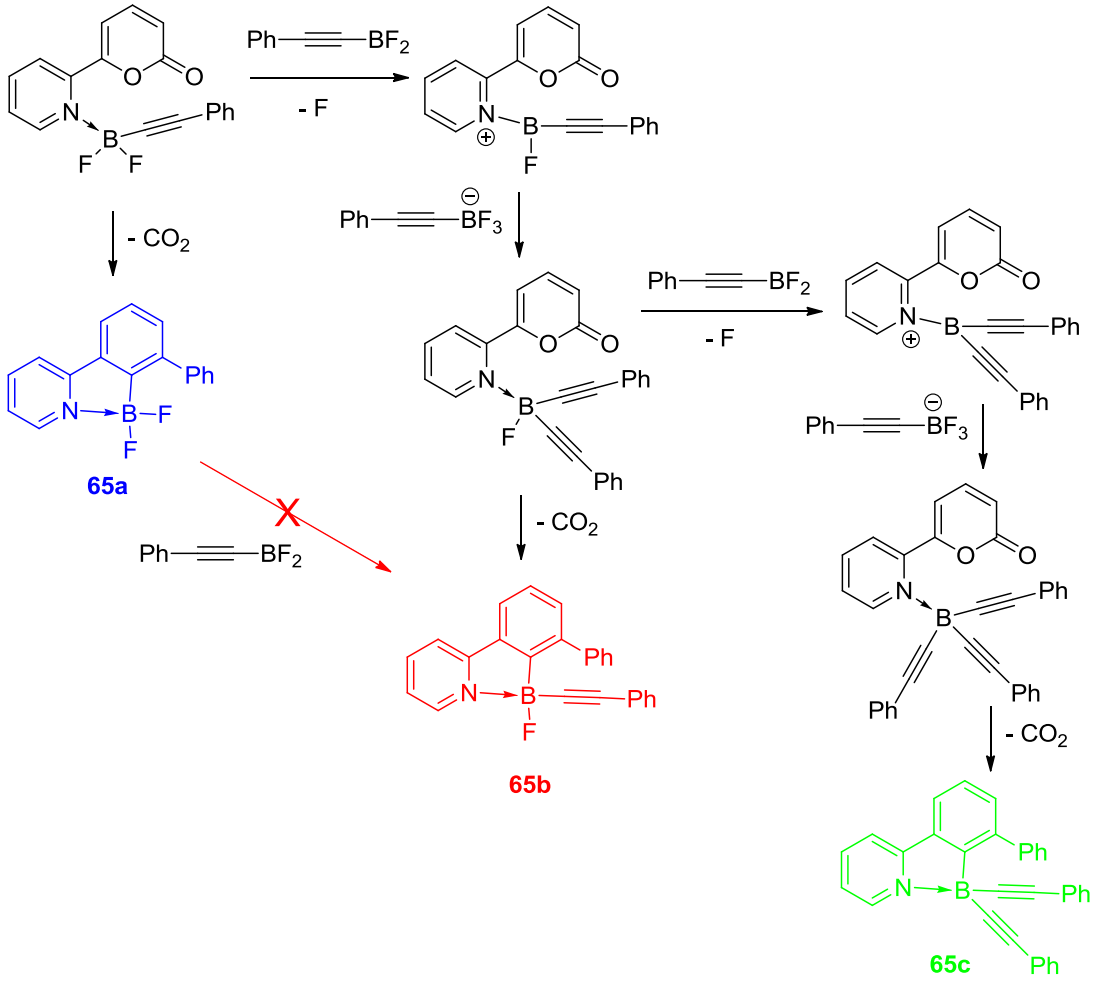
It was also shown that if pyridine is added to the *in situ* formed alkynyldifluoroborane, then 2-pyrone added to this mixture, the amount of alkynylated side products formed is significantly increased. The distribution of products shown in Scheme 102 has been calculated from the crude ^{1}H NMR spectrum of the reaction (Appendix, page 162). The ^{1}H NMR spectrum of the crude reaction mixture also contained a signal for a pyridine-H at around 9.5 ppm, consistent with the previously reported data for trialkynylated boron-pyridines.[124] This suggests that the formation of trialkynylboron species is facilitated by pyridine coordination to boron. A similar effect has been reported in the literature, where pyridine-BF_3 species have undergone fluorine removal using a Lewis acid.[125] The subsequent dearomatised intermediates can then undergo nucleophilic addition.



Scheme 102 – Effect of Pyridine on 2-Pyrone Cycloaddition

From these results, a mechanism has been hypothesised to account for the formation of alkynylated side products. Initial coordination of the pyridyl-2-pyrone to an

alkynyldifluoroborane species would form a boronate complex, which can then undergo removal of fluorine, possibly facilitated by an external alkynyldifluoroborane. This would form a dearomatised intermediate, which can then accept an alkyne via nucleophilic addition of an alkynyltrifluoroborate. Cycloaddition of this intermediate allows for formation of the mono-alkynylated substrates, whilst removal of another fluorine, and subsequent alkyne addition would lead to the di-alkynylated substrates (Scheme 103).

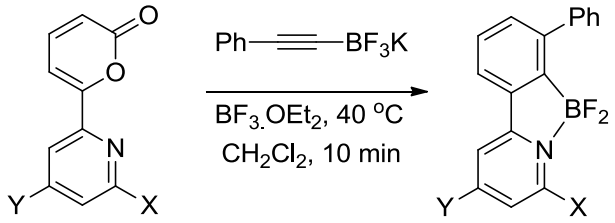


Scheme 103 – Theoretical Mechanism for Alkynylated Cycloadduct Formation

3.3.4 Cycloadditions of 6-Substituted 2-Pyrones

Having established the optimal reaction conditions, the scope of the reaction was next examined. Pleasingly, under optimal conditions the *para*-OMe and *ortho*-Me substituted pyridyl substrates **61** and **62** undergo cycloaddition, with high yields of the required difluoroborane species obtained in each case (Table 22). 2-Pyrone **61**

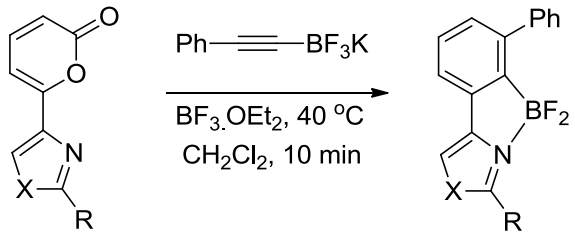
gave slightly lower yields of the required difluoroborane species, due to the formation of alkynylated side products, which were not isolated. Methyl substituted 2-pyrone **62** gave the difluoroborane adducts in excellent yield, with no side product formation observed, presumably due to the increased steric hindrance from the methyl group, which would encourage cycloaddition by forcing the coordinated alkyne to sit in close proximity to the 2-pyrone ring.



X	Y	Yield / %
H	OMe	**66**; 70
Me	H	**67**; 82

Table 22 - Cycloadditions of 6-Pyridyl-2-pyrones

We were also pleased to discover that the oxazole and thiazole substituted 2-pyrones **63** and **64** could be used in the reaction. Again, high yields of the desired substrates were obtained in each case (Table 23).

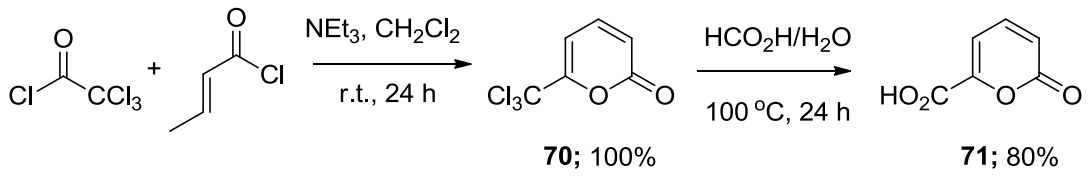


X	R	Yield / %
O	Me	**68**; 67
S	H	**69**; 74

Table 23 - Cycloadditions of 6-Heteroaryl-2-pyrones

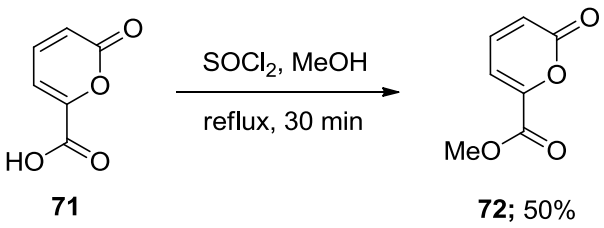
3.3.5 – Synthesis and Directed Cycloadditions of 6-Amido-2-Pyrones

Having demonstrated that various heterocycles can be employed as directing groups for alkynyldifluoroborane cycloadditions, we turned our attention to the synthesis of 2-pyrones containing non-aromatic directing groups. Dunkelblum reported that carboxylic acid substituted 2-pyrone **71** can be easily synthesised in two steps from readily available starting materials.[126] It was found that the conditions previously reported for the acid hydrolysis of **70** to **71** gave variable results, due to the final product being difficult to isolate. Using 10% water in formic acid allowed for a more reproducible method, with higher yields of **71** obtained.



Scheme 104 – Synthesis of 2-Pyrone-6-carboxylic Acid **73**

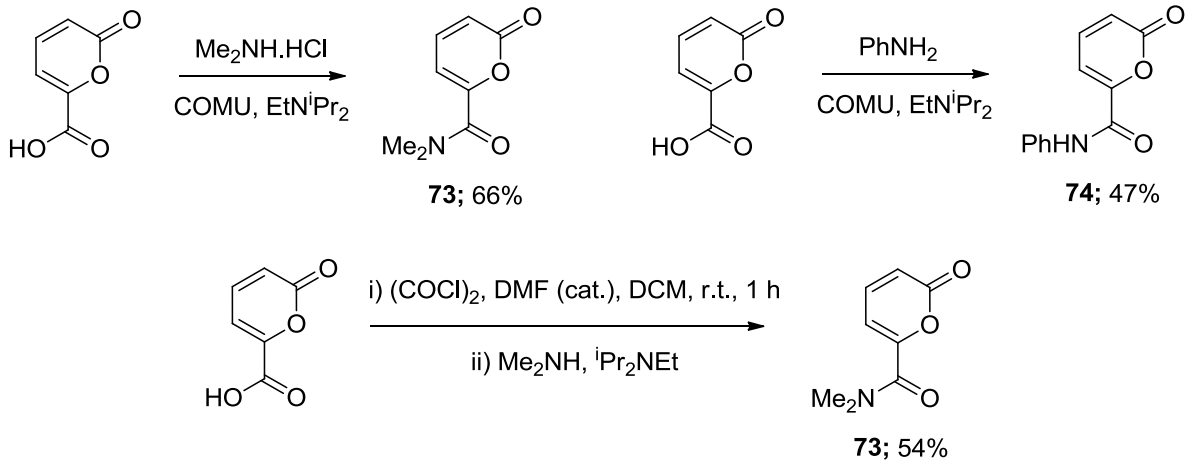
With a reliable route to **71** in hand, attention was turned to the conversion of the carboxylic acid into suitable Lewis basic groups. Dunkelblum also demonstrated that the acid is easily converted to the methyl ester, via the acid chloride. This was repeated successfully, affording 2-pyrone **72**.



Scheme 105 – Synthesis of 2-Pyrone **72**

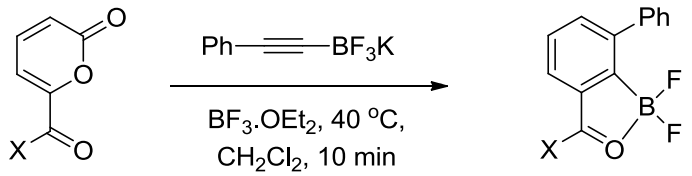
We envisaged that an amido group would be suitably Lewis basic for coordination to alkynyldifluoroboranes in order to affect a directed cycloaddition. Initially, the synthesis of the 6-dimethylamido-2-pyrone **73** and *N*-phenylamido-2-pyrone **74** was achieved using the peptide coupling agent (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbeniumhexafluorophosph-ate

(COMU®). This method afforded the required amides in reasonable yields, however purification of the products proved troublesome, due to the presence of amide by-products from the degradation of COMU®. Fortunately, conversion of the carboxylic acid to the acid chloride, using oxalyl chloride, followed by treatment with dimethylamine and Hünig's base, afforded the desired amide cleanly in reproducible yields (Scheme 106).



Scheme 106 – Synthesis of 6-Amido-2-pyrones

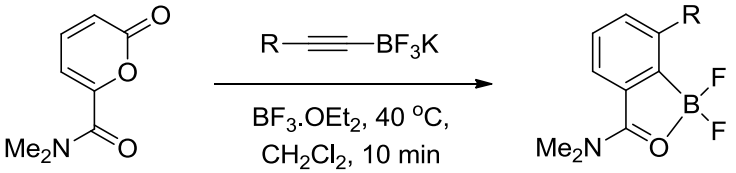
With these 2-pyrones in hand, attention was turned to the directed cycloadditions. Unfortunately, ester and secondary amide substituted 2-pyrones **72** and **74** were found to be unreactive towards cycloaddition. Fortunately, it was discovered that using the tertiary amide as a directing group, the reaction occurs cleanly in high yield (Table 24). In fact, the *N*,*N*-dimethylamido-2-pyrone **73** gave better yields of the difluoroborane cycloadduct than any of the previously utilised heterocycles, with no side product formation observed.



X	Yield / %
OMe	0
NHPh	0
NMe_2	**75;** 92

Table 24 - Cycloaddition of 6-Substituted 2-Pyrones

To demonstrate the general utility of this method, 2-pyrone **73** was then reacted with a variety of substituted alkynyltrifluoroborates, affording trimethylsilyl, ^{n}butyl and 1-cyclohexenyl substituted products in excellent yields (Table 25). Again, each reaction was complete within 10 min at 40 ^{o}C, with no side product formation observed.



R	Yield / %
^{n}Bu	**76;** 65
$SiMe_3$	**77;** 70
1-Cyclohexene	**78;** 93

Table 25 - Amido Substituted 2-Pyrone Cycloadditions

It could be envisaged that either the nitrogen or the oxygen of the amide group can act as the Lewis basic site in this reaction. In order to determine which atom the donation occurs from, we decided to record an X-ray crystal structure of **75**. This would also allow us to definitively determine the product regiochemistry. As expected the amide group is situated adjacent to the difluoroborane group, with the

oxygen of the amide coordinated to the vacant p-orbital of the difluoroborane (Figure 15).

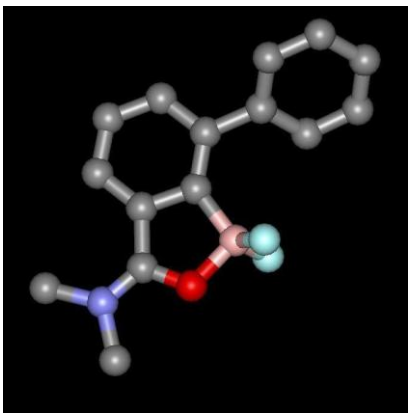
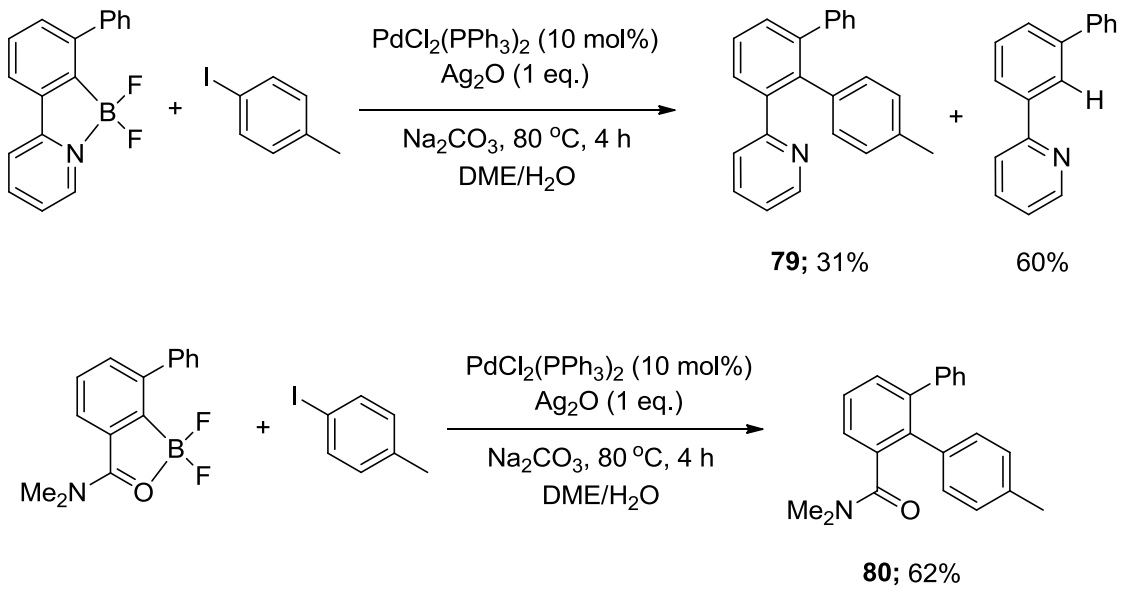


Figure 15 – Crystal Structure of **75**

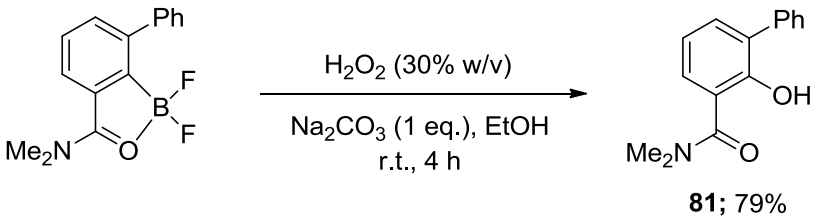
3.3.6 Functionalisation of Difluoroborane Cycloadducts

In order to further elaborate the products, palladium catalysed cross-coupling reactions were performed using cycloadducts **65** and **75** with 4-iodotoluene. Previous studies in the group have shown that pyridazine difluoroborane cycloadducts undergo efficient coupling using $PdCl_2(PPh_3)_2$ alongside Ag_2O.[10] Using these conditions with pyridine substituted difluoroborane **65**, the cross coupling product was obtained in modest yield; however a large amount of deboronated product was also obtained. Fortunately, the amido substituted cycloadduct underwent cross-coupling smoothly, with high yields obtained under the conditions (Scheme 107). Interestingly, in the absence of Ag_2O, no cross-coupling product was observed, with quantitative amounts of difluoroborane starting material recovered after prolonged reaction times. This suggests that the silver salt plays an important role in speeding up the transmetallation step of the reaction, possibly by removing a halide from the organo-palladium complex formed after oxidative addition.



Scheme 107 – Cross-coupling of Difluoroboranes

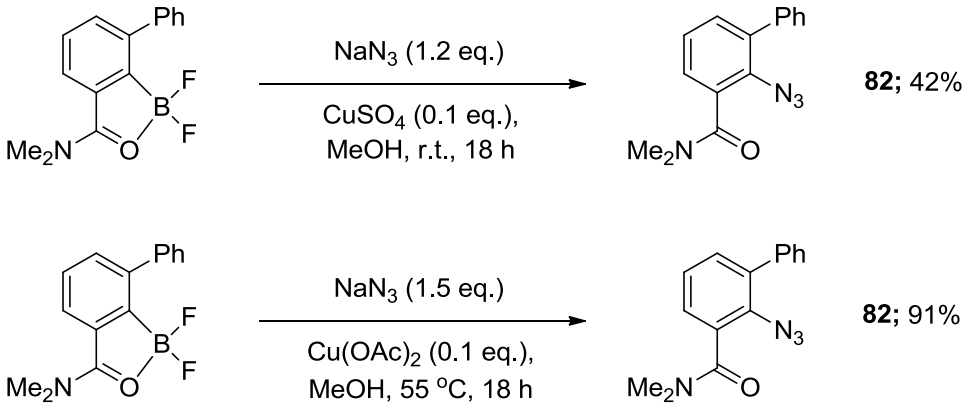
Alternative functionalisations of the difluoroborane cycloadducts have also been achieved. Oxidation to the corresponding phenol product **81** was achieved directly from the difluoroborane substrate using conditions previously utilised in the group.[95] A high yield of the oxidation product was obtained after just 4 h at room temperature (Scheme 108).



Scheme 108 – Oxidation of Difluoroborane

Organoboron substrates have also been shown to undergo copper catalysed azidonation reactions. Guo was the first to demonstrate this, by achieving the synthesis of aryl azides in high yields from aromatic boronic acids, using copper(II) sulphate as catalyst.[127] The direct conversion of difluoroborane **75** was attempted using Guo's conditions. Pleasingly, the corresponding aryl azide was obtained, but in low yield. An alternative method for azidonation has been developed recently by

Aldrich, who has achieved the direct azidonation of aromatic boronic esters and aromatic trifluoroborate salts.[128] Using these conditions, we were delighted to find that an excellent yield for the desired aryl azide **82** could be obtained (Scheme 109).



Scheme 109 – Azidonation of Difluoroborane

3.4 Conclusions

The reaction between 2-pyrones and alkynylboron species has been dramatically improved using directed cycloadditions. By incorporating a Lewis basic site into the 2-pyrone ring, both the reaction time and temperature have been significantly reduced. The reaction has been shown to be regioselective for a wide range of 2-pyrone and alkyne partners.

A variety of heterocyclic systems have been shown to be viable directing groups for this method, with good yields and regioselectivities obtained for each substrate used. Di-substituted amides can also be used in this methodology, with the *N*,*N*-dimethylamido functionalised 2-pyrone proving to be generally effective.

The difluoroborane cycloadducts obtained have been directly functionalised using a variety of carbon-boron bond functionalisation reactions. The palladium catalysed cross-coupling, oxidation and copper catalysed azidonation of substrate **75** were all performed smoothly, without the need for conversion to the more active boronic acid species.

3.5 Further Work

The incorporation of a Lewis basic site into the 6-position of the 2-pyrone ring has proved to be a generally effective method for affecting directed cycloadditions. It should be possible to observe the same effect if the same directing groups were incorporated into the 3-position of the 2-pyrone. If this reaction is found to be regioselective, it should afford products with the same regiochemistry as the ones synthesised here.

Utilising this chemistry, we have been able to synthesise aromatic substrates functionalised with an amide that is coordinated to an internal Lewis acidic group. Therefore, it is feasible to imagine that these amides would be activated, which could allow for transformations not normally achievable using standard aromatic amides.

It has been demonstrated that using the method of directing [4+2] cycloaddition reactions of usually unreactive dienes with a variety of alkyne partners, a variety of functionalised aromatics can be obtained smoothly under mild conditions. We envisage that this methodology could be used to improve the cycloadditions of a number of alternative dienes which are usually unreactive towards cycloaddition.

Chapter Four – Experimental Section

General Procedures

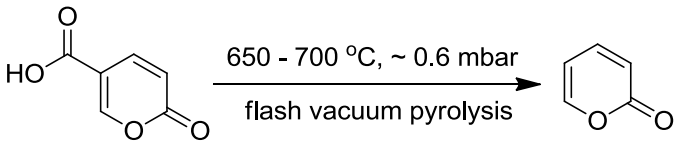
Infrared (IR) Spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Samples were recorded as thin films using sodium chloride plates, as a DCM solution. Bands are characterised as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, q = quartet, pent = pentet, sext = sextet, br = broad, m = multiplet, app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz) or AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm). Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. 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. Certain compounds were found to be not amenable to standard techniques, and in these cases a Waters® Atmospheric Solids Analysis Probe was employed (AP^+).

Melting points performed on recrystallised 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). Starting alkynyl boronates were prepared according to established procedures.[17] Coumalic acid, methyl coumalate and aryl aldehydes were purchased from Aldrich chemical co. and used as received. Flash chromatography was performed on silica

gel (BDH Silica Gel 60 43-60). 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: Ultraviolet light or potassium permanganate.

4.1 Alkynylboronate Cycloadditions Towards Aromatic Boronic Esters

Synthesis of 2-pyrone 1[129]

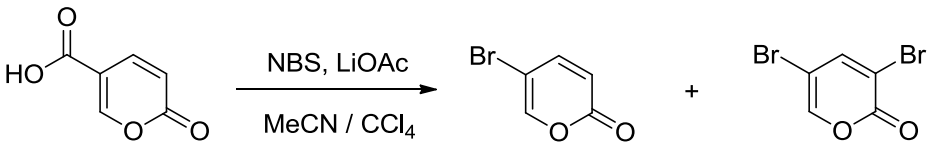


9 **1**

Coumalic acid **9** (2.05 g, 14.6 mmol) was heated to 170 °C under a pressure of 0.6 mbar. The temperature was then raised slowly, over 30 min, to 250 °C. The sublimed material was passed through an oven held at 650 – 700 °C. Compound **1** was collected, in a trap held at -78 °C, as a brown oil, 1.19 g, 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (1H, ddd, *J* = 1.0, 5.0, 6.5 Hz, Ar-*H*), 6.35 (1H, dt, *J* = 1.5, 9.5 Hz, Ar-*H*), 7.34 (1H, ddd, *J* = 2.0, 6.5, 9.5 Hz, Ar-*H*), 7.51 (1H, ddd, *J* = 1.5, 2.0, 5.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 105.9, 117.0, 142.7, 152.0, 162.1. The compound gave satisfactory spectroscopic data.[129]

Synthesis of 5-bromo-2-pyrone 7 and 3,5-dibromo-2-pyrone 13[130]



9 **7** **13**

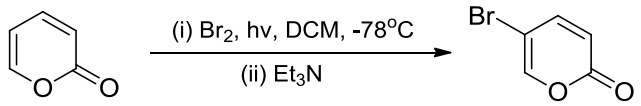
To a solution of coumalic acid **9** (5.0 g, 36 mmol) in 50 mL CCl_4 and 25 mL MeCN was added *N*-bromosuccinimide (25.5 g, 143 mmol), lithium acetate (3.6 g, 36

mmol) and a spatula tip of Bu_4NBr under nitrogen. The resulting mixture was heated at 65 ^oC for 9 h. The reaction mixture was partitioned into CH_2Cl_2 (250 mL) and H_2O (250 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow solid. The crude material was purified by flash chromatography (eluting solvent 10% ethyl acetate in petrol), affording **7** as a pale yellow solid m.pt. = 59 – 61 ^oC (lit.[131] 61 – 63 ^oC), 0.6 g, 11% yield, and **13** as a colourless solid m.pt. = 66 – 68 ^oC (lit.[130] 66 – 67 ^oC), 2.8 g, 31% yield.

7; ^1H NMR (400 MHz, $CDCl_3$): δ 6.31 (1H, dd, *J* = 1.0, 10.0 Hz, Ar-*H*), 7.36 (1H, dd, *J* = 2.5, 10.0 Hz, Ar-*H*), 7.60 (1H, dd, *J* = 1.0, 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 100.8, 117.6, 145.9, 149.8, 159.5. The compound gave satisfactory spectroscopic data.[132]

13; ^1H NMR (250 MHz, $CDCl_3$): δ 7.58 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.74 (1H, d, *J* = 2.5 Hz, Ar-*H*). The compound gave satisfactory spectroscopic data.[130]

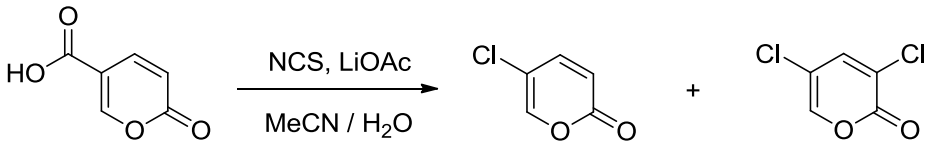
Synthesis of 5-bromo-2-pyrone 7[132]



1 **7**

To a solution of 2-pyrone **1** (1.10 g, 11.5 mmol) in 60 mL DCM at -78 ^oC, was added bromine (1.87 g, 11.7 mmol), slowly over a 50 min period. After each portion of bromine was added, the mixture was irradiated using a 400 W tungsten lamp. When reaction appeared complete, the light was removed, and the mixture left to stir for 30 min. To the resulting orange solution was added Et_3N (1.74 g, 17.2 mmol), and the mixture stirred for 1 h. The reaction mixture was partitioned into diethyl ether/water (1:1, 400 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give **7** as a colourless solid, 1.61 g, 81% yield. The compound gave the same spectroscopic data as for **7** above.

Synthesis of 5-chloro-2-pyrone 10 and 3,5-dibromo-2-pyrone 11[55a]



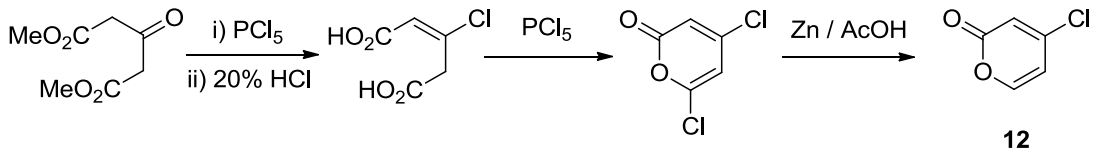
9 **10** **11**

To a solution of coumalic acid **9** (2.67 g, 19 mmol) in 50 mL MeCN and 10 mL H_2O was added *N*-chlorosuccinimide (5.09 g, 38 mmol) and lithium acetate (2.52 g, 38 mmol) under nitrogen. The resulting mixture was stirred at r.t. for 6 days. The reaction mixture was partitioned into ethyl acetate (100 mL) and H_2O (100 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow solid. The crude material was purified by flash chromatography (eluting solvent 20% ethyl acetate in petrol), affording **10** as a pale yellow solid m.pt. = 53 – 55 ^oC (lit.[55a] = 54 – 58 ^oC), 0.15 g, 6% yield, and **11** as a yellow oil, 0.13 g, 4% yield.

10; ^1H NMR (400 MHz, $CDCl_3$): δ 6.33 (1H, dd, *J* = 1.0, 10.0 Hz, Ar-*H*), 7.29 (1H, dd, *J* = 3.0, 10.0 Hz, Ar-*H*), 7.60 (1H, dd, *J* = 1.0, 3.0 Hz, Ar-*H*). The compound gave satisfactory spectroscopic data.[55a]

11; ^1H NMR (250 MHz, $CDCl_3$): δ 7.50 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.54 (1H, d, *J* = 2.5 Hz, Ar-*H*). The compound gave satisfactory spectroscopic data.[55a]

Synthesis of 4-chloro-2-pyrone 12[55b]



12

Dimethyl-1,3-acetonedicarboxylate (5.00 g, 29 mmol) was charged to a three necked round bottom flask under nitrogen. To this, PCl_5 (6.00 g, 29 mmol) was added portionwise. After addition was complete, the mixture was heated to 50 ^oC for 30 min. The resulting brown solution was poured onto ice, then partitioned into CH_2Cl_2 (200 mL) and H_2O (200 mL). The organic layer was separated, dried ($MgSO_4$) then concentrated *in vacuo*. To the resulting brown residue, 2 M HCl (30 mL) was added, and the resulting red oil heated at reflux for 2.5 h. After cooling, solvent was

removed *in vacuo*, and the residue dissolved in diethyl ether, then dried over anhydrous $CaCl_2$. The mixture was then filtered and concentrated *in vacuo*, affording an orange solid, 3.41 g, 72% yield, which was used without further purification.

To this solid (3.41 g, 21 mmol) was added PCl_5 (8.64 g, 42 mmol) at 0 ^oC under nitrogen. The solid mixture was then warmed to r.t. and stirred for 1 h, followed by heating to 100 ^oC for 15 min. The resulting red solution was extracted using CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated, filtered through Celite^{TM}, then neutralised to pH 7 using $NaHCO_3$. After filtration, volatiles were removed *in vacuo*, affording a black crystalline solid, 1.87 g, 55% yield, which was used without further purification.

The solid (1.87 g, 11 mmol) was dissolved in acetic acid (12 mL), then zinc powder (0.90 g, 14 mmol) was added under nitrogen. The resulting mixture was stirred at r.t. for 42 h, filtered and the residual acetic acid was removed *in vacuo*. The resulting residue was extracted using CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was dried ($MgSO_4$), filtered and solvent removed *in vacuo*, to afford compound **12** as a yellow solid m.pt. = 57 – 59 ^oC (lit.[55b] = 59 ^oC), 0.43 g, 29% yield.

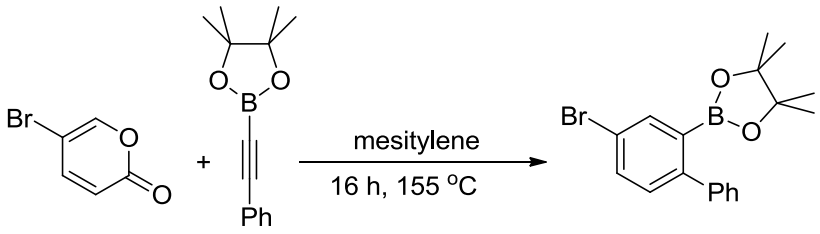
^1H NMR (250 MHz, $CDCl_3$): δ 6.29 (1H, dd, *J* = 2.0, 5.5 Hz, Ar-*H*), 6.39 (1H, dd, *J* = 1.0, 2.0 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 1.0, 5.5 Hz, Ar-*H*). The compound gave satisfactory spectroscopic data.[55b]

General Procedure 1: The cycloaddition of halo-2-pyrones with alkynyl boronic esters

A mixture of the 2-pyrone (0.2 mmol) and alkynylboronate (0.4 mmol) in mesitylene (0.2 mL) was heated at 155 ^oC and stirred for 16 h under nitrogen. The product was purified by flash column chromatography (starting with petroleum ether, ending with 10% ethyl acetate in petroleum ether).[a]

[a] The carbon attached to the boron is not visible in the ^{13}C NMR of any of the aromatic boronic esters formed, presumably due to the long relaxation time of this quaternary carbon.

Synthesis of 2-(4-bromobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 17a

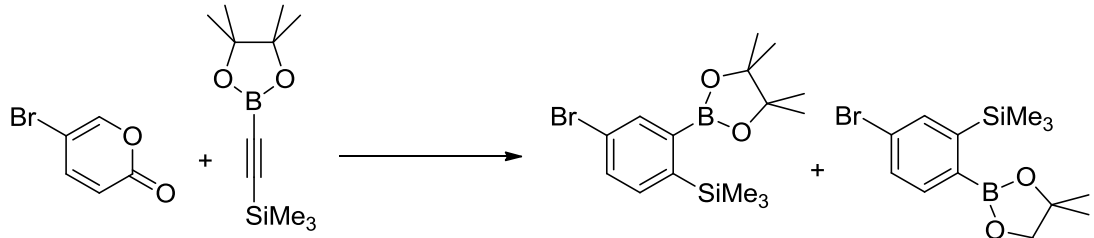


7 **15** **17a**

Using General Procedure 1, with 2-pyrone **7** (25 mg, 0.29 mmol), the product was isolated as a yellow oil, **17a**, 47 mg, 46% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (12H, s, C*H*$_3$), 7.26 (1H, d, *J* = 8.0, Ar-*H*), 7.37 – 7.39 (5H, m, Ar-*H*), 7.59 (1H, dd, *J* = 2.5, 8.0 Hz, Ar-*H*), 7.85 (1H, d, *J* = 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.6, 84.1, 121.1, 127.2, 127.9, 129.0, 130.8, 133.0, 137.0, 142.0, 146.4. FTIR (CH_2Cl_2, thin film): 2981 (w), 1459 (w) cm^{-1}. HRMS calculated for $C_{18}H_{20}{}^{11}B^{79}BrO_2$ (EI^+): 359.0652. Found: 359.0650.

Synthesis of (4-bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) trimethylsilane 18a and (5-bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)trimethylsilane 18b



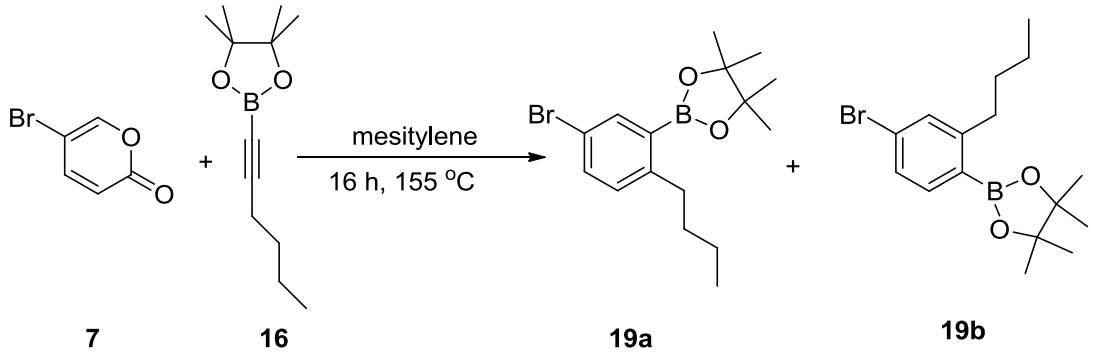
7 **14** **18a** **18b**

Using General Procedure 1, with 2-pyrone **7** (50 mg, 0.29 mmol), the product was isolated as an inseparable mixture of compounds **18a** and **18b** (3:2 ratio), as a clear oil, 82 mg, 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): **18 a or b**: δ 0.36 (9H, s, Si-C*H*$_3$), 1.38 (12H, s, C*H*$_3$), 7.49 – 7.51 (1H, m, Ar-*H*), 7.53 – 7.56 (1H, m, Ar-*H*), 8.06 (1H, d, *J* = 2.0 Hz, Ar-

H); **18 a or b**: δ 0.38 (9H, s, Si-C*H*$_3$), 1.38 (12H, s, C*H*$_3$), 7.46 – 7.48 (1H, m, Ar-*H*), 7.74 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.80 (1H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **18a and b:** δ 0.5 (x2), 25.0 (x2), 84.0, 84.2, 123.4, 125.9, 130.8, 132.6, 136.0, 137.0, 137.9, 138.7, 145.6, 150.3. FTIR (CH_2Cl_2, thin film): 2980 (s), 2977 (w), 1454 (w) cm^{-1}. HRMS calculated for $C_{15}H_{24}{}^{11}B^{79}BrO_2Si$ (EI^+): 355.1504. Found: 355.1507.

Synthesis of 2-(5-bromo-2-butyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 19a and 2-(4-bromo-2-butyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 19b

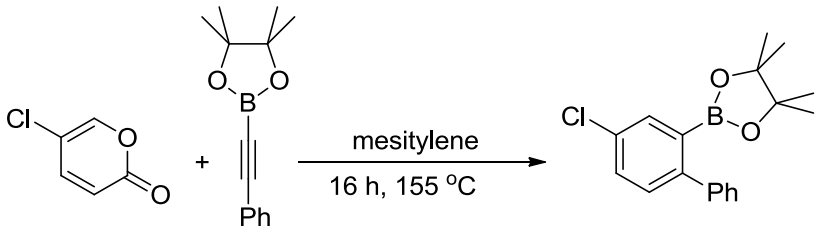


7 **16** **19a** **19b**

Using General Procedure 1, with 2-pyrone **7** (50 mg, 0.29 mmol), the product was isolated as an inseparable mixture of compounds **19a** and **19b** (3:2 ratio), as a brown oil, 43 mg, 44% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **19a**: δ 0.94 (3H, t, *J* = 7.0 Hz, C*H*$_3$); 1.23 – 1.60 (4H, m, C*H*$_2$), 1.36 (12H, s, C*H*$_3$), 2.80 – 2.88 (2H, m, C*H*$_2$), 7.05 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 8.0, 2.5 Hz, Ar-*H*), 7.88 (1H, d, *J* = 2.5 Hz, Ar-*H*); **19b**: δ 0.94 (3H, t, *J* = 7.0 Hz, C*H*$_3$); 1.23 – 1.60 (4H, m, C*H*$_2$), 1.35 (12H, s, C*H*$_3$), 2.80 – 2.88 (2H, m, C*H*$_2$), 7.28 – 7.34 (2H, m, Ar-*H*), 7.63 (1H, d, *J* = 8.0, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **19a and b**: δ 13.9, 22.7, 24.8, 34.9, 35.3, 35.4, 83.6, 83.7, 119.1, 125.6, 128.0, 131.0, 132.1, 133.5, 137.6, 138.4, 148.9, 152.4. FTIR (CH_2Cl_2, thin film): 2958 (s), 2871 (m), 1715 (m), 1584 (m), 1345 (s), 1145 (s), 865 (m) cm^{-1}. HRMS calculated for $C_{16}H_{24}{}^{11}B^{79}BrO_2$ (M^+): 338.1053. Found: 338.1066.

Synthesis of 2-(4-chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20a

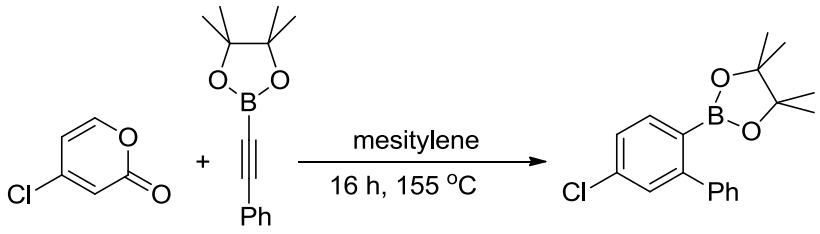


10 **15** **20a**

Using General Procedure 1, with 2-pyrone **10** (25 mg, 0.19 mmol), the product was isolated as a yellow oil, **20a**, 13 mg, 21% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (12H, s, C*H*$_3$), 7.26 (1H, d, *J* = 8.0, Ar-*H*), 7.37 – 7.39 (5H, m, Ar-*H*), 7.59 (1H, dd, *J* = 2.5, 8.0 Hz, Ar-*H*), 7.85 (1H, d, *J* = 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.6, 84.1, 121.1, 127.2, 127.9, 129.0, 130.8, 133.0, 137.0, 142.0, 146.4. FTIR (CH_2Cl_2, thin film): 2977 (s), 1544 (m), 1315 (s), 1141 (s) cm^{-1}. HRMS calculated for $C_{18}H_{20}{}^{11}B^{35}ClO_2$ (EI^+): 314.1245. Found: 314.1238.

Synthesis of 2-(3-chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20b



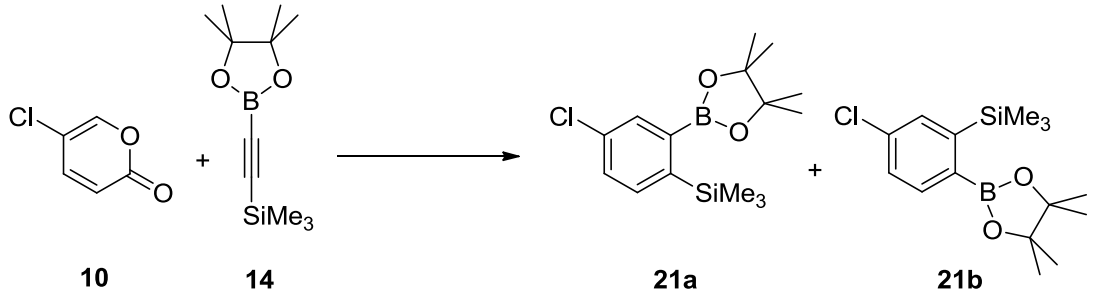
12 **15** **20b**

Using General Procedure 1, with 2-pyrone **12** (25 mg, 0.19 mmol), the product was isolated as a yellow oil, **20b**, 15 mg, 25% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (12H, s, C*H*$_3$), 7.30 – 7.45 (7H, m, Ar-*H*), 7.67 (1H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.6, 83.9, 126.4, 127.2, 127.4, 127.9, 129.0, 129.1, 130.0, 134.2, 135.9. FTIR (CH_2Cl_2, thin film): 2977 (s),

1544 (m), 1315 (s), 1141 (s) cm^{-1}. HRMS calculated for $C_{18}H_{20}{}^{11}B^{35}ClO_2$ (EI^+): 314.1245. Found: 314.1238.

Synthesis of (4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) trimethylsilane 21a and (5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)trimethylsilane 21b

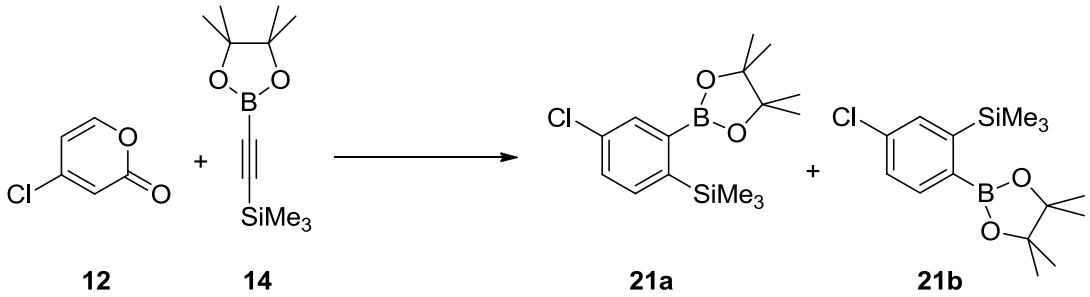


10 **14** **21a** **21b**

Using General Procedure 1, with 2-pyrone **10** (25 mg, 0.19 mmol), the product was isolated as an inseparable mixture of compounds **21a** and **21b** (4:3 ratio), as a clear oil, 41 mg, 70% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **21 a or b**: δ 0.35 (9H, s, Si-C*H*$_3$), 1.38 (12H, s, C*H*$_3$), 7.38 (1H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.55 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.89 (1H, d, *J* = 2.0 Hz, Ar-*H*); **21 a or b**: δ 0.37 (6.75H, s, Si-C*H*$_3$), 1.38 (9H, s, C*H*$_3$), 7.34 (0.75H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.57 (0.75H, d, *J* = 2.0 Hz, Ar-*H*), 7.87 (0.75H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **21a and b**: δ 0.0, 0.1, 24.6 (x2), 83.6, 86.9, 127.4, 129.2, 130.7, 132.3, 133.8, 135.0, 135.4, 135.5, 136.3, 137.3. FTIR (CH_2Cl_2, thin film): 2980 (s), 1570 (m), 1388 (s), 1340 (s), 1145 (s), 845 (s) cm^{-1}. HRMS calculated for $C_{15}H_{24}{}^{11}B^{35}ClO_2Si$ (EI^+): 310.1327. Found: 310.1335.

Synthesis of (4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) trimethylsilane 21a and (5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)trimethylsilane 21b

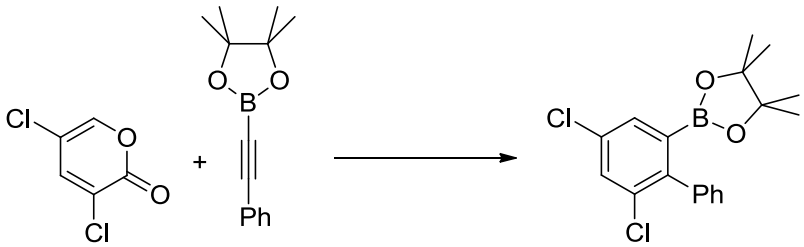


12 **14** **21a** **21b**

Using General Procedure 1, with 2-pyrone **12** (25 mg, 0.19 mmol), the product was isolated as an inseparable mixture of compounds **21a** and **21b** (5:3 ratio), as a clear oil, 40 mg, 70% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **21 a or b**: δ 0.35 (5.4H, s, Si-CH_3), 1.38 (7.2H, s, CH_3), 7.38 (0.6H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.55 (0.6H, d, *J* = 8.0 Hz, Ar-*H*), 7.89 (0.6H, d, *J* = 2.0 Hz, Ar-*H*); **21 a or b**: δ 0.37 (9H, s, Si-CH_3), 1.38 (12H, s, CH_3), 7.34 (1H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.57 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.87 (1H, d, *J* = 8.0 Hz, Ar-*H*). The mixture provided the same ^{13}C NMR, IR and HRMS data as for the compounds above.

Synthesis of 2-(2,4-dichlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane 22a

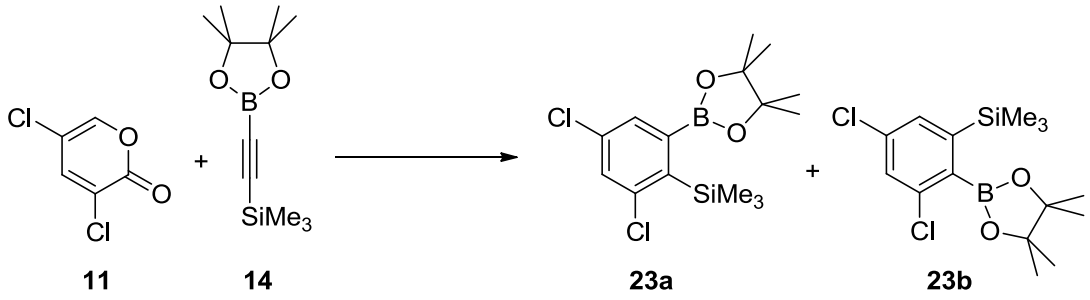


11 **15** **22a**

Using General Procedure 1, with 2-pyrone **11** (25 mg, 0.15 mmol), the product was isolated as a yellow oil, **22a**, 17 mg, 32% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **22a** δ 1.10 (12H, s, C*H*$_3$), 7.24 – 7.28 (2H, m, Ar-*H*), 7.36 – 7.42 (3H, m, Ar-*H*), 7.53 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.56 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **22a**: δ 24.5, 84.1, 127.5, 127.6, 129.7, 130.7, 132.0, 132.9, 133.3, 134.0, 139.2. FTIR (CH_2Cl_2, thin film): 2979 (s), 1547 (m), 1328 (s), 1144 (s) cm^{-1}. HRMS calculated for $C_{18}H_{19}{}^{11}B^{35}Cl_2O_2$ (EI^+): 348.0855. Found: 348.0869.

Synthesis of 2-(2,4-dichloro-6-trimethylsilanyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane 23a and 2-(3,5-dichloro-2-trimethylsilanyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane 23b

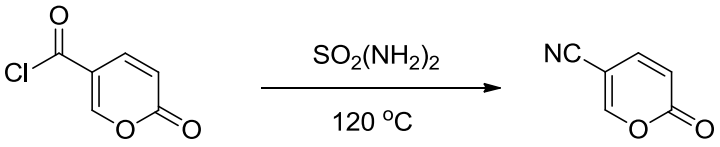


11 **14** **23a** **23b**

Using General Procedure 1, with 2-pyrone **11** (25 mg, 0.15 mmol), the product was isolated as an inseparable mixture of compounds **23a** and **23b** (1:1 ratio), as a clear oil, 37 mg, 71% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **23a and b**: δ 0.36 (9H, s, Si-C*H*$_3$), 0.43 (9H, s, Si-C*H*$_3$), 1.39 (12H, s, C*H*$_3$), 1.45 (12H, s, C*H*$_3$), 7.34 – 7.44 (4H, m, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **23a and b**: δ 0.0, 1.7, 25.3, 25.8, 84.6, 84.9, 113.2, 115.6, 119.1, 128.7, 130.3, 131.9 (x2), 135.0, 135.3, 138.7. FTIR (CH_2Cl_2, thin film): 2981 (s), 1562 (m), 1318 (s), 1142 (s), 1050 (m), 846 (s) cm^{-1}. HRMS calculated for $C_{15}H_{23}{}^{11}B^{35}Cl_2O_2Si$ (EI^+): 344.0937. Found: 344.0932.

Synthesis of 5-cyano-2-pyrone 25[57]

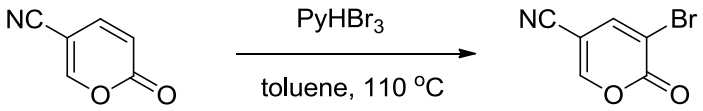


24 **25**

Sulfamide (1.09 g, 11 mmol) was added to 2-pyrone **24** (1.50 g, 9 mmol) under nitrogen. The solid mixture was heated to 120 °C, at which temperature gas was evolved and a brown solution formed. After stirring at this temperature for 1 h, a brown solid formed. After cooling to r.t., the residue was dissolved in CH_2Cl_2 (50 mL), then extracted from $NaHCO_{3(aq.)}$ (50 mL), then brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, then concentrated *in vacuo*, to afford compound **25** as a pale orange solid m.pt. = 97 – 98 °C (lit.[57a] = 98 – 99 °C), 0.30 g, 28% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.45 (1H, dd, *J* = 1.0, 10.0 Hz, Ar-*H*), 7.37 (1H, dd, *J* = 2.5, 10.0 Hz, Ar-*H*), 8.07 (1H, dd, *J* = 1.0, 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 113.5, 117.3, 140.7, 157.2, 160.0, 167.1. The compound gave satisfactory spectroscopic data.[133]

Synthesis of 2-bromo-5-cyano-2-pyrone 26[57]



25 **26**

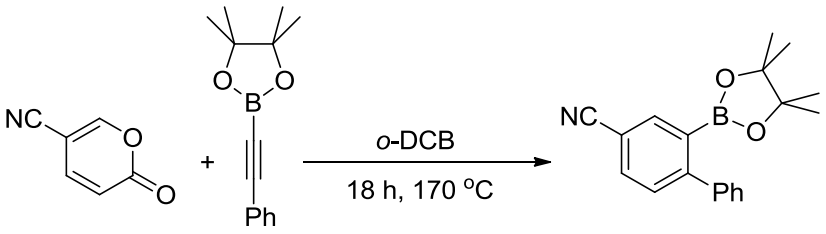
To a solution of **25** (0.25 g, 2.1 mmol) in toluene (5 mL) and DME (2 mL) was added $PyHBr_3$ (0.66 g, 2.1 mmol) under nitrogen. The mixture was heated at 110 °C for 4 h. The resulting dark orange solution was poured onto H_2O (50 mL), then extracted with CH_2Cl_2 (50 mL). The organic layer was dried ($MgSO_4$), filtered, then concentrated *in vacuo*. The crude material was purified via flash silica chromatography (eluting solvent 20% ethyl acetate in petrol), affording **26** as an orange oil, 0.16 g, 38% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.06 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 112.2, 113.4, 131.1, 141.2, 158.1, 167.2. The compound gave satisfactory spectroscopic data.[57]

General Procedure 2: The cycloaddition of nitrile-2-pyrones with alkynylboronic esters

A mixture of the 2-pyrone (0.2 mmol) and the alkynylboronate (0.4 mmol) in *o*-dichlorobenzene (0.2 mL) was heated at 175 °C and stirred for 18 h under nitrogen. The product was purified by flash column chromatography (starting with petroleum ether, ending with 10% ethyl acetate in petroleum ether).[b]

Synthesis of 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 27a



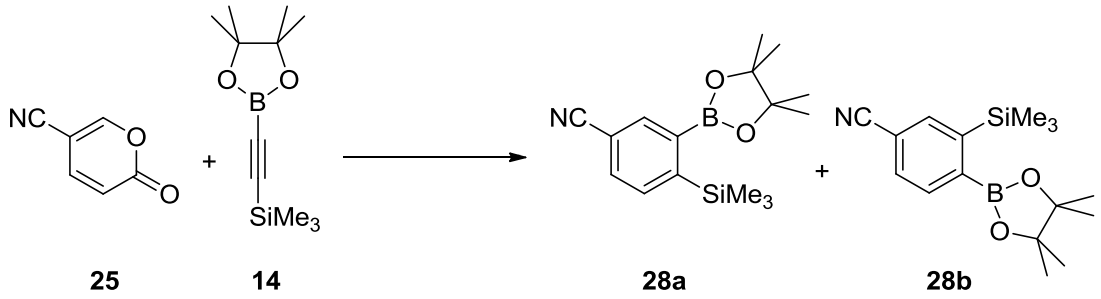
25 **15** **27a**

Using General Procedure 2, with 2-pyrone **25** (25 mg, 0.207 mmol), the product was isolated as a clear oil, **27a**, 48 mg, 76% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (12H, s, C*H*$_3$), 7.36 – 7.44 (5H, m, Ar-*H*), 7.49 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.74 (1H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 8.02 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): 24.6, 84.5, 109.9, 119.0, 128.0, 128.1, 128.9, 129.6, 133.4, 138.3, 141.4, 151.9. FTIR (CH_2Cl_2, thin film): 2979 (m), 2228 (m), 1598 (m), 1346 (s) cm^{-1}. HRMS calculated for $C_{19}H_{20}{}^{11}BNO_2$ (ES^+): 306.1665. Found: 306.1664.

[b] The carbon attached to boron is not visible in the ^{13}C NMR of any of the aromatic boronic esters formed, presumably due to the long relaxation time of this quaternary carbon.

Synthesis of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-4-trimethylsilanyl-benzonitrile 28a and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trimethylsilanyl-benzonitrile 28b

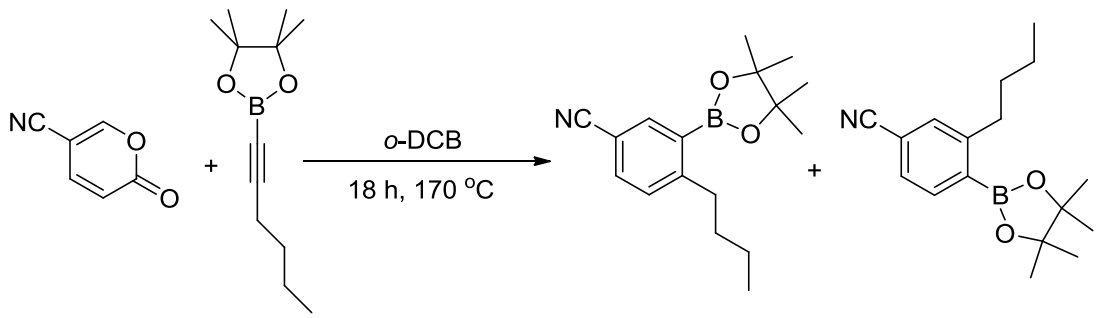


25 **14** **28a** **28b**

Using General Procedure 2, with 2-pyrone **25** (25 mg, 0.21 mmol), the product was isolated as an inseparable mixture of compounds **28a** and **28b** (1:1 ratio), as a clear oil, 62 mg, 99% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **28a and b**: δ 0.37 (18H, s, Si-C*H*$_3$), 1.38 (24H, s, C*H*$_3$), 7.60 – 7.73 (3H, m, Ar-*H*), 7.85 (1H, d, *J* = 1.0 Hz, Ar-*H*), 7.98 (1H, d, *J* = 7.5 Hz, Ar-*H*), 8.17 (1H, d, *J* = 1.0 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **28a and b**: δ 0.0, 0.1, 24.7 (x2), 84.3 (x2), 111.6, 113.1, 118.8, 119.1, 130.6, 132.1, 134.3, 135.8, 137.0, 138.7, 148.4, 153.4. FTIR (CH_2Cl_2, thin film): 2980 (s), 2229 (s), 1342 (s), 1143 (s) cm^{-1}. HRMS calculated for $C_{16}H_{24}{}^{11}BNO_2Si$ (EI^+): 302.1748. Found: 302.1735.

Synthesis of 4-Butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile 29a and 3-Butyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile 29b

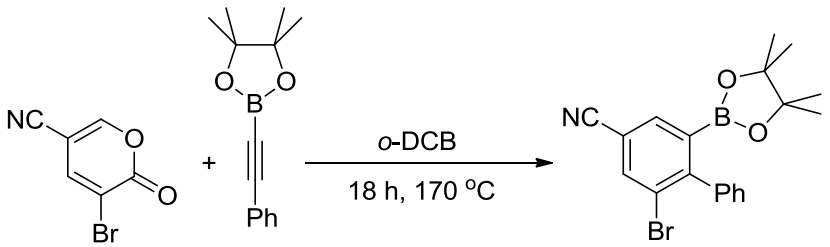


25 **16** **29a** **29b**

Using General Procedure 2, with 2-pyrone **25** (25 mg, 0.21 mmol), the product was isolated as an inseparable mixture of compounds **29a** and **29b** (5:1 ratio), as a yellow oil, 32 mg, 53% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **29 a or b**: δ 0.94 (3H, t, *J* = 7.0 Hz, C*H*$_3$); 1.23 – 1.60 (4H, m, C*H*$_2$), 1.36 (12H, s, C*H*$_3$), 2.80 – 2.88 (2H, m, C*H*$_2$), 7.05 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 8.0, 2.5 Hz, Ar-*H*), 7.88 (1H, d, *J* = 2.5 Hz, Ar-*H*); **29 a or b**: δ 0.94 (3H, t, *J* = 7.0 Hz, C*H*$_3$); δ 1.23 – 1.60 (4H, m, C*H*$_2$), 1.35 (12H, s, C*H*$_3$), 2.80 – 2.88 (2H, m, C*H*$_2$), 7.28 – 7.34 (2H, m, Ar-*H*), 7.63 (1H, d, *J* = 8.0, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **29a and b**: δ 13.9, 22.7, 24.8, 34.9, 35.3, 35.4, 83.6, 83.7, 119.1, 125.6, 128.0, 131.0, 132.1, 133.5, 137.6, 138.4, 148.9, 152.4. FTIR (CH_2Cl_2, thin film): 2958 (s), 2228 (w), 1715 (m), 1584 (m), 1345 (s), 1145 (s) cm^{-1}. HRMS calculated for $C_{16}H_{24}{}^{11}B^{79}BrO_2$ (M^+): 338.1053. Found: 338.1066.

Synthesis of 2-Bromo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 30a

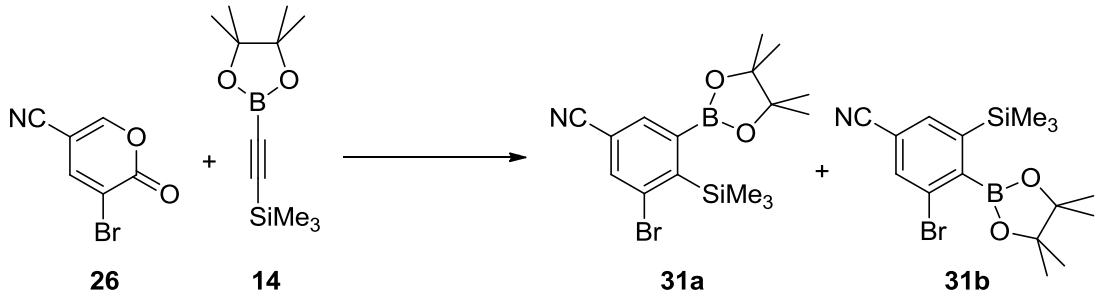


26 **15** **30a**

Using General Procedure 2, with 2-pyrone **26** (25 mg, 0.13 mmol), the product was isolated as a yellow oil, **30a**, 45 mg, 94% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (12H, s, C*H*$_3$), 7.19 – 7.26 (2H, m, Ar-*H*), 7.39 – 7.45 (3H, m, Ar-*H*), 7.91 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.99 (1H, d, *J* = 1.5 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.5, 84.5, 112.4, 117.4, 124.3, 127.7, 128.1, 129.1, 136.2, 137.0, 140.6, 151.9. FTIR (CH_2Cl_2, thin film): 2979 (s), 2229 (w), 1590 (m), 1339 (s), 1142 (s), cm^{-1}. HRMS calculated for $C_{19}H_{19}{}^{11}B^{79}BrNO_2$ (EI^+): 383.0692. Found: 383.0680.

Synthesis of 3-bromo-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-4-trimethylsilanyl-benzonitrile 31a and 3-bromo-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trimethylsilanyl-benzonitrile 31b

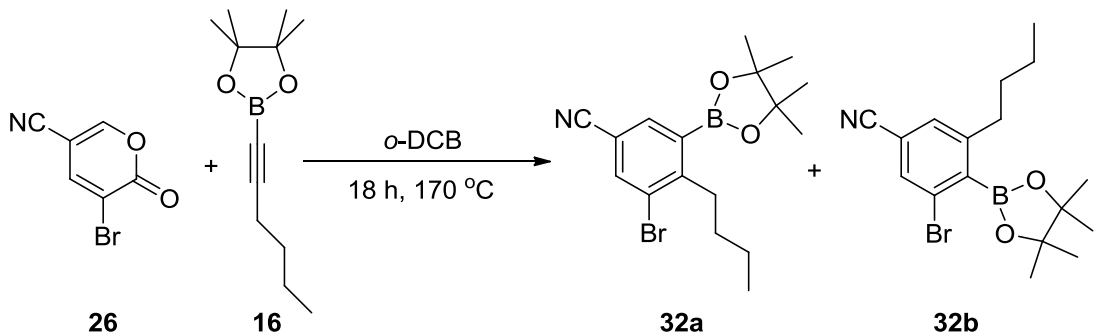


26 **14** **31a** **31b**

Using General Procedure 2, with 2-pyrone **26** (25 mg, 0.13 mmol), the product was isolated as an inseparable mixture of compounds **31a** and **31b** (1:1 ratio), as a clear oil, 46 mg, 96% yield.

^{1}H NMR (250 MHz, $CDCl_3$): **31a and b**: δ 0.38 (9H, s, Si-CH_3), 0.48 (9H, s, Si-CH_3), 1.39 (12H, s, CH_3), 1.48 (12H, s, CH_3), 7.71 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.75 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.77 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.81 (1H, d, *J* = 1.5 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **31a and b**: δ 0.0, 1.9, 25.5, 26.1, 85.1, 85.6, 113.5, 113.8, 117.6, 117.9, 127.9, 131.3, 131.5, 134.8, 135.2, 135.3, 136.5, 149.0. FTIR (CH_2Cl_2, thin film): 2981 (s), 2232 (m), 1332 (s), 1140 (s), 1048 (m), 847 (s) cm^{-1}. HRMS calculated for $C_{16}H_{23}{}^{11}B^{79}BrNO_2Si$ (EI^+): 379.0774. Found: 379.0777.

Synthesis of 3-Bromo-4-butyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile 32a and 3-Bromo-5-butyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile 32b



26 **16** **32a** **32b**

Using General Procedure 2, with 2-pyrone **26** (25 mg, 0.13 mmol), the product was isolated as an inseparable mixture of compounds **32a** and **32b** (11:1 ratio), as a yellow oil, 31 mg, 65% yield.

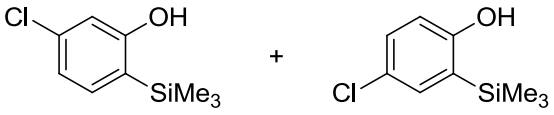
^{1}H NMR (250 MHz, $CDCl_3$): **32a and b**: δ 0.97 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 1.26 (1.1H, s, CH_3), 1.37 (12H, s, CH_3), 1.45 – 1.49 (4H, m, $CH_2CH_2CH_3$), 7.87 (1H, d, *J* = 1.5 Hz, Ar-*H*), 8.00 (1H, d, *J* = 1.5 Hz, Ar-*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): **32a and b**: δ 13.8, 22.9, 24.8, 33.1, 35.2, 84.4, 110.6, 117.5, 125.5, 137.8, 138.6, 154.2. FTIR (CH_2Cl_2, thin film): 2977 (s), 2232 (m), 1337 (s), 1140 (s), 849 (s) cm^{-1}. HRMS calculated for $C_{17}H_{23}{}^{11}B^{79}BrNO_2$ (EI^+): 363.1005. Found: 363.1003.

4.2 2-Pyrone Cycloadditions as a Route to Benzyne Precursors

General Procedure 3: The oxidation of aromatic boronic esters[95]

To a mixture of the aromatic boronic ester (0.2 mmol) dissolved in ethanol (8 mL), was added Na_2CO_3 (0.2 mmol). To this mixture 30% w/v H_2O_2 (2 mL) was added dropwise. The reaction was stirred at r.t.. Upon completion of reaction, 20 mL H_2O was added, and the product extracted from DCM (3 x 20 mL). The organic layers were combined and dried over $MgSO_4$, then concentrated *in vacuo*. The product was purified by flash column chromatography (eluting solvent 10 % ethyl acetate in petroleum ether).

Synthesis of 5-chloro-2-trimethylsilanyl-phenol 33a and 4-chloro-2-trimethylsilanyl-phenol 33b

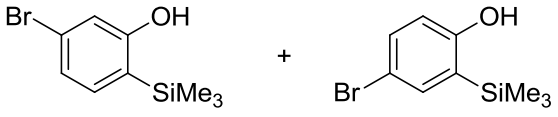


33a **33b**

Using General Procedure 3, with **21a,b** (63 mg, 0.20 mmol), the product was isolated as an inseparable mixture of compounds **33a** and **33b** (5:3 ratio) as a clear oil, 30 mg, 75 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): **33a and b**: δ 0.32 (5.4H, s, Si-C*H*$_3$), 0.33 (9H, s, Si-C*H*$_3$), 4.87 (1H, br s, O*H*), 4.98 (0.6H, br s, O*H*), 6.63 (1H, d, *J* = 8.5 Hz, Ar-*H*), 6.72 (0.6H, d, *J* = 2.0 Hz, Ar-*H*), 6.94 (0.6H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.19 (1H, dd, *J* = 2.5, 8.5 Hz, Ar-*H*), 7.28 – 7.30 (1.6H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **33a and b**: -0.7, -0.6, 115.2, 116.3, 121.2, 124.4, 126.1, 128.5, 130.6, 135.2, 136.3, 136.6, 159.1, 161.3. FTIR (CH_2Cl_2, thin film): 3425 (br, s), 2956 (m), 1589 (m), 1381 (s) cm^{-1}. HRMS calculated for $C_9H_{14}{}^{35}ClOSi$ (ES^+): 200.0424. Found: 200.0428.

Synthesis of 5-bromo-2-trimethylsilanyl-phenol 34a and 4-bromo-2-trimethylsilanyl-phenol 34b

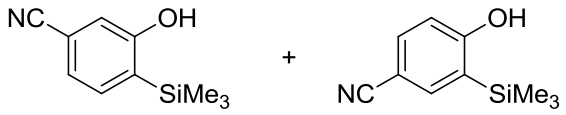


34a **34b**

Using General Procedure 3, with **18a,b** (130 mg, 0.37 mmol), the product was isolated as an inseparable mixture of compounds **34a** and **34b** (3:2 ratio) as a clear oil, 67 mg, 75 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **34a and b**: δ 0.33 (9H, s, Si-C*H*$_3$), 0.34 (6H, s, Si-C*H*$_3$), 5.01 (1H, br s, O*H*), 5.13 (0.67H, br s, O*H*), 6.59 (0.67H, d, *J* = 8.5 Hz, Ar-*H*), 6.88 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.10 (1H, dd, *J* = 1.5, 8.0 Hz, Ar-*H*), 7.24 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.34 (0.67H, dd, *J* = 2.0, 8.5 Hz, Ar-*H*), 7.45 (0.67H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **34a and b**: -0.7, -0.6, 113.8, 116.9, 118.1, 124.1, 124.4, 125.0, 129.3, 133.6, 136.9, 138.1, 160.0, 161.4. FTIR (CH_2Cl_2, thin film): 3347 (br, s), 2956 (m), 2232 (s), 1588 (s) cm^{-1}. HRMS calculated for $C_9H_{13}{}^{79}BrOSi$ (EI^+): 243.9919. Found: 243.9925.

Synthesis of 3-hydroxy-4-trimethylsilanyl-benzonitrile 35a and 4-hydroxy-3-trimethylsilanyl-benzonitrile 35b

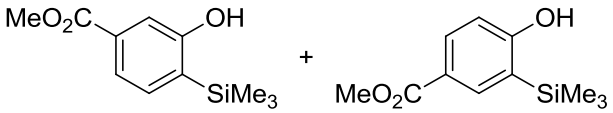


35a **35b**

Using General Procedure 3, with **28a,b** (49 mg, 0.16 mmol), the product was isolated as an inseparable mixture of compounds **35a** and **35b** (1:1 ratio) as a colourless solid, 11 mg, 71 % yield, m.pt. = 82 – 84 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): **35a and b**: δ 0.34 (18H, s, Si-C*H*$_3$), 5.34 (1H, br s, O*H*), 5.75 (1H, br s, O*H*), 7.00 (1H, d, *J* = 1.0 Hz, Ar-*H*), 7.24 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 7.46 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.48 (1H, dd, *J* = 2.0, 8.0 Hz, Ar-*H*), 7.74 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.80 (1H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **35a and b**: δ -1.3 (x2), 103.6, 113.3, 115.1, 116.9, 118.8, 119.7, 123.9, 127.9, 133.3, 134.9, 136.1, 139.9, 160.6, 164.1. FTIR (CH_2Cl_2, thin film): 3347 (br, s), 2956 (m), 2232 (s), 1588 (s) cm^{-1}. HRMS calculated for $C_{10}H_{13}NOSi$ (MH^+): 192.0845. Found: 192.0846.

Synthesis of 3-hydroxy-4-trimethylsilanyl-benzoic acid methyl ester 36a and 4-hydroxy-3-trimethylsilanyl-benzoic acid methyl ester 36b



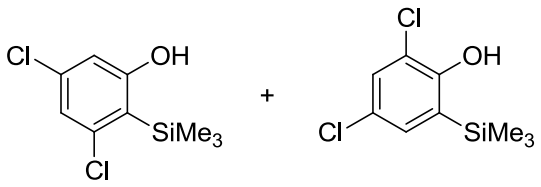
36a **36b**

Using General Procedure 3, (385 mg, 1.15 mmol), the product was isolated as an inseparable mixture of compounds **36a** and **36b** (3:2 ratio) as a clear oil, 180 mg, 70 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **36a and b**: δ 0.35 (15H, s, Si-C*H*$_3$), 3.92 (2H, s, C*H*$_3$), 3.94 (3H, s, C*H*$_3$), 5.60 (1H, br s, O*H*), 5.77 (0.67H, br s, O*H*), 6.74 (0.67H, d, *J* = 8.5 Hz, Ar-*H*), 7.44 – 7.46 (2H, m, Ar-*H*), 7.59 (1H, dd, *J* = 1.5, 7.5 Hz, Ar-*H*), 7.96 (0.67H, dd, *J* = 2.0, 8.5 Hz, Ar-*H*), 8.09 (0.67H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR

(100.6 MHz, $CDCl_3$): **36a and b**: δ -1.1, -1.2, 51.9, 52.3, 114.3, 114.9, 121.3, 122.3, 125.7, 132.1 (x2), 132.9, 135.4, 137.6, 160.6, 164.5, 167.3, 167.4. FTIR (CH_2Cl_2, thin film): 3375 (br, s), 2957 (m), 1687 (s), 1593 (m), 1395 (s) cm^{-1}. HRMS calculated for $C_{11}H_{16}O_3Si$ (MH^+): 225.0947. Found: 225.0948.

Synthesis of 3,5-dichloro-2-trimethylsilanyl-phenol 37a and 2,4-dichloro-6-trimethylsilanyl-phenol 37b

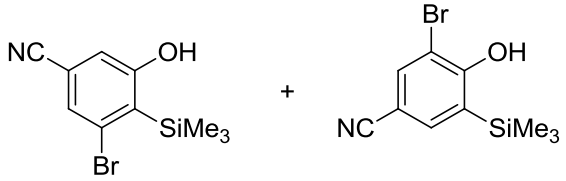


37a **37b**

Using General Procedure 3, with **23a,b** (123 mg, 0.36 mmol), the product was isolated as an inseparable mixture of compounds **37a** and **37b** (1:1 ratio) as a clear oil, 56 mg, 95 % yield.

^1H NMR (250 MHz, $CDCl_3$): **37a and b**: δ 0.33 (9H, s, Si-C*H*$_3$), 0.46 (9H, s, Si-C*H*$_3$), 4.70 – 6.23 (2H, br, O*H*), 6.65 (1H, d, *J* = 2.0 Hz, Ar-*H*), 6.96 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.20 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.34 (1H, d, *J* = 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **37a and b**: -1.3, 1.7, 114.2, 119.9, 121.9, 122.4, 125.4, 129.0, 129.1, 133.4, 136.0, 142.1, 153.9, 161.8. FTIR (CH_2Cl_2, thin film): 3415 (br, s), 2959 (s), 1698 (s), 1577 (s) cm^{-1}. HRMS calculated for $C_9H_{12}{}^{35}Cl_2OSi$ (EI^+): 234.0034. Found: 234.0024.

Synthesis of 3-bromo-5-hydroxy-4-trimethylsilanyl-benzonitrile 38a and 3-bromo-4-hydroxy-5-trimethylsilanyl-benzonitrile 38b

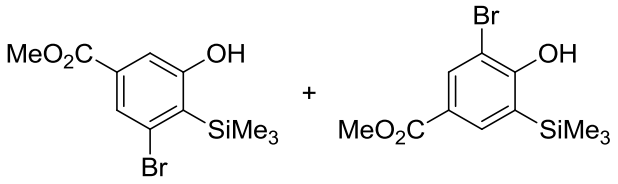


38a **38b**

Using General Procedure 3, with **31a,b** (43 mg, 0.14 mmol), the product was isolated as an inseparable mixture of compounds **38a** and **38b** (3:2 ratio) as a clear oil, 26 mg, 84 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **38a and b**: δ 0.34 (9H, s, Si-C*H*$_3$), 0.50 (6H, s, Si-C*H*$_3$), 6.21 (0.67H, br s, O*H*), 6.24 (1H, br s, O*H*), 6.96 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.40 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.59 (0.67H, d, *J* = 2.0 Hz, Ar-*H*), 7.80 (0.67H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **38a and b**: -1.1, 2.3, 105.7, 110.9, 114.8, 117.2, 117.6, 118.5, 128.9, 129.4, 131.6, 133.4, 136.9, 139.2, 160.1, 162.2. FTIR (CH_2Cl_2, thin film): 3354 (br s), 2925 (s), 2232 (m), 1580 (m), 1249 (s) cm^{-1}. HRMS calculated for $C_{10}H_{11}{}^{79}BrNOSi$ (M^-): 267.9793. Found: 267.9793.

Synthesis of 3-bromo-5-hydroxy-4-trimethylsilanyl-benzoic acid methyl ester 39a and 3-bromo-4-hydroxy-5-trimethylsilanyl-benzoic acid methyl ester 39b



39a **39b**

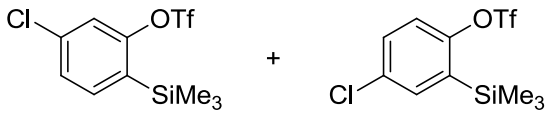
Using General Procedure 3, (201 mg, 0.49 mmol), the product was isolated as an inseparable mixture of compounds **39a** and **39b** (3:2 ratio) as a colourless solid, 119 mg, 81 % yield, m.pt. = 97 – 99 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): **39a and b**: δ 0.35 (9H, s, Si-C*H*$_3$), 0.50 (6H, s, Si-C*H*$_3$), 3.91 (2H, s, C*H*$_3$), 3.92 (3H, s, C*H*$_3$), 6.22 (1H, br s, O*H*), 6.85 (0.67H, br s, O*H*), 7.45 (0.67H, d, *J* = 1.5 Hz, Ar-*H*), 7.74 (0.67H, d, *J* = 1.5 Hz, Ar-*H*). 8.00 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.19 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **39a and b**: δ -0.9, -0.3, 52.6, 52.8, 110.7, 123.2, 124.1, 127.4, 127.5, 131.8, 133.2, 133.8, 135.2, 136.4, 136.8, 140.7, 166.3, 166.6. FTIR (CH_2Cl_2, thin film): 3315 (br, s), 2951 (m), 1703 (s), 1687 (s), 1258 (s) cm^{-1}. HRMS calculated for $C_{11}H_{15}{}^{79}BrO_3Si$ (MH^+): 303.0052. Found: 303.0057.

General Procedure 4: The sulfonylation of *o*-trimethylsilyl phenols[96]

A mixture of the phenol (1.0 mmol) and $^{i}Pr_2NEt$ (2.0 mmol), dissolved in DCM (1 mL), was cooled to 0 ^{o}C and stirred for 10 mins. To this mixture Tf_2O (1.5 mmol) was added dropwise. The reaction was stirred at 0 ^{o}C for a further 10 mins, then left stirring overnight at r.t.. To the reaction was added Et_2O (approx. 20 mL), then this mixture washed successively with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic layers were then combined, dried with $MgSO_4$ and concentrated *in vacuo*. If necessary, products were purified by flash column chromatography (eluting solvent 10 % ethyl acetate in petroleum ether).

Synthesis of trifluoromethanesulfonic acid 5-chloro-2-trimethylsilanyl-phenyl ester 40a and trifluoromethanesulfonic acid 4-chloro-2-trimethylsilanyl-phenyl ester 40b

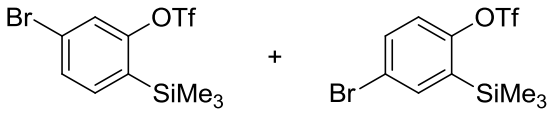


40a **40b**

Using General Procedure 4 with **33a,b** (30 mg, 0.10 mmol), the product was isolated as an inseparable mixture of compounds **40a** and **40b** (5:3 ratio) as a brown oil, 48 mg, 94 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **40a and b**: δ 0.37 (5.4H, s, *CH*$_3$), 0.39 (9H, s, *CH*$_3$), 7.24 – 7.52 (4.8H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **40a and b**: δ -1.0, -0.9, 118.4 (x2) (q, *J* = 320 Hz, *C*F_3), 120.2, 121.0, 127.9, 131.0, 131.1, 133.5, 135.3, 135.9, 136.6, 136.9, 153.1, 154.7. FTIR (CH_2Cl_2, thin film): 2928 (m), 1587 (s), 1424 (s), 1214 (s) cm^{-1}. HRMS calculated for $C_{10}H_{12}{}^{35}ClF_3O_3SSi$ (AP^+): 332.9992. Found: 332.9995.

Synthesis of trifluoromethanesulfonic acid 5-bromo-2-trimethylsilanyl-phenyl ester 41a and trifluoromethanesulfonic acid 4-bromo-2-trimethylsilanyl-phenyl ester 41b

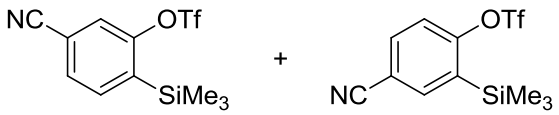


41a **41b**

Using General Procedure 4 with **34a,b** (67 mg, 0.27 mmol), the product was isolated as an inseparable mixture of compounds **41a** and **41b** (3:2 ratio) as a brown oil, 114 mg, 100 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **41a and b**: δ 0.38 (9H, s, C*H*$_3$), 0.40 (6H, s, C*H*$_3$), 7.24 (0.67H, d, *J* = 9.0 Hz, Ar-*H*), 7.42 – 7.44 (1H, m, Ar-*H*), 7.50 – 7.52 (2H, m, Ar-*H*), 7.57 (0.67H, dd, *J* = 2.5, 9.0 Hz, Ar-*H*), 7.63 (0.67H, d, *J* = 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **41a and b**: δ -0.6, -0.5, 118.8 (x2) (q, *J* = 320 Hz, *C*F_3), 121.8, 122.1, 123.4, 124.6, 131.2, 132.0, 134.4, 136.2, 137.6, 139.2, 154.1, 155.1. FTIR (CH_2Cl_2, thin film): 2960 (m), 1581 (s), 1424 (s), 1215 (s) cm^{-1}. HRMS calculated for $C_{10}H_{12}{}^{79}BrF_3O_3SSi$ (EI^+): 375.9412. Found: 375.9412.

Synthesis of trifluoromethanesulfonic acid 5-cyano-2-trimethylsilanyl-phenyl ester 42a and trifluoromethanesulfonic acid 4-cyano-2-trimethylsilanyl-phenyl ester 42b



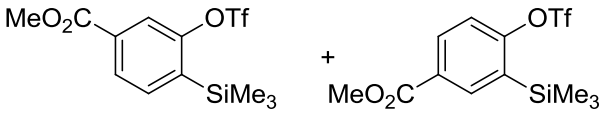
42a **42b**

Using General Procedure 4 with **35a,b** (200 mg, 1.05 mmol), the product was isolated as an inseparable mixture of compounds **42a** and **42b** (1:1 ratio) as a brown oil, 375 mg, 100 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **42a and b**: δ 0.41 (18H, s, *CH*$_3$), 7.50 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.64 – 7.66 (3H, m, Ar-*H*), 7.77 (1H, dd, *J* = 2.0, 8.5 Hz, Ar-*H*), 7.84

(1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **42a and b**: δ -0.72, -0.68, 114.8 (x2) (q, *J* = 478 Hz, *C*F_3), 115.3, 117.5, 118.1, 120.4, 120.6, 123.1, 131.1, 135.4, 135.5, 137.6, 140.3, 140.7, 154.7, 157.5. FTIR (CH_2Cl_2, thin film): 2924 (s), 2236 (s), 1426 (s), 1216 (s) cm^{-1}. HRMS calculated for $C_{11}H_{12}F_3NO_3SSi$ (AP^+): 324.0338. Found: 324.0329.

Synthesis of 3-trifluoromethanesulfonyloxy-4-trimethylsilanyl-benzoic acid methyl ester 43a and 4-trifluoromethanesulfonyloxy-3-trimethylsilanyl-benzoic acid methyl ester 43b

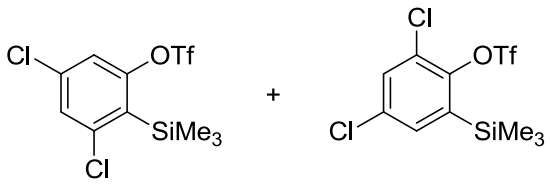


43a **43b**

Using General Procedure 4 with **36a,b** (120 mg, 0.54 mmol), the product was isolated as an inseparable mixture of compounds **43a** and **43b** (3:2 ratio) as a clear oil, 187 mg, 98 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **43a and b**: δ 0.41 (15H, s, *CH*$_3$), 3.95 (2H, s, *CH*$_3$), 3.96 (3H, s, *CH*$_3$) 7.44 (0.67H, d, *J* = 9.0 Hz, Ar-*H*), 7.64 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.96 – 7.98 (1H, m, Ar-*H*), 8.01 (1H, dd, *J* = 1.5, 7.5 Hz, Ar-*H*), 8.12 (0.67H, dd, *J* = 2.0, 9.0 Hz, Ar-*H*), 8.22 (0.67H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **43a and b**: δ -0.6 (x2), 52.9, 53.1, 118.9 (x2) (q, *J* = 320 Hz, *C*F_3), 119.7, 120.8, 128.6, 129.6, 133.2, 133.5, 133.7, 136.8, 138.2, 139.1, 155.2, 158.3, 165.8, 166.3. FTIR (CH_2Cl_2, thin film): 2958 (m), 1732 (s), 1602 (w), 1424 (s) cm^{-1}. HRMS calculated for $C_{12}H_{15}F_3O_5SSi$ (ES^+): 357.0440. Found: 357.0432.

Synthesis of trifluoromethanesulfonic acid 3,5-dichloro-2-trimethylsilanyl-phenyl ester 44a and trifluoromethanesulfonic acid 2,4-dichloro-6-trimethylsilanyl-phenyl ester 44b

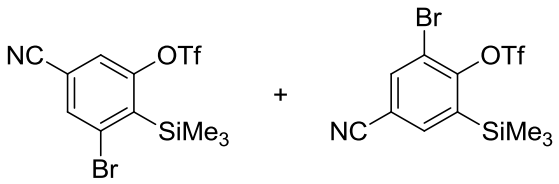


44a **44b**

Using General Procedure 4 with **37a,b** (21 mg, 0.09 mmol), the product was isolated as an inseparable mixture of compounds **44a** and **44b** (1:1 ratio) as a brown oil, 18 mg, 53 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **44 a or b**: δ 0.50 (9H, s, *C*H_3), 7.29 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.41 (1H, d, *J* = 2.0 Hz, Ar-*H*). **44 a or b**: δ 0.43 (9H, s, *C*H_3), 7.40 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.52 (1H, d, *J* = 2.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **44a and b:** δ 0.2, 1.7, 118.9 (q, *J* = 321 Hz, *C*F_3), 119.0 (q, *J* = 321 Hz, *C*F_3), 120.0, 128.9, 130.2, 130.9, 132.4, 134.8, 134.9, 136.8, 139.8, 143.3, 147.0, 154.6. FTIR (CH_2Cl_2, thin film): 2927 (s), 1732 (w), 1607 (m), 1416 (s) cm^{-1}. HRMS calculated for $C_{10}H_{11}Cl_2F_3O_3SSi$ (EI^+): 365.9527. Found: 365.9541.

Synthesis of trifluoromethanesulfonic acid 3-bromo-5-cyano-2-trimethylsilanyl-phenyl ester 45a and trifluoromethanesulfonic acid 2-bromo-4-cyano-6-trimethylsilanyl-phenyl ester 45b

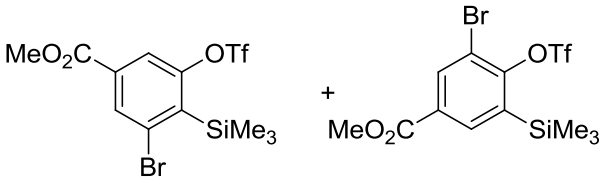


45a **45b**

Using General Procedure 4 with **38a,b** (248 mg, 0.92 mmol), the product was isolated as an inseparable mixture of compounds **45a** and **45b** (1:1 ratio) as a clear oil, 220 mg, 60 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **45a and b**: δ 0.44 (9H, s, *C*H_3), 0.55 (9H, s, *C*H_3), 7.58 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.80 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.87 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.98 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **45a and b**: δ 0.3, 1.8, 115.8, 116.0, 116.2 (q, *J* = 403 Hz, *C*F_3), 116.7, 118.9 (q, *J* = 321 Hz, *C*F_3), 123.0, 132.5, 136.3, 139.1, 139.8, 139.1, 139.8, 140.6, 141.7, 152.0, 154.2. FTIR (CH_2Cl_2, thin film): 2926 (m), 2237 (s), 1524 (m), 1414 (s) cm^{-1}. HRMS calculated for $C_{11}H_{11}BrF_3NO_3SSi$ (AP^+): 401.9443. Found: 401.9429.

Synthesis of 3-bromo-5-trifluoromethanesulfonyloxy-4-trimethylsilanyl-benzoic acid methyl ester 46a and 3-bromo-4-trifluoromethanesulfonyloxy-5-trimethylsilanyl-benzoic acid methyl ester 46b



46a **46b**

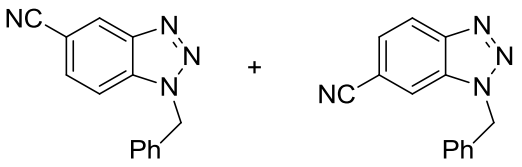
Using General Procedure 4 with **39a,b** (121 mg, 0.40 mmol), the product was isolated as an inseparable mixture of compounds **46a** and **46b** (3:2 ratio) as a clear oil, 132 mg, 76 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **46a and b**: δ 0.46 (9H, s, C*H*$_3$), 0.55 (6H, s, C*H*$_3$), 3.95 – 3.99 (5H, br s, C*H*$_3$), 7.90 (0.67H, d, *J* = 1.5 Hz, Ar-*H*), 8.18 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.23 (0.67H, d, *J* = 1.5 Hz, Ar-*H*), 8.34 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **46a and b**: δ -0.9, -0.3, 52.6, 52.8, 110.7, 115.6 (x2) (q, *J* = 320 Hz, *C*F_3), 123.2, 124.1, 127.5, 131.8, 133.2, 133.8, 135.2, 136.4, 136.8, 140.7, 160.2, 166.3, 166.6. FTIR (CH_2Cl_2, thin film): 2960 (m), 1732 (s), 1428 (s), 1214 (s) cm^{-1}. HRMS calculated for $C_{12}H_{14}{}^{79}BrF_3O_5SSi$ (AP^+): 434.9545. Found: 434.9541.

General Procedure 5: The cycloaddition of benzyne precursors with benzyl azide[75]

To a mixture of benzyne precursor (0.12 mmol) and benzyl azide (0.10 mmol), dissolved in MeCN (0.12 mL), was added CsF (0.2 mmol). The reaction was then left to stir at r.t. for 18 hrs. The mixture was poured onto sat. aq. $NaHCO_3$, and then extracted with DCM (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (eluting solvent 10 % ethyl acetate in petroleum ether).

Synthesis of 1-benzyl-1H-benzotriazole-5-carbonitrile 47a and 3-benzyl-3H-benzotriazole-5-carbonitrile 47b

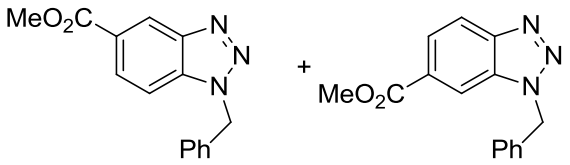


47a **47b**

Using General Procedure 5, with benzyne precursor **42a,b** (25 mg, 0.08 mmol), the product was isolated as an inseparable mixture of compounds **47a** and **47b** (2:1 ratio), as a brown solid, 10 mg, 65 % yield, m.pt.= 72 – 74 ^oC.

^1H NMR (250 MHz, $CDCl_3$): **47a and b**: δ 5.91 (2H, s, CH_2), 5.92 (1H, s, CH_2), 7.29 – 7.43 (7.5H, m, Ar-*H*), 7.47 (1H, dd, *J* = 0.5, 8.5 Hz), 7.57 (0.5H, dd, *J* = 1.5, 8.5 Hz, Ar-*H*), 7.63 (1H, dd, *J* = 1.5, 8.5 Hz, Ar-*H*), 7.74 (0.5H, s, Ar-*H*), 8.19 (0.5H, dd, *J* = 0.5, 8.5 Hz, Ar-*H*), 8.47 (1H, s, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **47a and b**: δ 52.8, 53.0, 107.9, 111.0, 111.4, 115.7, 118.4, 118.5, 121.6, 126.2, 126.4, 127.7 (x2), 129.0, 129.1, 129.3, 129.4, 129.7, 132.1, 133.6, 133.8, 134.4, 137.6, 145.5. FTIR (CH_2Cl_2, thin film): 3069 (m), 2229 (s), 1614 (w), 1456 (m), 1222 (m) cm^{-1}. HRMS calculated for $C_{14}H_{10}N_4$ (MH^+): 235.0984. Found: 235.0975.

Synthesis of 1-benzyl-1H-benzotriazole-5-carboxylic acid methyl ester 48a and 3-benzyl-3H-benzotriazole-5-carboxylic acid methyl ester 48b

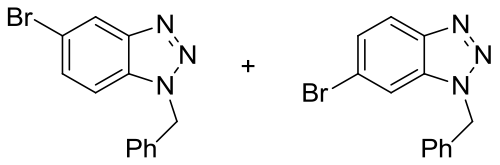


48a **48b**

Using General Procedure 5, with benzyne precursor **43a,b** (50 mg, 0.14 mmol), the product was isolated as an inseparable mixture of compounds **48a** and **48b** (1:1 ratio), as a brown solid, 21 mg, 67 % yield, m.pt.= 75 – 78 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): **48a and b**: δ 3.97 (3H, s, *CH*$_3$), 3.99 (3H, s, *CH*$_3$), 5.90 (2H, s, C*H*$_2$), 5.92 (2H, s, *CH*$_2$), 7.30 – 7.43 (11H, m, Ar-*H*), 8.05 (1H, dd, *J* = 1.5, 8.5 Hz, Ar-*H*), 8.10 – 8.15 (2H, m, Ar-*H*), 8.19 (1H, dd, *J* = 1.0, 1.5 Hz, Ar-*H*), 8.82 (1H, dd, *J* = 1.0, 1.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **48a and b**: δ 52.9 (x3), 53.0, 110.0, 112.7, 120.4, 123.4, 125.1, 126.8, 128.0 (x2), 128.7, 129.1, 129.6, 129.7, 133.0, 134.7, 134.8, 135.5, 146.5, 148.7, 149.1, 157.0, 166.9 (x2). FTIR (CH_2Cl_2, thin film): 2953 (m), 1722 (s), 1436 (s) cm^{-1}. HRMS calculated for $C_{15}H_{13}N_3O_2$ (M^+): 268.1086. Found: 268.1086.

Synthesis of 1-benzyl-5-bromo-1H-benzotriazole 49a and 1-benzyl-6-bromo-1H-benzotriazole 49b



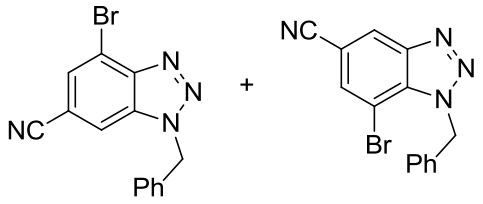
49a **49b**

Using General Procedure 5, with benzyne precursor **41a,b** (50 mg, 0.08 mmol), the product was isolated as an inseparable mixture of compounds **49a** and **49b** (2:1 ratio), as a brown solid, 23 mg, 70 % yield, m.pt.= 83 – 85 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): **49a and b**: δ 5.84 (0.67H, s, C*H*$_2$), 5.86 (1.33H, s, *CH*$_2$), 7.27 – 7.33 (1.65H, m, Ar-*H*), 7.34 – 7.43 (3.35H, m, Ar-*H*), 7.25 (0.67H, dd,

J = 0.5, 9.0 Hz, Ar-*H*), 7.47 (0.33H, dd, *J* = 1.5, 9.0 Hz, Ar-*H*), 7.51 (0.67H, dd, *J* = 1.5, 9.0 Hz, Ar-*H*), 7.57 (0.33H, dd, *J* = 0.5, 1.5 Hz, Ar-*H*), 7.96 (0.33H, dd, *J* = 0.5, 9.0 Hz, Ar-*H*), 8.25 (0.66H, dd, *J* = 0.5, 1.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **49a and b**: δ 52.8, 53.0, 111.5, 113.0, 117.7, 121.7, 122.2, 123.1, 126.4, 128.0, 128.2, 129.1, 129.5, 129.6, 131.2, 132.2, 134.3, 134.7, 141.2, 145.6, 148.0, 151.2. FTIR (CH_2Cl_2, thin film): 2923 (m), 1605 (m), 1474 (m), 1203 (s) cm^{-1}. HRMS calculated for $C_{13}H_{10}{}^{79}BrN_3$ (ES^+): 288.0136. Found: 288.0132.

Synthesis of 3-benzyl-7-bromo-3H-benzotriazole-5-carbonitrile 50a and 1-benzyl-7-bromo-1H-benzotriazole-5-carbonitrile 50b



50a **50b**

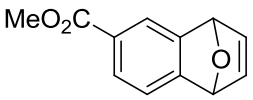
To a mixture of benzyne precursor **45a and b** (50 mg, 0.12 mmol) and benzyl azide (80 mg, 0.60 mmol), dissolved in MeCN (0.6 mL), was added CsF (91 mg, 0.60 mmol). The reaction was then left to stir at r.t. for 18 hrs. The mixture was then poured onto sat. aq. $NaHCO_3$, and then extracted from DCM (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (eluting solvent 10 % ethyl acetate in petroleum ether). The product was isolated as an inseparable mixture of compounds **50a** and **50b** (5:1 ratio), as a brown oil, 11 mg, 29 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **50a and b**: δ 5.92 (2H, s, C*H*$_2$), 6.23 (0.4H, s, C*H*$_2$), 7.08 – 7.46 (6H, m, Ar-*H*), 7.67 (1H, d, *J* = 1.0 Hz, Ar-*H*), 7.78 (1H, d, *J* = 1.0 Hz, Ar-*H*), 7.87 (0.2H, d, *J* = 1.0 Hz, Ar-*H*), 8.45 (0.2H, d, *J* = 1.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **50a and b**: δ 52.9, 53.6, 112.0, 112.7, 114.5, 114.8 (x2), 115.2, 117.1, 117.3, 117.9, 123.4, 123.9, 125.3, 126.8, 127.1, 127.7, 129.0, 129.1, 129.4, 129.5, 133.1, 133.3, 157.2. FTIR (CH_2Cl_2, thin film): 2924 (m), 2232 (m), 1569 (m), 1432 (m) cm^{-1}. HRMS calculated for $C_{14}H_9{}^{79}BrN_4$ (ES^+): 313.0078. Found: 313.0089.

General Procedure 6: The cycloaddition of benzyne precursors with furans

To a mixture of benzyne precursor (0.10 mmol) and furan (0.50 mmol), dissolved in MeCN (3 mL), was added CsF (0.30 mmol). The reaction was then left to stir at r.t. for 18 hrs. The mixture was then poured onto sat. aq. $NaHCO_3$, and then extracted from DCM (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (eluting solvent 10 % ethyl acetate in petroleum ether).

Synthesis of 11-Oxa-tricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6,9-tetraene-4-carboxylic acid methyl ester 51

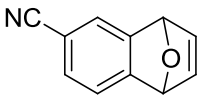


51

Using General Procedure 6, with benzyne precursor **43a,b** (25 mg, 0.07 mmol), the product **51** was isolated as a colourless solid, 10 mg, 68 % yield. The compound gave satisfactory spectroscopic data.[92]

^{1}H NMR (250 MHz, $CDCl_3$): δ 3.91 (3H, s, C*H*$_3$), 5.76 – 5.78 (2H, m, C*H*), 7.04 – 7.06 (2H, m, C*H*), 7.32 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.78 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.89 (1H, s, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): 52.5, 82.6 (x2), 120.4, 121.1, 127.7, 128.5, 142.8, 143.8, 150.0, 154.8, 167.4.

Synthesis of 11-Oxa-tricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6,9-tetraene-4-carbonitrile 52

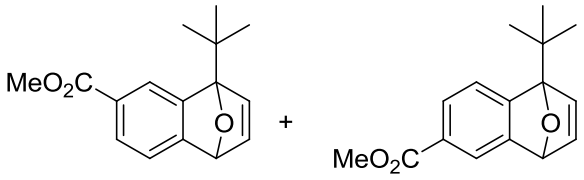


52

Using General Procedure 6, with benzyne precursor **42a,b** (50 mg, 0.16 mmol), the product **52** was isolated as a colourless solid, 17 mg, 66 % yield. The compound gave satisfactory spectroscopic data.[134]

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.78 – 5.80 (2H, m, C*H*), 7.05 – 7.07 (2H, m, C*H*), 7.35 – 7.37 (2H, m, Ar-*H*), 7.48 (1H, s, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 82.3, 82.6, 119.6, 121.1, 123.2, 131.4, 135.4, 140.9, 143.0, 143.5, 155.8.

Synthesis of 1-tert-Butyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene-4-carboxylic acid methyl ester 53a and 8-tert-Butyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene-4-carboxylic acid methyl ester 53b

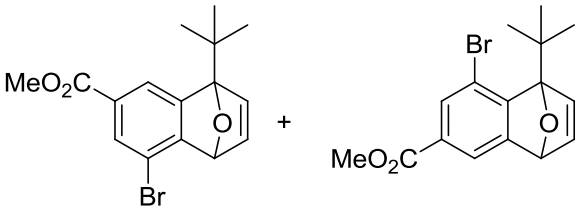


53a **53b**

Using General Procedure 6, with benzyne precursor **43a,b** (30 mg, 0.08 mmol), the product was isolated as an inseparable mixture of compounds **53a** and **53b** (1:1 ratio), 14 mg, 63 % yield.

^{1}H NMR (250 MHz, $CDCl_3$): **53a and b:** δ 1.29 (9H, s, CH_3), 1.33 (9H, s, CH_3), 3.90 (3H, s, CH_3) 3.91 (3H, s, CH_3), 5.68 – 5.69 (1H, m, C*H*), 5.70 – 5.71 (1H, m, C*H*), 6.93 – 7.08 (4H, m, C*H*), 7.26 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.45 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.73 – 7.75 (2H, m, Ar-*H*), 7.82 (1H, d, *J* = 1.0 Hz, Ar-*H*), 7.99 – 8.01 (1H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **53a and b**: δ 27.0 (x2), 32.9 (x2), 52.5 (x2), 81.6, 81.7, 100.1 (x2), 120.0, 120.6, 121.7, 122.4, 127.0, 127.1, 127.9, 128.0, 142.7, 143.6, 144.2, 145.2, 150.2, 153.1, 155.3, 158.0, 167.4, 167.5. FTIR (CH_2Cl_2, thin film): 2958 (m), 1720 (s), 1435 (s), 1258 (s) cm^{-1}. HRMS calculated for $C_{16}H_{18}O_3$ (ES^+): 259.1334. Found: 259.1337.

Synthesis of 1-*tert*-butyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene-6-bromo-4-carboxylic acid methyl ester 54a and 8-*tert*-butyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene-6-bromo-4-carboxylic acid methyl ester 54b

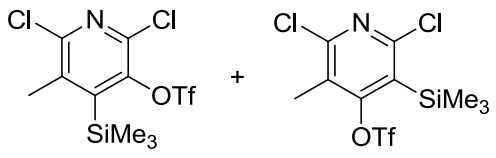


54a **54b**

Using General Procedure 6, with benzyne precursor **46a,b** (94 mg, 0.22 mmol), the products were isolated separately as yellow oils **54a**, 12 mg, 16% yield and **54b**, 3 mg, 4% yield, (overall 20% yield, 4:1 ratio).

^{1}H NMR (400 MHz, $CDCl_3$): **54a:** δ 1.41 (9H, s, CH_3), 3.91 (3H, s, CH_3), 5.67 (1H, d, *J* = 2.0 Hz, C*H*), 6.93 (1H, d, *J* = 5.5 Hz, C*H*), 7.03 (1H, dd, *J* = 2.0, 5.5 Hz, C*H*), 7.70 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.92 (1H, d, *J* = 1.5 Hz, Ar-*H*). **54b:** δ 1.30 (9H, s, CH_3), 3.92 (3H, s, CH_3), 5.77 (1H, d, *J* = 2.0 Hz, C*H*), 7.04 (1H, d, *J* = 5.5 Hz, C*H*), 7.08 (1H, dd, *J* = 2.0, 5.5 Hz, C*H*), 7.84 (1H, d, *J* = 1.5 Hz, Ar-*H*), 7.91 (1H, d, *J* = 1.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): **54a**: δ 27.9, 32.4, 52.3, 81.0, 103.2, 114.6, 118.5, 128.8, 134.1, 141.9, 144.5, 155.5, 156.0, 165.5. **54b**: 26.5, 32.6, 52.3, 81.8, 100.9, 113.8, 120.7, 128.9, 132.7, 143.1, 143.7, 152.4, 157.8, 165.8. FTIR (CH_2Cl_2, thin film): 2966 (w), 1719 (m), 1273 (m) cm^{-1}. HRMS calculated for $C_{16}H_{17}{}^{79}BrO_3$ (ES$^+$): 337.0439. Found: 337.0425.

Synthesis of 2,6-dichloro-5-methyl-4-(trimethylsilyl)-pyridin-3-yl trifluoromethanesulfonate 58a and 2,6-dichloro-3-methyl-5-(trimethylsilyl)-pyridin-4-yl trifluoromethanesulfonate 58b



58a **58b**

Using General Procedure 2, with oxazinone **55** (100 mg, 0.56 mmol), the product was isolated as an inseparable mixture of compounds **56a** and **56b** (1:4 ratio) as a clear oil, 146 mg, 73% yield.

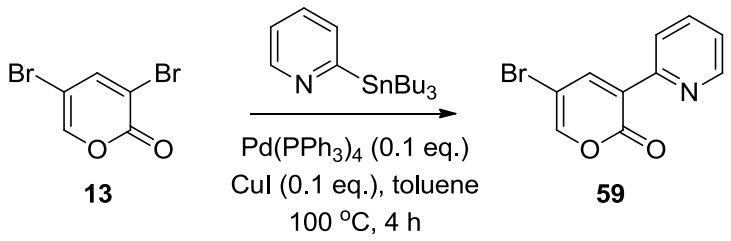
Using General Procedure 3, with **56a,b** (146 mg, 0.41 mmol), the product was isolated as an inseparable mixture of compounds **57a** and **57b** (1:4 ratio) as a clear oil, 87 mg, 86 % yield.

Using General Procedure 4, with **57a,b** (87 mg, 0.35 mmol), the product was isolated as an inseparable mixture of compounds **58a** and **58b** (1:4 ratio) as a clear oil, 107 mg, 81 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): **58a and b:** δ 0.52 (9H, s, SiCH_3), 2.37 (2.4H, s, CH_3), 2.52 (0.6H, s, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): **58a and b**: δ 0.6, 1.1, 14.1, 21.0, 118.5 (x2) (q, J = 321 Hz, CF_3), 126.2, 129.2, 138.5, 143.4, 150.3, 153.2, 154.4 (x2), 158.3 (x2). FTIR (CH_2Cl_2, thin film): 2982 (w), 2254 (m), 1224 (s) cm^{-1}. HRMS calculated for $C_{10}H_{12}Cl_2F_3NO_3SSi$ (ES^+): 381.9715. Found: 381.9728.

4.3 Directed Cycloadditions of 2-Pyrones

Synthesis of 5-bromo-3-(pyridin-2-yl)-2H-2-pyrone 59[122]



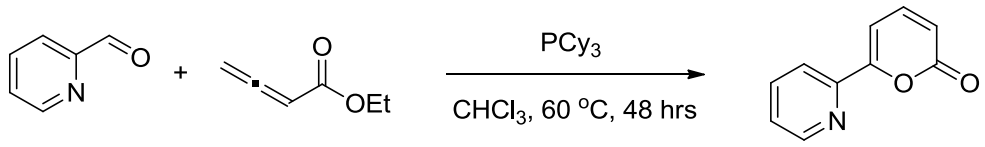
To a solution of **13** (310 mg, 1.33 mmol) in toluene (13 mL) was added 2-tri-*n*-butyltin-pyridine (588 mg, 1.60 mmol), $Pd(PPh_3)_4$ (154 mg, 0.13 mmol) and copper iodide (191 mg, 0.13 mmol) under nitrogen. The reaction mixture was heated to 100 ^{o}C for 4 h. After cooling to r.t., KF was added, and the mixture diluted with diethyl ether and filtered through Celite^{TM}. The filtrate was concentrated *in vacuo*, and the crude residue purified via flash silica chromatography (eluting solvent 10% ethyl acetate in petrol), affording **59** as a yellow solid, 180 mg, 54% yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (1H, ddd, *J* = 1.0, 5.0, 7.5 Hz, Ar-*H*), 7.69 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.79 (1H, td, *J* = 2.0, 7.5 Hz, Ar-*H*), 8.39 – 8.41 (1H, m, Ar-*H*), 8.52 (1H, d, *J* = 2.5 Hz, Ar-*H*), 8.67 (1H, ddd, *J* = 1.0, 2.0, 5.0 Hz, Ar-*H*). The compound gave satisfactory spectroscopic data. [122]

General Procedure 7: Synthesis of 6-aryl-2-pyrones[123]

Aryl carboxaldehyde (5.0 mmol) and tricyclohexyl phosphine (1.5 mmol) were dissolved in $CHCl_3$ (10 mL) in a sealable tube. To this mixture ethyl allenoate (1.0 mmol) was added dropwise, resulting in a deep red solution. Reaction was sealed, and then heated to 65 ^{o}C. After 48 hours, reaction was cooled to room temperature, then concentrated *in vacuo*. The dark brown residue obtained was purified via flash column chromatography (50% ethyl acetate in petrol).

Synthesis of 6-(pyridin-2-yl)-2H-2-pyrone 60

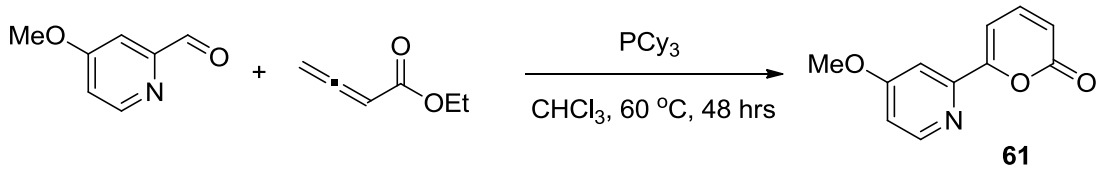


60

Using General Procedure 7, with 2-pyridinecarboxaldehyde (478 mg, 4.46 mmol), the product was isolated as a colourless solid, **60**, 130 mg, 84% yield, m.pt. = 154 – 156 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.40 (1H, dd, *J* = 1.0, 9.0 Hz, Ar-*H*), 7.31 – 7.40 (2H, m, Ar-*H*), 7.51 (1H, dd, *J* = 7.0, 9.0 Hz, Ar-*H*), 7.83 (1H, dt, *J* = 2.0, 8.0 Hz, Ar-*H*), 8.02 (1H, dt, *J* = 1.0, 8.0 Hz, Ar-*H*), 8.65 (1H, ddd, *J* = 1.0, 2.0, 4.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 103.0, 116.0, 120.5, 125.0, 137.0, 144.0, 149.0, 150.0, 159.5, 161.5. FTIR: 2256 (m), 1637 (m), 1375 (m) cm^{-1}. HRMS calculated for $C_{10}H_7NO_2$ (ES^+): 174.0555. Found: 174.0548.

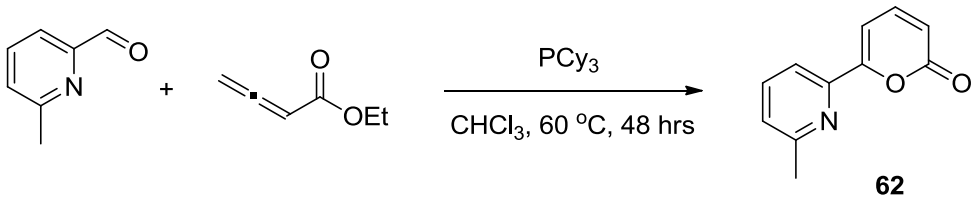
Synthesis of 6-(4-methoxypyridin-2-yl)-2H-2-pyrone 61



Using General Procedure 7, with 4-methoxypyridine-2-carboxaldehyde (1.06 g, 7.74 mmol), the product was isolated as a pale brown solid, **61**, 478 mg, 30% yield, m.pt. = 144 – 146 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 3.95 (3H, s, C*H*$_3$), 6.41 (1H, dd, *J* = 0.5, 9.0 Hz, Ar-*H*), 6.88 (1H, dd, 2.5, 5.5 Hz, Ar-*H*), 7.36 (1H, dd, *J* = 0.5, 7.0 Hz, Ar-*H*), 7.52 (1H, dd, *J* = 7.0, 9.0 Hz, Ar-*H*), 7.55 (1H, d, *J* = 2.5 Hz, Ar-*H*), 8.46 (1H, d, *J* = 5.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5, 103.0, 106.5, 111.5, 116.0, 144.0, 150.5, 151.0, 159.5, 161.5, 167.0. FTIR: 2922 (w), 1721 (s), 1541 (s), 795 (s) cm^{-1}. HRMS calculated for $C_{11}H_9NO_3$ (ES^+): 204.0661. Found: 204.0651.

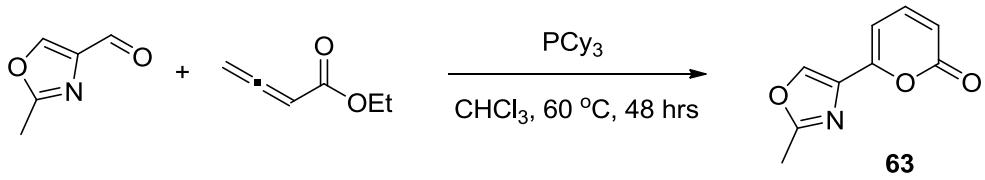
Synthesis of 6-(6-methylpyridin-2-yl)-2H-2-pyrone 62



Using General Procedure 7, with 6-methylpyridine-2-carboxaldehyde (1.08 g, 8.93 mmol), the product was isolated as a pale brown solid, **62**, 277 mg, 83% yield, m.pt. = 127 – 128 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.61 (3H, s, C*H*$_3$), 6.39 (1H, dd, *J* = 0.5, 9.0 Hz, Ar-*H*), 7.22 (1H, d, 7.5 Hz, Ar-*H*), 7.38 (1H, dd, *J* = 0.5, 7.0 Hz, Ar-*H*), 7.52 (1H, dd, *J* = 7.0, 9.0 Hz, Ar-*H*), 7.72 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.84 (1H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5, 102.5, 115.5, 117.5, 125.0, 137.5, 144.0, 148.0, 159.0, 160.0, 161.5. FTIR: 2923 (w), 1716 (s), 1085 (m), 783 (s) cm^{-1}. HRMS calculated for $C_{11}H_9NO_3$ (ES^+): 204.0661. Found: 204.0651.

Synthesis of 6-(2-methyloxazol-4-yl)-2H-2-pyrone 63



63

Using General Procedure 7, with 2-methyloxazole-4-carboxaldehyde (793 mg, 7.13 mmol), the product was isolated as a pale brown solid, **63**, 120 mg, 38% yield, m.pt. = 134 – 136 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.51 (3H, s, C*H*$_3$), 6.27 (1H, dd, *J* = 1.0, 9.0 Hz, Ar-*H*), 6.74 (1H, dd, 1.0, 6.5Hz, Ar-*H*), 7.44 (1H, dd, *J* = 6.5, 9.0 Hz, Ar-*H*), 8.03 (1H, s, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 101.4, 114.7, 134.4, 137.7, 143.7, 154.7, 161.1, 162.7. FTIR: 2162 (m), 1606 (s), 1514 (s), 842 (s) cm^{-1}. HRMS calculated for $C_9H_7NO_3$ (ES^+): 178.0504. Found: 178.0504.

Synthesis of 6-(thiazol-4-yl)-2H-2-pyrone 64

64

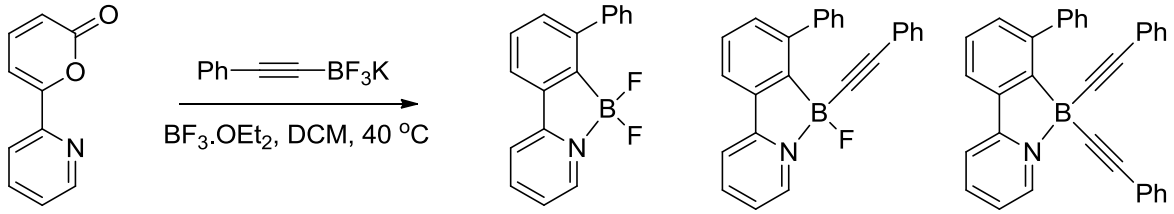
Using General Procedure 7, with thiazole-4-carboxaldehyde (404 mg, 3.57 mmol), the product was isolated as a pale yellow solid, **64**, 57 mg, 36% yield, m.pt. = 120 – 122 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.33 (1H, dd, *J* = 0.5, 9.5 Hz, Ar-*H*), 7.08 (1H, dd, 0.5, 6.5 Hz, Ar-*H*), 7.50 (1H, dd, *J* = 6.5, 9.5 Hz, Ar-*H*), 8.00 (1H, d, *J* = 2.0 Hz, Ar-*H*), 8.86 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 102.5, 115.0, 118.9, 144.0, 148.7, 153.9, 156.1, 161.3. FTIR: 1735 (m), 1265 (s), 732 (s) cm^{-1}. HRMS calculated for $C_8H_5NO_2S$ (ES^+): 118.0119. Found: 118.0115.

General Procedure 8: Cycloaddition of 2-pyrones and alkynyltrifluoroborates

$BF_3.OEt_2$ (3.0 mmol) was added dropwise to 2-pyrone (1.0 mmol), and potassium alkynyltrifluoroborate (3.0 mmol) in dichloromethane (10 mL) at 40°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at 40 °C for 10 min. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL), and washed with saturated aqueous sodium bicarbonate (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was triturated with ether, then purified by flash silica chromatography where required (elution gradient 10 to 100% ethyl acetate in petrol).[c]

Synthesis of 2-(2-(difluoroboryl)biphenyl-3-yl)pyridine 65a, 2-(2-(fluoro(phenylethynyl)boryl)biphenyl-3-yl)pyridine 65b and 2-(2-(bis(phenylethynyl)boryl)biphenyl-3-yl)pyridine 65c



60 **65a** **65b** **65c**

Using General Procedure 8, with 2-pyrone **60** (98 mg, 0.57 mmol), products were isolated as colourless solids: **65a**, 128 mg, 82% yield, m.pt. = 196 – 198 °C; **65b**, 10 mg, 5% yield, m.pt. = 200 – 202 °C; **65c**, 12 mg, 5% yield, m.pt. = 204 – 206 °C.

65a: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33 – 7.57 (5H, m, Ar-*H*), 7.63 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 7.74 (1H, dd, *J* = 0.5, 7.0 Hz, Ar-*H*), 7.84 – 7.86 (2H, m, Ar-*H*), 7.95 (1H, d, *J* = 8.0 Hz, Ar-*H*), 8.14 (1H, dt, *J* = 1.5, 8.0 Hz, Ar-*H*), 8.54 (1H, d, *J* = 5.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 118.0, 120.5, 123.5, 127.5, 128.5 (x 2), 129.5, 132.5, 137.0, 141.5, 142.0, 143.5, 146.0, 156.0. ^{19}F NMR (235.1 MHz,

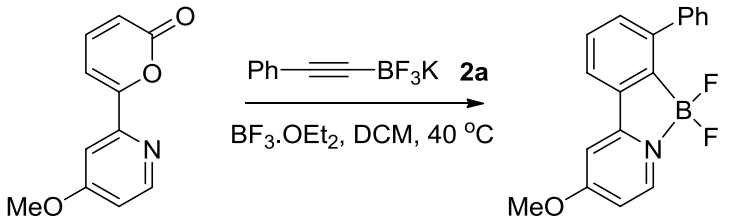
[c] The carbon attached to boron is not visible in the ^{13}C NMR of any of the aromatic difluoroboranes formed, presumably due to the long relaxation time of this quaternary carbon.

$CDCl_3$): δ -155.7. FTIR: 2922 (w), 1623 (m), 1076 (s), 766 (s) cm^{-1}. HRMS calculated for $C_{17}H_{12}{}^{11}BF_2N$ (ES^+): 280.1109. Found: 280.1097.

65b: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.03 – 7.20 (5H, m, Ar-*H*), 7.39 – 7.41 (1H, m, Ar-*H*), 7.45 – 7.57 (4H, m, Ar-*H*), 7.65 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 7.77 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 7.88 – 7.99 (3H, m, Ar-*H*), 8.13 (1H, dt, *J* = 1.5, 8.0 Hz, Ar-*H*), 8.76 (1H, dt, *J* = 1.0, 5.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 118.0, 120.5, 123.2, 124.6 (x2), 127.1, 127.2, 127.8, 128.1, 128.7, 129.1, 129.2, 131.7, 132.5, 137.1, 137.2, 142.1, 142.8, 143.1, 146.2, 157.0. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -173.3. FTIR: 1620 (m), 1485 (s), 755 (s) cm^{-1}. HRMS calculated for $C_{25}H_{17}{}^{11}BFN$ (ES^+) (-F): 342.1454. Found: 342.1444.

65c: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.12 – 7.25 (10H, m, Ar-*H*), 7.40 – 7.42 (1H, m, Ar-*H*), 7.45 – 7.57 (4H, m, Ar-*H*), 7.62 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 7.83 (1H, dd, *J* = 1.0, 7.5 Hz, Ar-*H*), 8.00 (1H, dt, *J* = 0.5, 8.0 Hz, Ar-*H*), 8.06 – 8.16 (3H, m, Ar-*H*), 8.94 (1H, dt, *J* = 1.0, 5.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 96.5, 118.2, 120.8, 122.8, 126.8 (x2), 127.7, 127.8 (x2), 129.7, 131.5 (x2), 132.5, 136.8, 141.5, 142.6, 143.9, 145.7, 157.7. FTIR: 1621 (m), 1486 (s), 753 (s) cm^{-1}. HRMS calculated for $C_{33}H_{22}{}^{11}BN$ (ES^+) ($-C_8H_5$): 342.1454. Found: 342.1444.

Synthesis of 2-(2-(difluoroboryl)biphenyl-3-yl)-4-methoxypyridine 66



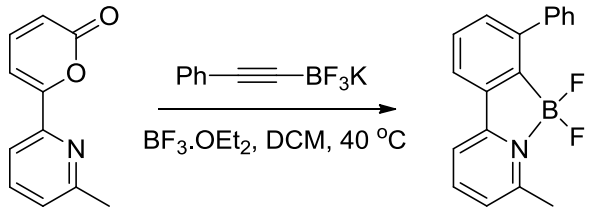
61 **66**

Using General Procedure 8, with 2-pyrone **61** (100 mg, 0.49 mmol), product was isolated as a colourless solid **66**, 106 mg, 70% yield, m.pt. = 174 – 176 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 4.06 (3H, s, C*H*$_3$), 6.92 (1H, dd, *J* = 2.5, 6.5 Hz, Ar-*H*), 7.31 (1H, d, *J* = 2.5 Hz, Ar-*H*), 7.38 – 7.40 (1H, m, Ar-*H*), 7.46 – 7.51 (3H, m, Ar-*H*), 7.61 (1H, dd, *J* = 0.5, 7.5 Hz, Ar-*H*), 7.68 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.84 – 7.86 (2H, m, Ar-*H*), 8.34 (1H, d, *J* = 6.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$):

δ 56.6, 102.6, 109.6, 120.2, 127.2, 128.4, 128.5, 129.0, 132.4, 136.1, 141.9, 142.6, 145.6, 159.6, 171.1. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -155.5. FTIR: 2923 (m), 1625 (s), 1488 (s), 701 (s) cm^{-1}. HRMS calculated for $C_{18}H_{14}{}^{11}BF_2NO$ (ES^+): 310.1215. Found: 310.1201.

Synthesis of 2-(2-(difluoroboryl)biphenyl-3-yl)-6-methylpyridine 67

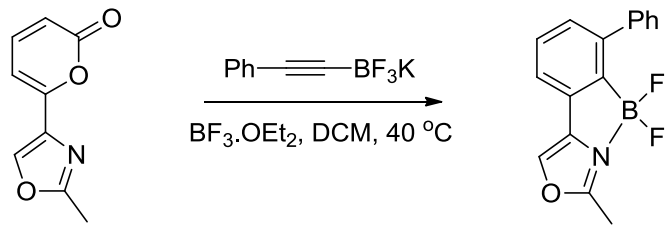


62 **67**

Using General Procedure 8, with 2-pyrone **62** (35 mg, 0.19 mmol), product was isolated as a colourless solid **67**, 45 mg, 82% yield, m.pt. = 146 – 148 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.88 (3H, s, C*H*$_3$), 7.22 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.39 – 7.41 (1H, m, Ar-*H*), 7.45 – 7.54 (3H, m, Ar-*H*), 7.59 (1H, dd, *J* = 0.5, 7.5 Hz, Ar-*H*), 7.69 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.73 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.81 – 7.86 (2H, m, Ar-*H*), 7.92 (1H, t, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.2, 115.0, 120.2, 124.8, 127.2, 128.3, 128.6, 129.1, 132.3, 137.3, 142.0, 142.8, 145.5, 155.9, 156.1. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -154.7. FTIR: 1576 (m), 1486 (m), 1068 (s), 751 (s) cm^{-1}. HRMS calculated for $C_{18}H_{14}{}^{11}BF_2N$ (ES^+): 294.1266. Found: 294.1269.

Synthesis of 2-(2-(difluoroboryl)biphenyl-3-yl)-6-methylpyridine 68

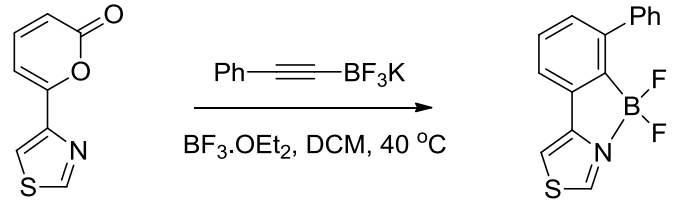


63 **68**

Using General Procedure 8, with 2-pyrone **63** (10 mg, 0.06 mmol), product was isolated as a colourless solid **68**, 11 mg, 67% yield, m.pt. = 163 – 165 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.78 (3H, s, C*H*$_3$), 7.34 – 7.51 (6H, m, Ar-*H*), 7.71 – 7.80 (3H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.4, 115.0 (x2), 120.7, 127.2, 128.2, 128.6, 129.1, 129.9, 130.7, 142.0, 146.2, 160.8. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -148.7 FTIR: 2913 (m), 1435 (m), 716 (s) cm^{-1}. HRMS calculated for $C_{16}H_{12}{}^{11}BF_2NO$ (ES^+): 284.1009. Found: 284.1017.

Synthesis of 4-(2-(difluoroboryl)biphenyl-3-yl)thiazole 69

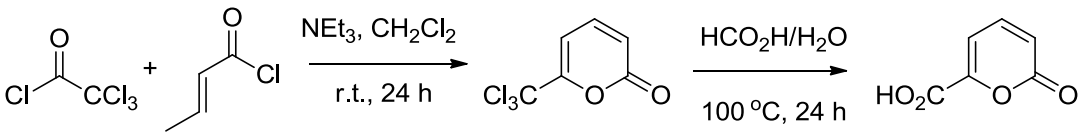


64 **69**

Using General Procedure 8, with 2-pyrone **64** (7 mg, 0.04 mmol), product was isolated as a colourless solid **69**, 9 mg, 74% yield, m.pt. = 151 – 153 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35 – 7.59 (7H, m, Ar-*H*), 7.77 – 7.80 (2H, m, Ar-*H*), 9.17 (1H, d, *J* = 2.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 107.9, 120.0, 127.2, 128.3, 128.6 (x3), 129.2, 131.1, 141.9, 151.6 (x2). ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -148.1. FTIR: 2922 (m), 1467 (m), 702 (s) cm^{-1}. HRMS calculated for $C_{15}H_{10}{}^{11}BF_2NS$ (ES^+): 286.0673. Found: 286.0676.

Synthesis of 2-pyrone-6-carboxylic acid 71[126]



70 **71**

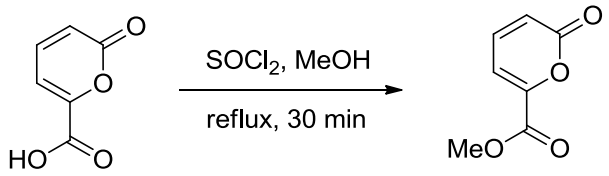
Triethylamine (11.7 mL, 84 mmol) was added dropwise to 2,2,2-trichloroacetyl chloride (8.5 mL, 77 mmol) and (*E*)-but-2-enoyl chloride (3.7 mL, 38 mmol) in

CH_2Cl_2 (50 mL) at -78 °C over a period of 30 min under nitrogen. The resulting solution was stirred at -78 °C for 1 h. The temperature was increased to 25°C and the reaction mixture was stirred for a further 24 hours. The reaction mixture was diluted with CH_2Cl_2 (50 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude **70** (10.4 g, quant.) as a black residue. This was used without further purification.

Water (1.0 mL) was added to **70** (4.2 g, 20 mmol) in formic acid (20 mL) at 25 °C. The resulting mixture was stirred at 100 °C for 24 h. After cooling to r.t., the reaction mixture was concentrated *in vacuo*. The crude residue was triturated with Et_2O to give a solid which was collected by filtration and dried under vacuum to give **71** as a brown solid m.pt. = 225 – 228 ^oC (lit.[135] = 226 – 227 ^oC), 2.2 g, 80% yield.

^1H NMR (400 MHz, DMSO-d_6): δ 6.59 (1H, dd, *J* = 1.0, 9.5 Hz, Ar-*H*), 7.12 (1H, dd, *J* = 1.0, 6.5 Hz, Ar-*H*), 7.63 (1H, dd, *J* = 6.5, 9.5 Hz, Ar-*H*) 13.00 – 15.00 (1H, br, COO*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 110.6, 120.5, 144.0, 150.0, 160.5, 160.9. The compound gave satisfactory spectroscopic data.[136]

Synthesis of methyl 2-oxo-2H-pyran-6-carboxylate 72[126]



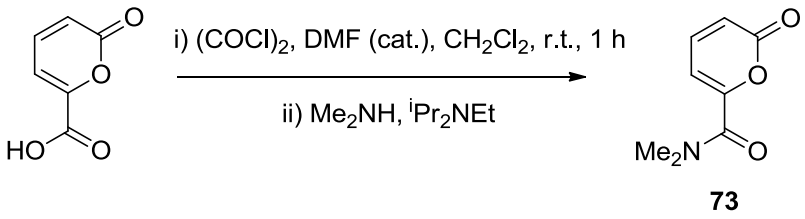
71 **72**

Thionyl chloride (383 mg, 3.2 mmol) was added dropwise to a solution of **71** (300 mg, 2.1 mmol) in methanol (18 mL) under nitrogen. The mixture was heated to reflux for 30 min. After cooling to r.t., volatiles were removed *in vacuo*, affording crude material. Flash silica chromatography (eluting solvent 50% ethyl acetate in petrol.) afforded **72** as a pale yellow solid m.pt. = 122 – 124 ^oC (lit.[137] = 124 – 125 ^oC), 165 mg, 50% yield.

^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (3H, s, CH_3), 6.58 (1H, dd, *J* = 1.0, 9.5 Hz, Ar-*H*), 7.13 (1H, dd, *J* = 1.0, 6.5 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 6.5, 9.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 53.1, 109.8, 121.0, 141.6, 149.5, 159.6, 159.8. FTIR:

2961 (w), 1730 (s), 1287 (s), 871 (s) cm^{-1}. HRMS calculated for $C_7H_6O_4$ (ES^+): 155.0344. Found: 155.0339.

Synthesis of *N*,*N*-dimethyl-2-oxo-2H-pyran-6-carboxamide 73

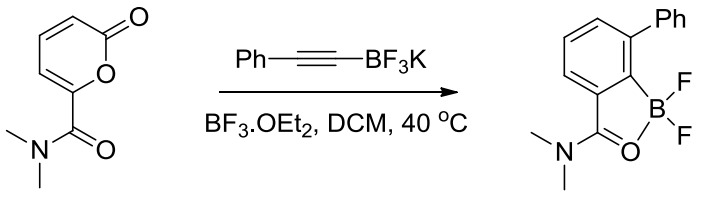


73

Oxalyl chloride (0.41 mL, 4.64 mmol) was added dropwise to 2-pyrone-6-carboxylic acid (500 mg, 3.57 mmol), and *N*,*N*-dimethylformamide (2.76 μL, 0.04 mmol) in CH_2Cl_2 (35 mL) at r.t. under nitrogen. The resulting solution was stirred at r.t. for 1 hr. Dimethylamine (1.79 mL, 3.57 mmol) and *N*,*N*-diisopropylethylamine (0.62 mL, 3.57 mmol) were added and the resulting solution was stirred for 1 hr. The reaction mixture was washed sequentially with saturated $NaHCO_3$ (40 mL), water (40 mL), and saturated brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 100% ethyl acetate in hexanes, affording a colourless solid **73**, 320 mg, 54 % yield, m.pt. = 58 – 60 ^oC.

^1H NMR (250 MHz, $CDCl_3$): δ 3.09 (3H, s, C*H*$_3$), 3.18 (3H, s, C*H*$_3$), 6.42 (1H, dd, *J* = 1.0, 9.5 Hz, Ar-*H*), 6.72 (1H, dd, *J* = 1.0, 6.5 Hz, Ar-*H*), 7.45 (1H, dd, *J* = 6.5, 9.5 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.3, 38.4, 107.1, 117.6, 142.9, 155.8, 159.7, 161.4. FTIR: 2949 (w), 1744 (s), 1652 (s), 808 (s) cm^{-1}. HRMS calculated for $C_8H_9NO_3$ (ES^+): 168.0661. Found: 168.0667.

Synthesis of 2-(difluoroboryl)-*N*,*N*-dimethylbiphenyl-3-carboxamide 75

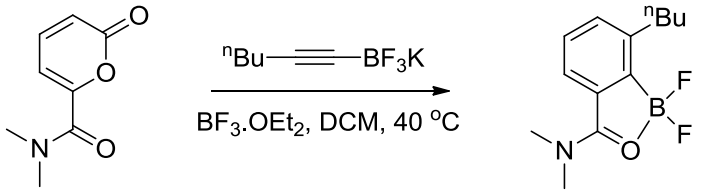


73 **75**

Using General Procedure 8, with 2-pyrone **73** (100 mg, 0.60 mmol), product was isolated as a colourless solid **75**, 150 mg, 92% yield, m.pt. = 121 – 123 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49 (3H, s, CH_3), 3.69 (3H, s, CH_3), 7.38 – 7.40 (1H, m, Ar-*H*), 7.47 – 7.52 (3H, m, Ar-*H*), 7.74 – 7.82 (4H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 40.5, 41.4, 124.9, 127.5, 128.5, 128.6, 128.8, 132.2, 134.2, 141.0, 145.4, 160.9. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -149.1. FTIR: 1621 (m), 860 (s), 722 (s) cm^{-1}. HRMS calculated for $C_{15}H_{14}{}^{11}BF_2NO$ (AP^+): 273.1137. Found: 273.1131.

Synthesis of 3-butyl-2-(difluoroboryl)-*N*,*N*-dimethylbenzamide 76



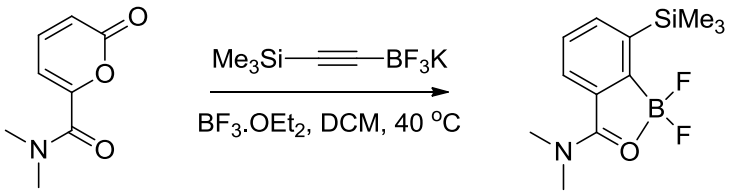
73 **76**

Using General Procedure 8, with 2-pyrone **73** (20 mg, 0.12 mmol), product was isolated as a colourless solid **76**, 13 mg, 65% yield, m.pt. = 118 – 120 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 1.42 (2H, sext, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.65 – 1.69 (2H, m, $CH_2CH_2CH_2$), 2.85 (2H, t, *J* = 8.0 Hz, Ar-CH_2CH_2), 3.47 (3H, s, CH_3), 3.66 (3H, s, CH_3), 7.33 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.44 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.60 (1H, d, *J* = 7.5Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 22.5, 33.5, 34.5, 40.3, 41.2, 123.6, 128.4, 131.3, 134.1, 146.6, 173.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -153.3. FTIR: 2905 (m), 1625 (m), 731 (s) cm^{-1}. HRMS calculated for $C_{13}H_{18}{}^{11}BF_2NO$ (ES^+): 254.1528. Found: 254.1534.

Synthesis of **76** was also performed on larger scale: Using General Procedure 8, with 2-pyrone **73** (100 mg, 0.60 mmol), the product was isolated as a colourless solid **76**, 85 mg, 56% yield.

Synthesis of 2-(difluoroboryl)-*N*,*N*-dimethyl-3-(trimethylsilyl)benzamide 77

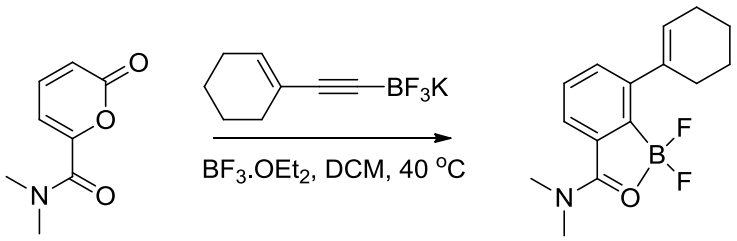


73 **77**

Using General Procedure 8, with 2-pyrone **73** (25 mg, 0.14 mmol), product was isolated as a colourless solid **77**, 28 mg, 70% yield, m.pt. = 127 – 129 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 0.39 (9H, s, Si-C*H*$_3$), 3.46 (3H, s, N-C*H*$_3$), 3.65 (3H, s, N-C*H*$_3$), 7.37 (1H, dd, *J* = 7.5, 8.0 Hz, Ar-*H*), 7.74 – 7.82 (2H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ -0.6, 40.4, 41.3, 126.4, 127.2, 130.7, 139.5, 144.9, 173.6. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -156.5. FTIR: 1631 (m), 904 (s), 725 (s) cm^{-1}. HRMS calculated for $C_{12}H_{18}{}^{11}BF_2NOSi$ (ES^+): 270.1297. Found: 280.1299.

Synthesis of 3-cyclohexenyl-2-(difluoroboryl)-*N*,*N*-dimethylbenzamide 78

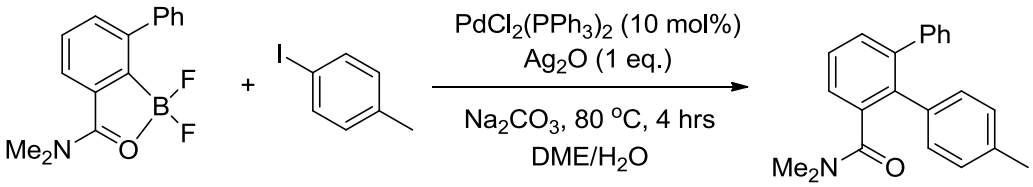


73 **78**

Using General Procedure 8, with 2-pyrone **73** (20 mg, 0.12 mmol), product was isolated as a colourless solid 7**8**, 31 mg, 93% yield, m.pt. = 125 – 127 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.65 – 1.86 (4H, m, C*H*$_2$C*H*$_2$), 2.21 – 2.30 (2H, m, CH=CC*H*$_2$), 2.46 – 2.53 (2H, m, C=CHC*H*$_2$), 3.49 (3H, s, N-C*H*$_3$), 3.67 (3H, s, N-C*H*$_3$), 6.15 – 6.19 (1H, m, C=C*H*CH$_2$), 7.35 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.53 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.64 (1H, d, *J* = 8.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.0, 23.2, 25.9, 28.5, 40.4, 41.3, 115.0, 124.0, 127.6, 128.3, 132.3, 137.6, 153.8, 169.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -150.7. FTIR: 2926 (m), 1638 (m), 728 (s) cm^{-1}. HRMS calculated for $C_{15}H_{18}{}^{11}BF_2NO$ (ES^+): 278.1528. Found: 278.1515.

Synthesis of 2-tolyl-*N,N*-dimethylbiphenyl-3-carboxamide 80[10]

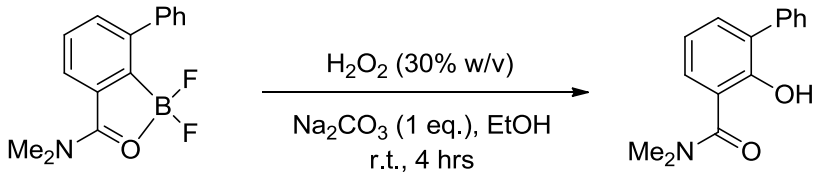


75 **80**

1-Iodo-4-methylbenzene (48 mg, 0.22 mmol) was added to **75** (30 mg, 0.11 mmol), silver oxide (26 mg, 0.11 mmol), (triphenylphosphine)palladium(II) chloride (8 mg, 0.01 mmol) and sodium carbonate (12 mg, 0.11 mmol) under nitrogen. Dimethoxyethane (0.4 mL) / water (0.4 mL) was added and the reaction mixture heated to 80 °C for 4 hrs. The crude reaction mixture was filtered through Celite™ and the filtrate was evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 - 100% ethyl acetate in heptanes, affording a colourless solid **80**, 21 mg, 62 % yield, m.pt. = 111 – 113 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.29 (3H, s, C*H*$_3$), 2.48 (3H, s, C*H*$_3$), 2.79 (3H, s, C*H*$_3$), 6.98 (2H, br, Ar-*H*), 7.07 – 7.11 (3H, m, Ar-*H*), 7.16 – 7.22 (4H, m, Ar-*H*), 7.37 (1H, dd, *J* = 4.0, 5.0 Hz, Ar-*H*), 7.45 (1H, d, *J* = 5.0 Hz, Ar-*H*), 7.46 (1H, d, *J* = 4.0 Hz, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.2, 34.4, 38.3, 125.8, 126.4, 127.7, 127.8, 128.3, 129.9, 130.2, 131.1, 135.2, 136.5, 136.9, 137.8, 141.3, 141.6, 160.3. FTIR: 2925 (m), 1637 (s), 762 (m) cm^{-1}. HRMS calculated for $C_{22}H_{21}NO$ (ES^+): 316.1701. Found: 316.1689.

Synthesis of 2-hydroxy-*N,N*-dimethylbiphenyl-3-carboxamide 81[95]



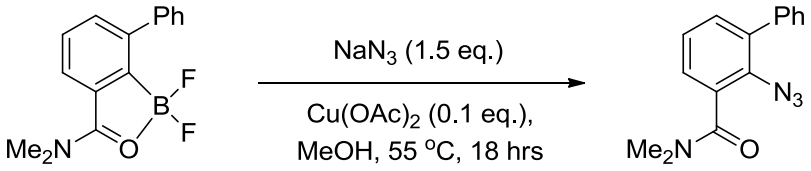
75 **81**

To a solution of **75** (25 mg, 0.09 mmol) dissolved in ethanol (3 mL), was added Na_2CO_3 (21 mg, 0.20 mmol). To this mixture 30% w/v H_2O_2 (1.2 mL) was added dropwise. The reaction was stirred at r.t. for 4 hrs. Upon completion of reaction, 20

mL water was added, and the product extracted from CH_2Cl_2 (3 x 20 mL). The organic layers were combined and dried over $MgSO_4$, then concentrated *in vacuo*. The product was purified by flash column chromatography (eluting solvent 50 % ethyl acetate in petroleum ether), to provide a colourless solid **81**, 17 mg, 79% yield, m.pt. = 131 – 133 ^oC.

^1H NMR (250 MHz, $CDCl_3$): δ 3.22 (6H, s, C*H*$_3$), 6.95 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.31 – 7.49 (5H, m, Ar-*H*), 7.58 – 7.62 (2H, m, Ar-*H*), 10.13 (1H, s, O*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 117.6, 118.3, 127.3, 127.9, 128.2, 129.4, 130.7, 131.5, 133.4, 137.6, 156.1, 172.2. FTIR: 3030 (m), 2925 (m), 1617 (s), 761 (s) cm^{-1}. HRMS calculated for $C_{15}H_{15}NO_2$ (ES^+): 242.1181. Found: 241.1171.

Synthesis of 2-azido-*N*,*N*-dimethylbiphenyl-3-carboxamide 82[127]



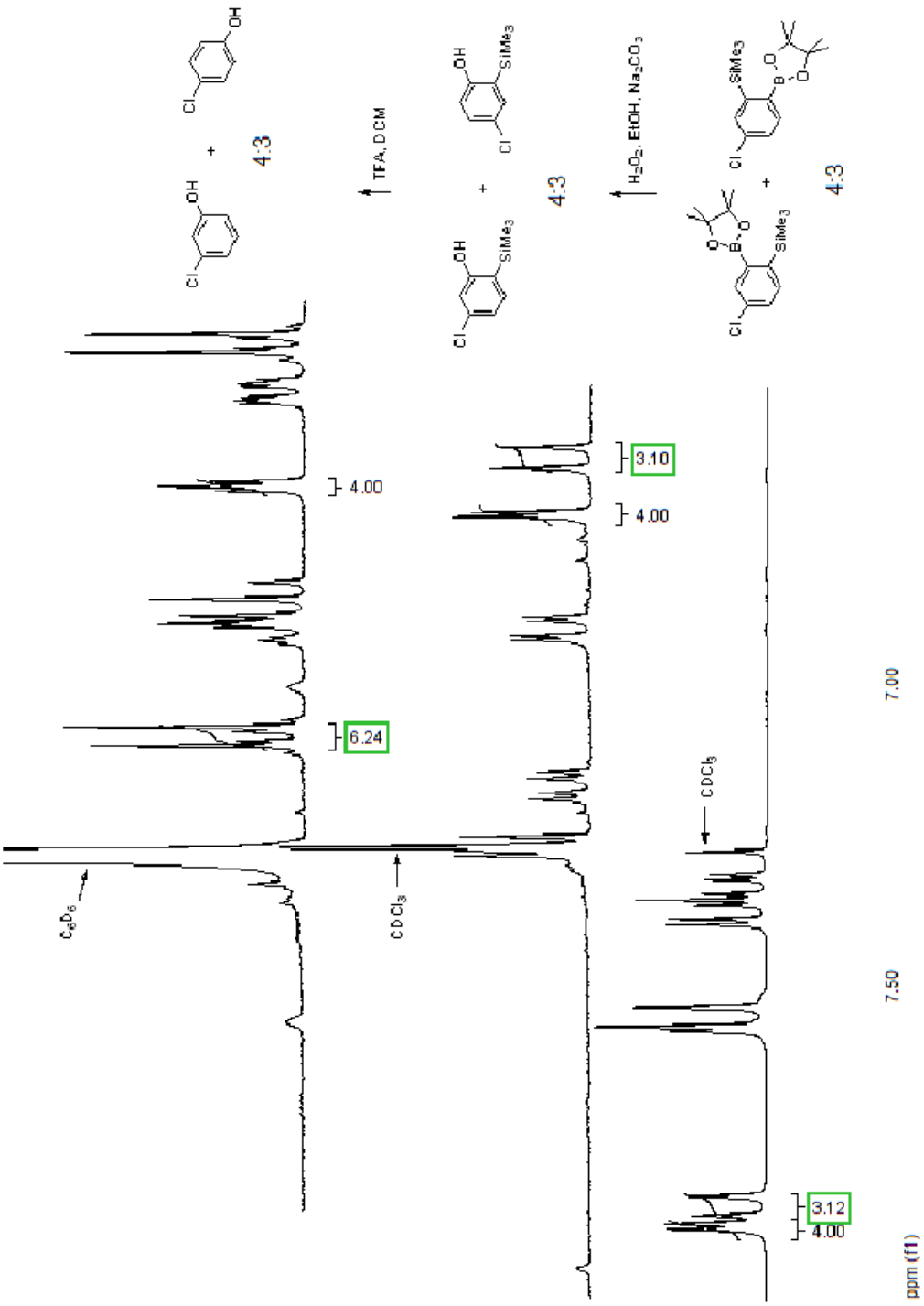
75 **82**

To a solution of **75** (8 mg, 0.03 mmol) dissolved in methanol (0.15 mL), was added NaN_3 (3 mg, 0.04 mmol) and $Cu(OAc)_2$ (0.5 mg, 0.003 mmol). The reaction was stirred at 55 ^oC for 18 hrs. Upon completion of reaction, the mixture was filtered through Celite^{TM}. The product was purified by filtration through a small silica plug (eluting solvent 100% ethyl acetate), providing a yellow oil **82**, 7 mg, 91% yield.

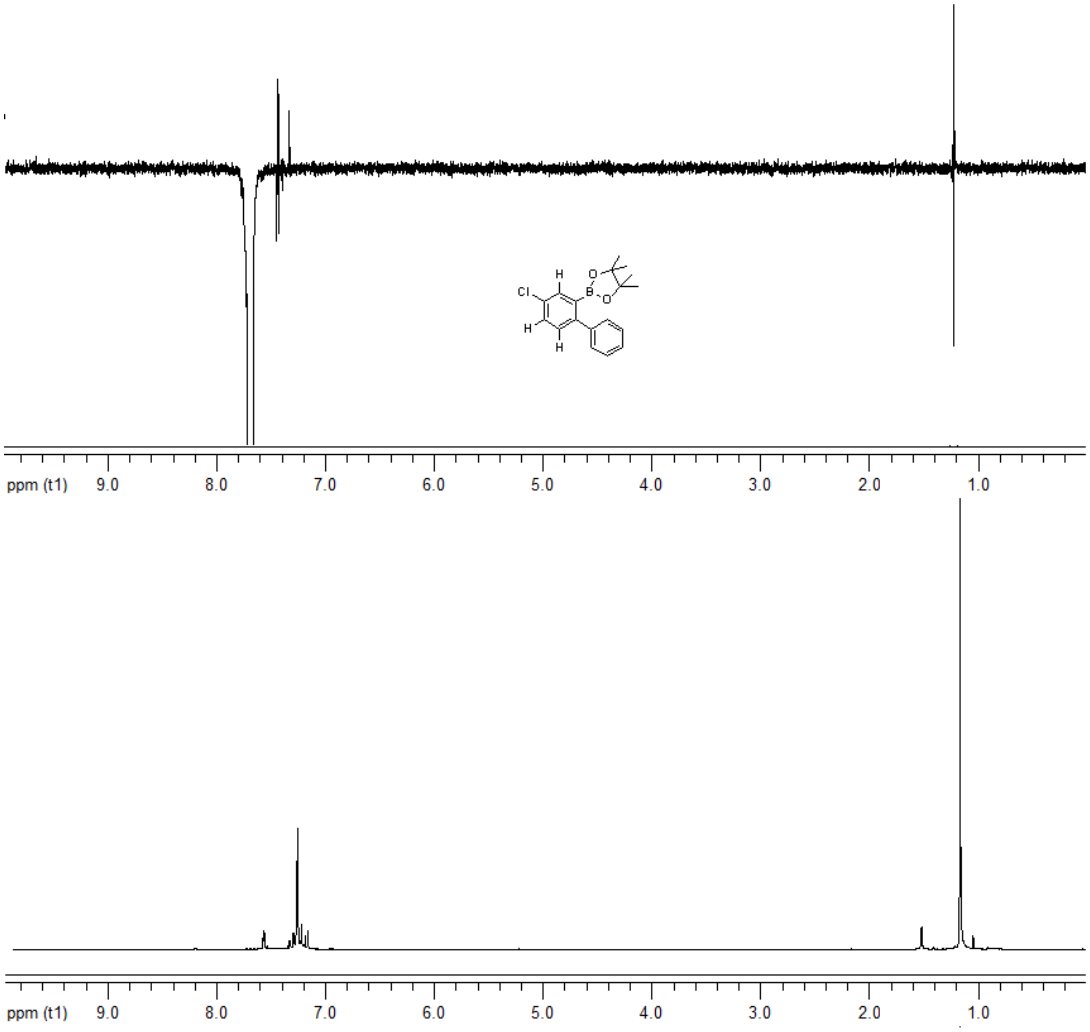
^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (3H, s, C*H*$_3$), 3.18 (3H, s, C*H*$_3$), 7.28 – 7.31 (2H, m, Ar-*H*), 7.34 (1H, dd, *J* = 4.0, 5.5 Hz, Ar-*H*), 7.42 – 7.50 (5H, m, Ar-*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 34.7, 38.6, 125.7, 127.0, 128.1, 128.5, 129.3, 131.1, 131.9, 136.3, 137.5, 143.1, 168.6. FTIR: 1632 (m), 903 (s), 724 (s) cm^{-1}. HRMS calculated for $C_{15}H_{14}N_4O$ (ES^+): 267.1242. Found: 267.1246.

Chapter 5 – Appendix

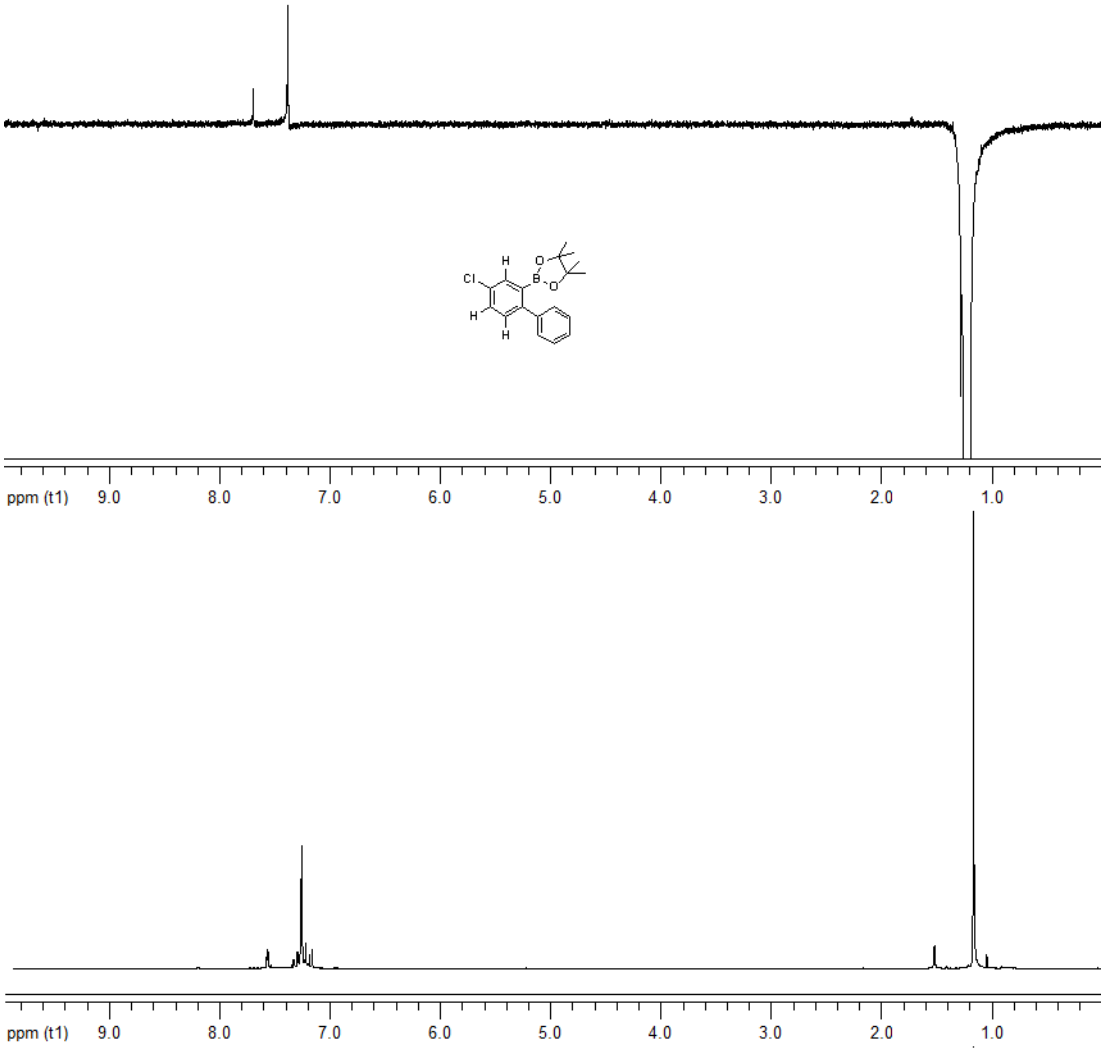
^{1}H NMR Spectrum of 21a and 21b and identification of major regioisomer by conversion to corresponding 3-chloro-phenol and 4-chloro-phenol



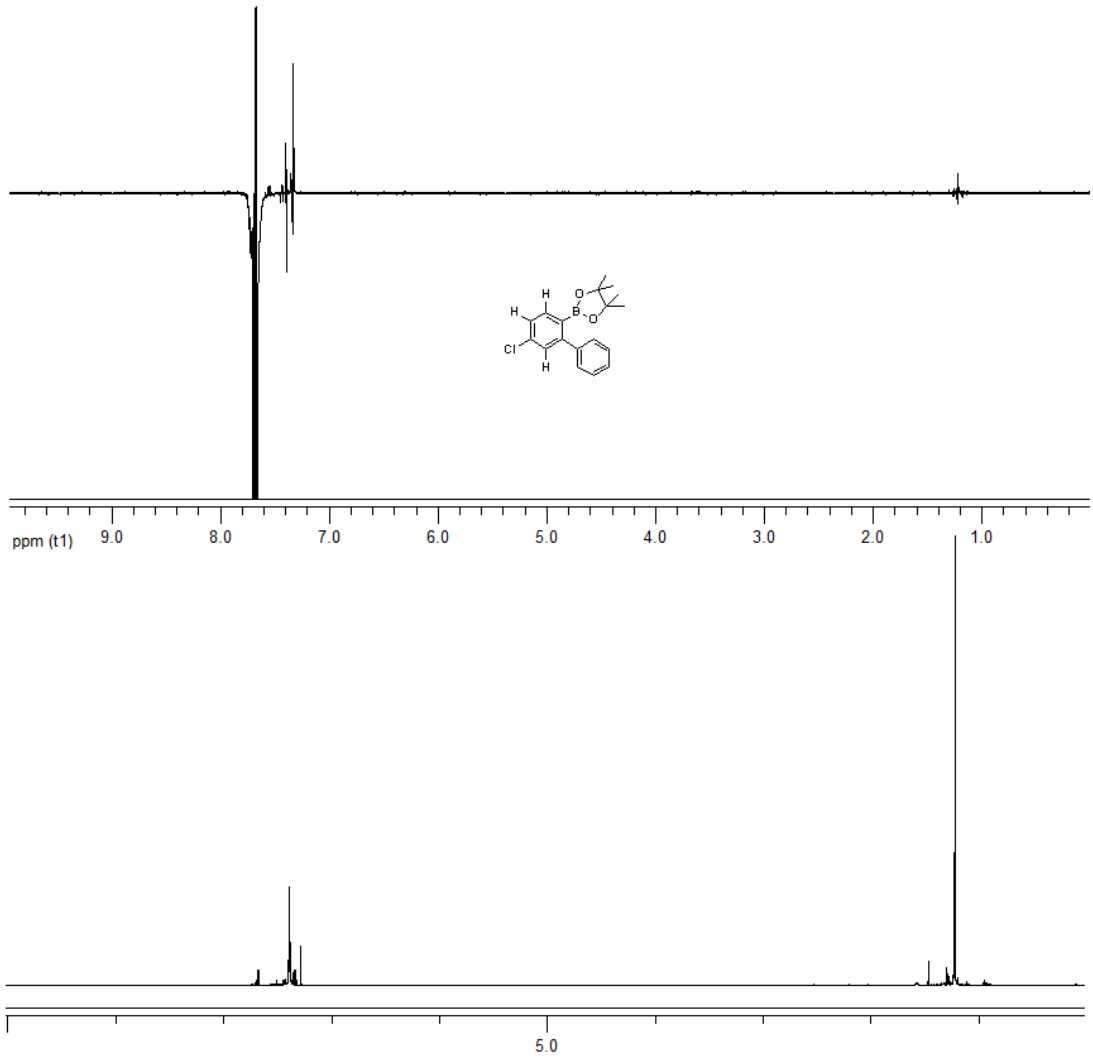
nOe Spectrum of 2-(4-Chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20a



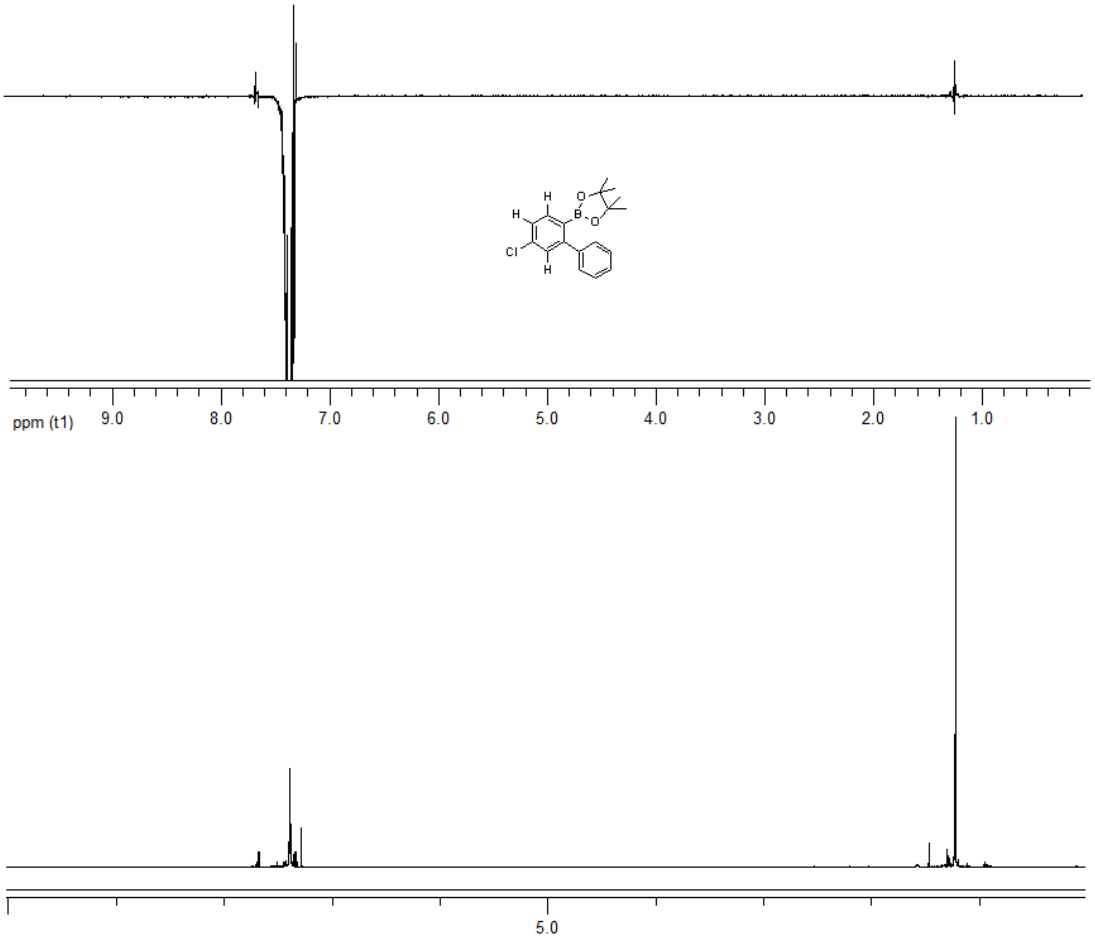
nOe Spectrum of 2-(4-Chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20a



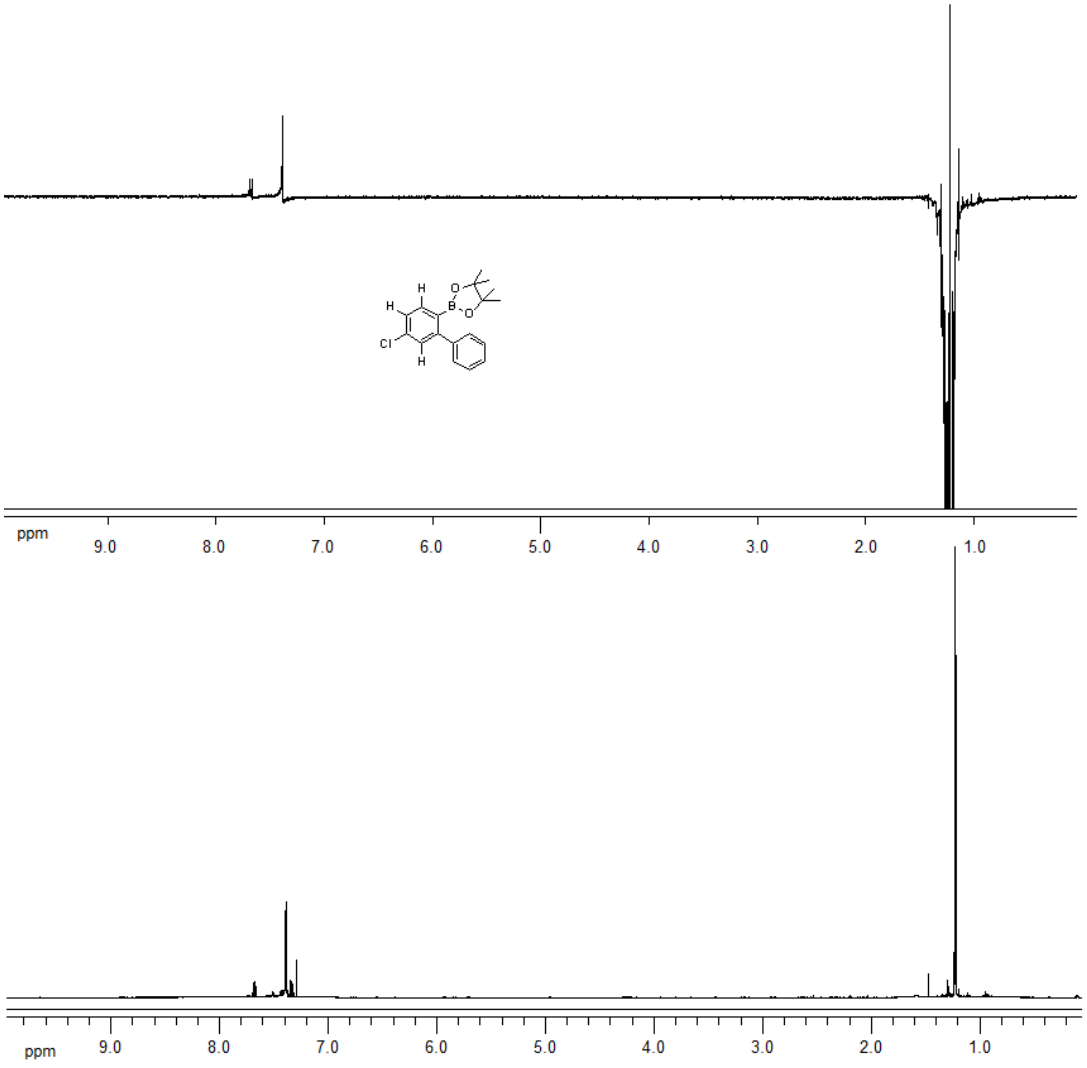
nOe Spectrum of 2-(3-Chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20b



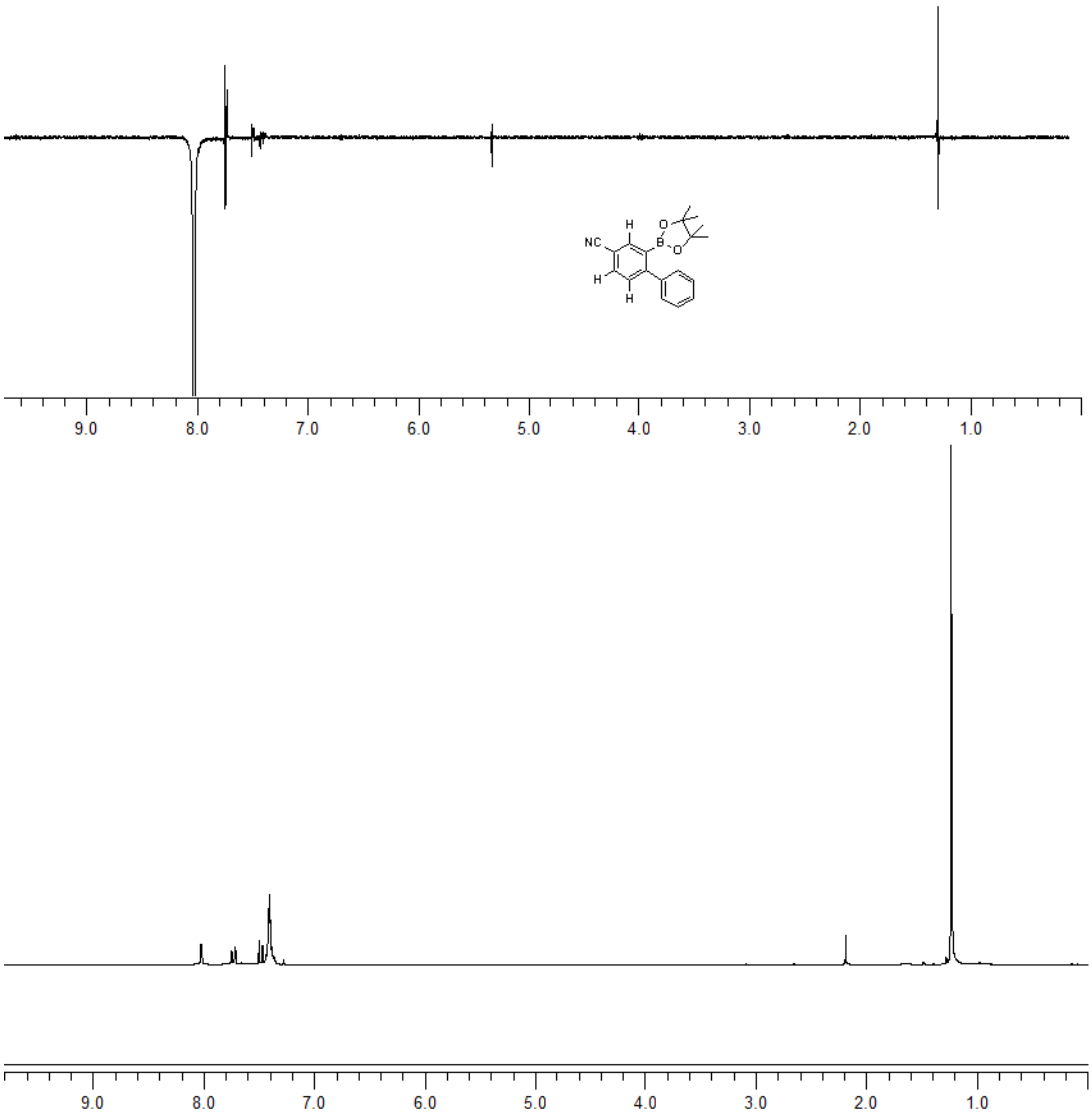
nOe Spectrum of 2-(3-Chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20b



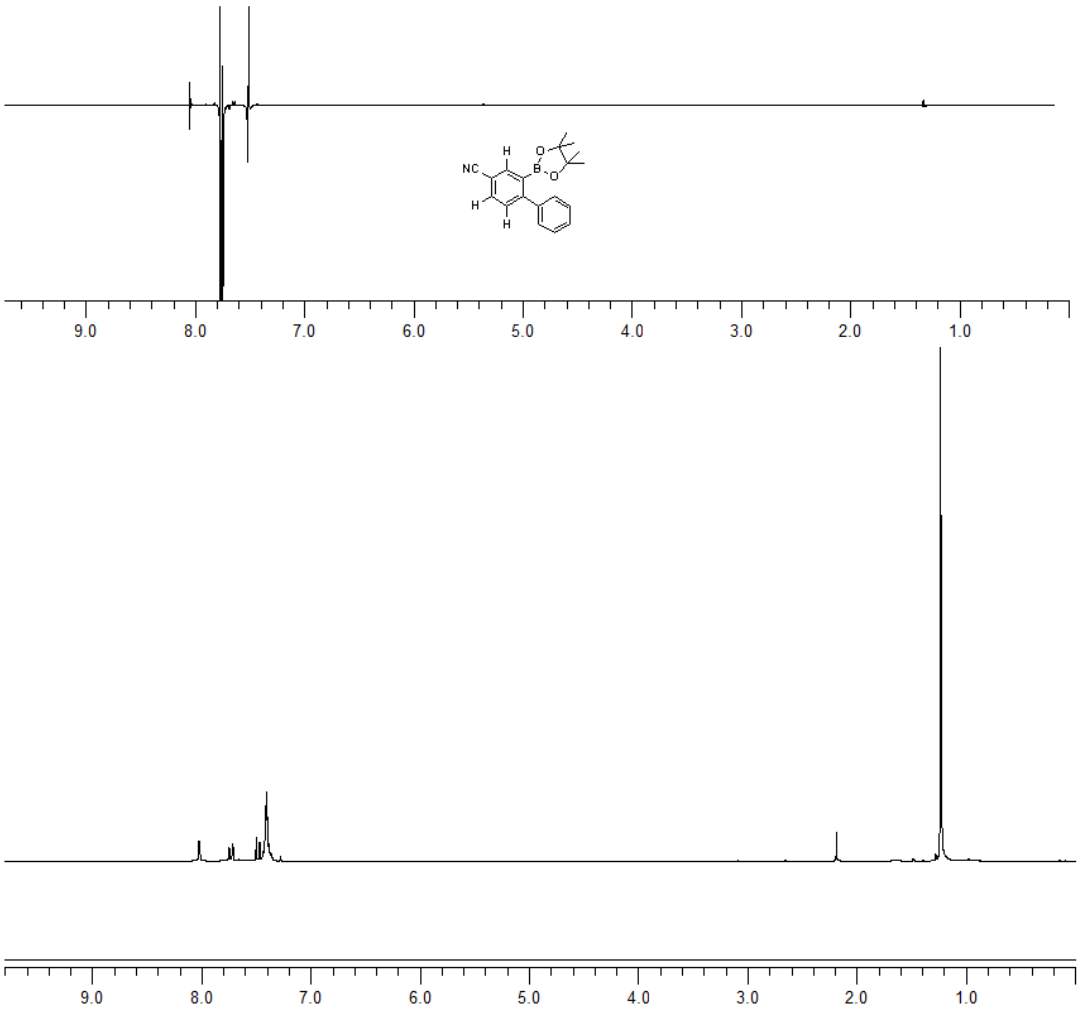
nOe Spectrum of 2-(3-Chlorobiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 20b



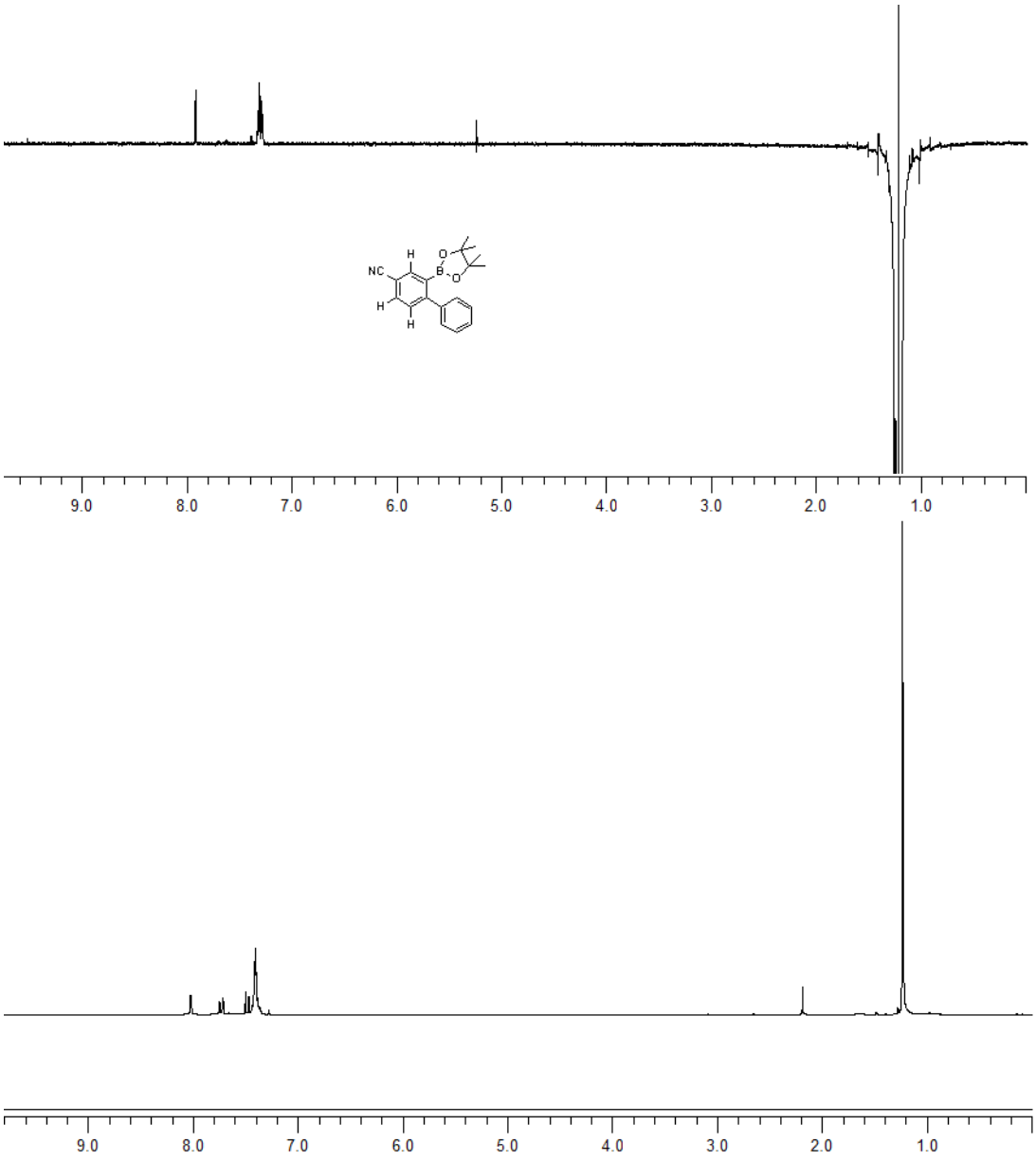
nOe Spectrum of 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 27a



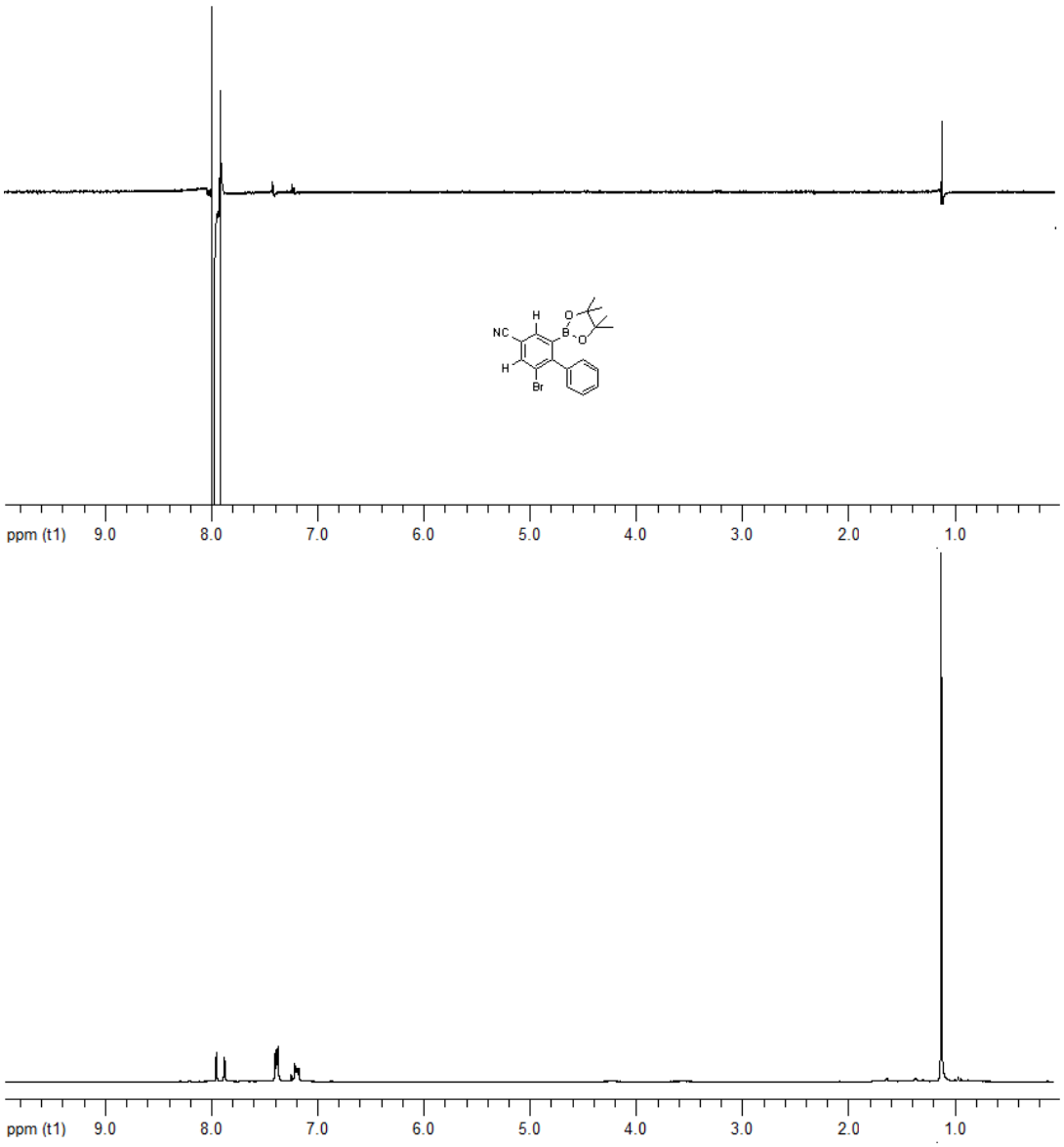
nOe Spectrum of 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 27a



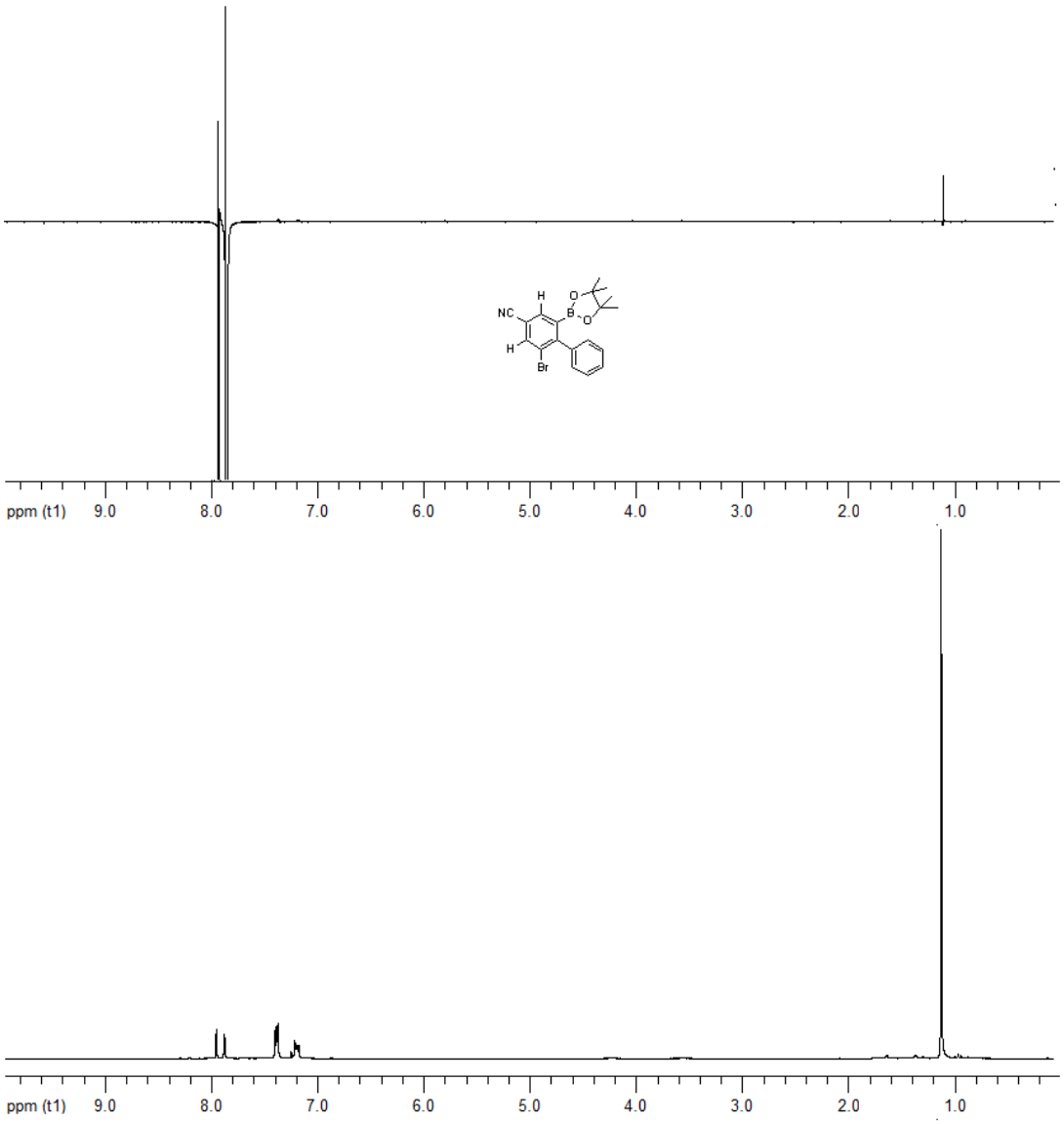
nOe Spectrum of 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 27a



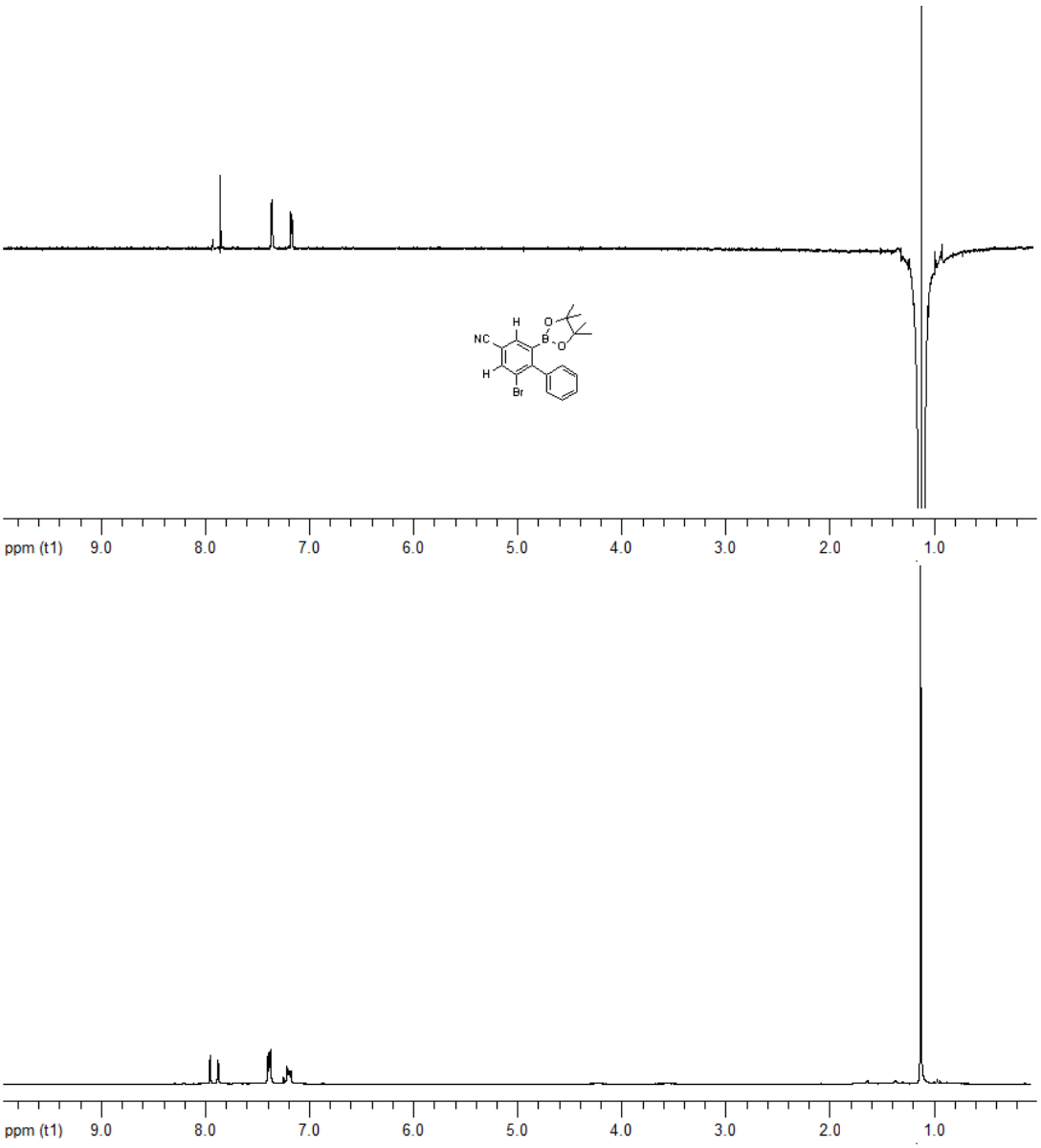
nOe Spectrum of 2-Bromo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 30a



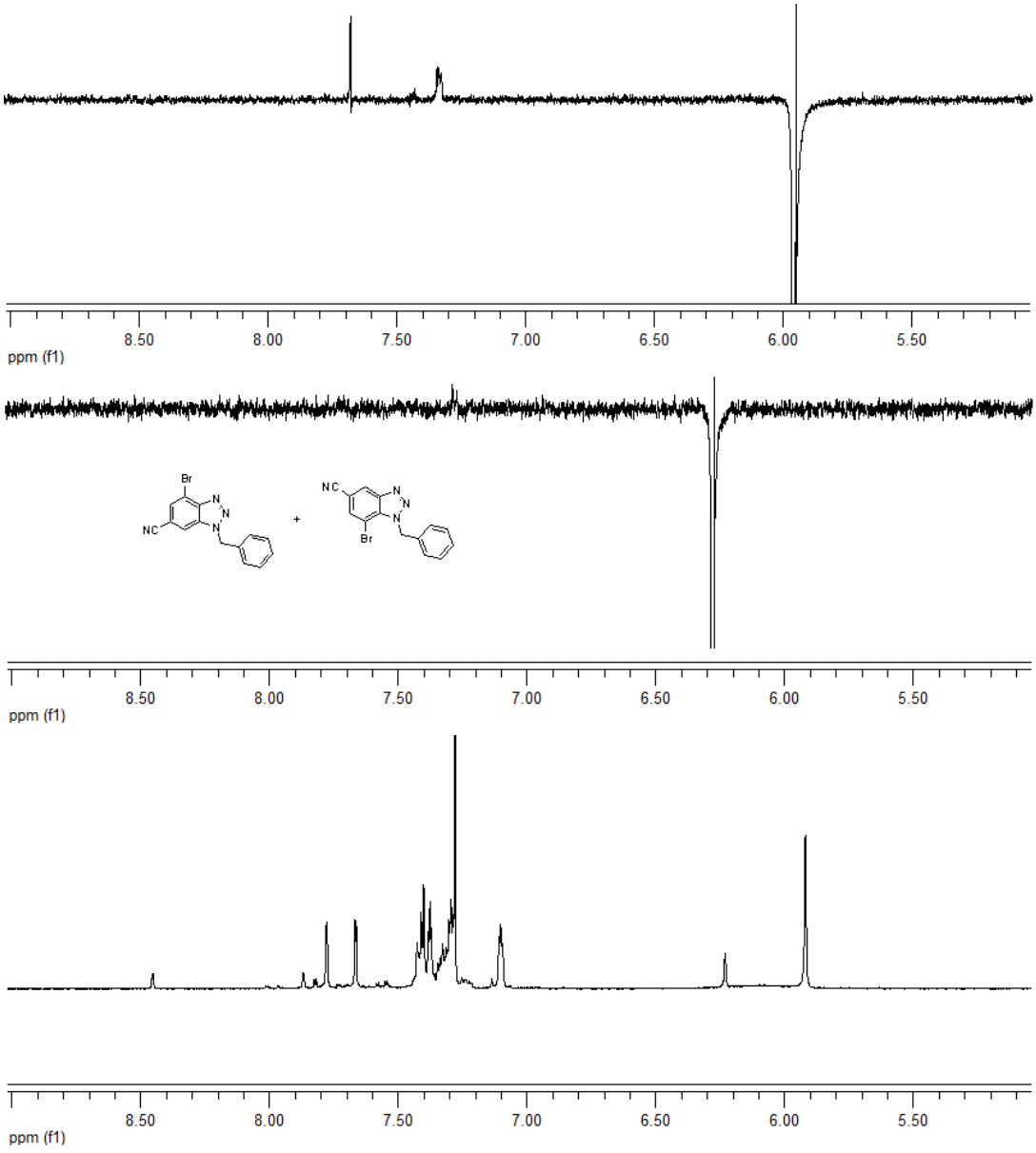
nOe Spectrum of 2-Bromo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 30a



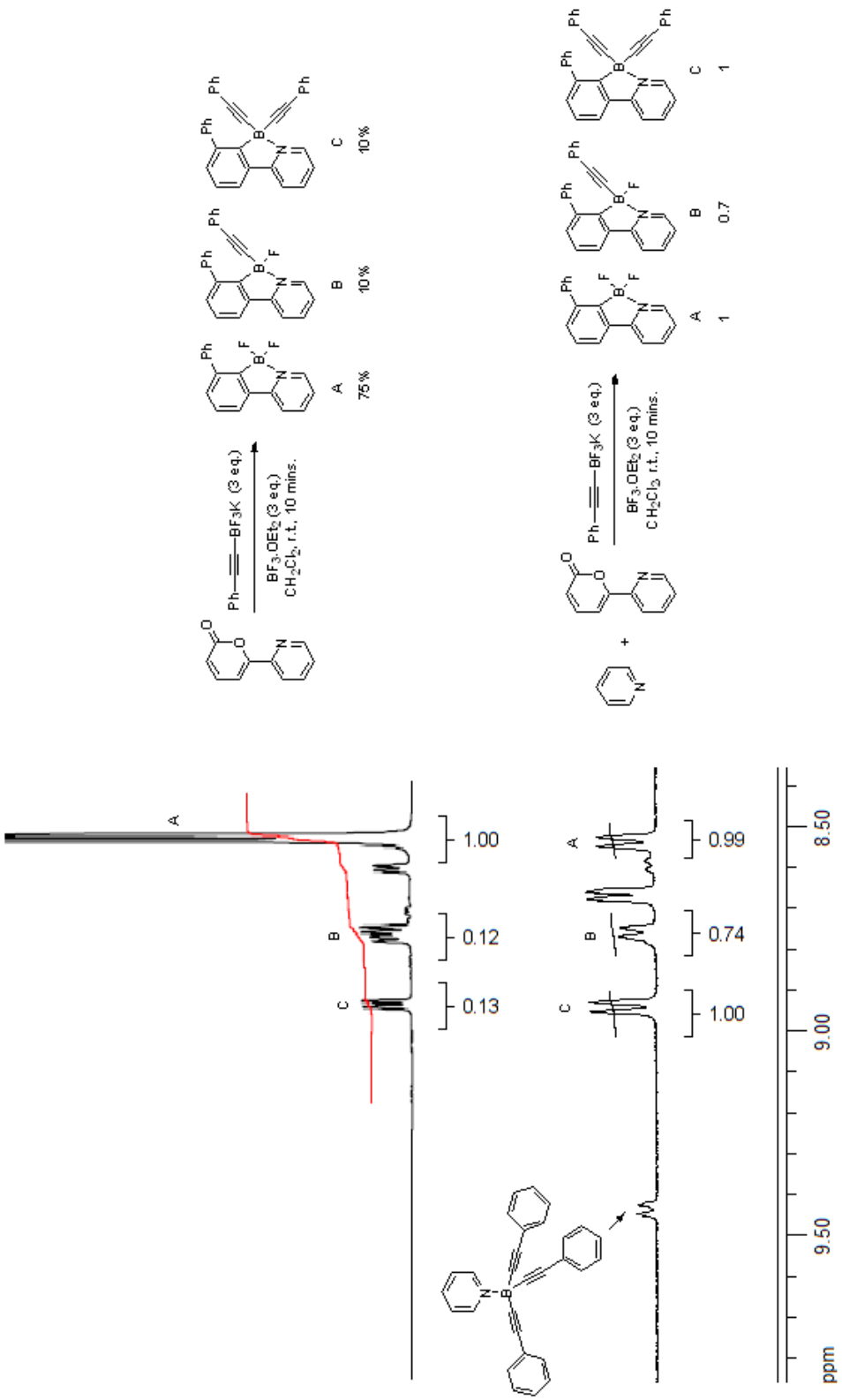
nOe Spectrum of 2-Bromo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-4-carbonitrile 30a



nOe Spectrum of 3-Benzyl-7-bromo-3H-benzotriazole-5-carbonitrile 50a and 1-Benzyl-7-bromo-1H-benzotriazole-5-carbonitrile 50b



^{1}H NMR Spectrum of the formation of 65a, 65b and 65c in the presence of pyridine



X-Ray Crystal Structure Data for 2-(Difluoroboryl)-*N*,*N*-dimethylbiphenyl-3-carboxamide 75

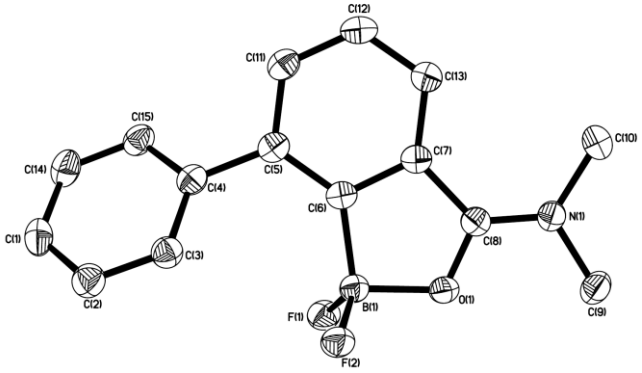


Table 1. Crystal data and structure refinement for JK471.

Identification code	jk471	
Empirical formula	C15 H14 B F2 N O	
Formula weight	273.08	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 7.8403(19) Å	α= 90°.
b = 6.9461(17) Å	β= 96.398(7)°.	
c = 23.997(7) Å	γ = 90°.	
Volume	1298.7(6) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	

F(000)	568
Crystal size	0.23 x 0.06 x 0.02 mm^3
Theta range for data collection	2.66 to 28.19°.
Index ranges	-9<=h<=9, -8<=k<=9, -31<=l<=29
Reflections collected	11382
Independent reflections	2838 [R(int) = 0.0888]
Completeness to theta = 25.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9979 and 0.9761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2838 / 0 / 183
Goodness-of-fit on F^2	0.991
Final R indices [I>2sigma(I)]	R1 = 0.0572, wR2 = 0.1268
R indices (all data)	R1 = 0.1248, wR2 = 0.1560
Largest diff. peak and hole	0.314 and -0.262 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for JK471. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
F(1)	3312(2)	759(2)	1099(1)	33(1)
F(2)	3477(2)	4019(2)	1023(1)	31(1)
O(1)	2909(2)	2196(2)	202(1)	27(1)
N(1)	1589(3)	2295(3)	-668(1)	26(1)

C(1)	591(4)	2359(4)	2929(1)	34(1)
C(2)	1586(4)	3417(4)	2598(1)	33(1)
C(3)	1203(3)	3470(4)	2022(1)	28(1)
C(4)	-227(3)	2502(3)	1761(1)	26(1)
C(5)	-697(3)	2585(3)	1142(1)	25(1)
C(6)	530(3)	2505(3)	757(1)	22(1)
C(7)	-40(3)	2499(3)	180(1)	24(1)
C(8)	1490(3)	2335(3)	-130(1)	25(1)
C(9)	3302(3)	2143(4)	-865(1)	34(1)
C(10)	111(3)	2492(4)	-1096(1)	31(1)
C(11)	-2429(3)	2735(3)	933(1)	28(1)
C(12)	-2953(3)	2775(3)	363(1)	31(1)
C(13)	-1773(3)	2631(3)	-24(1)	29(1)
C(14)	-817(4)	1373(4)	2676(1)	36(1)
C(15)	-1234(3)	1458(4)	2101(1)	31(1)
B(1)	2602(4)	2367(4)	827(1)	26(1)

Table 3. Bond lengths [Å] and angles [°] for JK471.

F(1)-B(1)	1.380(3)
F(2)-B(1)	1.391(3)
O(1)-C(8)	1.299(3)
O(1)-B(1)	1.549(3)
N(1)-C(8)	1.301(3)

N(1)-C(10)	1.466(3)
N(1)-C(9)	1.477(3)
C(1)-C(14)	1.381(4)
C(1)-C(2)	1.384(4)
C(1)-H(1)	0.9500
C(2)-C(3)	1.382(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.394(4)
C(3)-H(3)	0.9500
C(4)-C(15)	1.399(3)
C(4)-C(5)	1.491(4)
C(5)-C(11)	1.399(4)
C(5)-C(6)	1.408(3)
C(6)-C(7)	1.405(3)
C(6)-B(1)	1.617(4)
C(7)-C(13)	1.395(4)
C(7)-C(8)	1.486(3)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(12)	1.384(4)
C(11)-H(11)	0.9500

C(12)-C(13)	1.384(4)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-C(15)	1.382(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500

C(8)-O(1)-B(1)	111.96(19)
C(8)-N(1)-C(10)	124.2(2)
C(8)-N(1)-C(9)	118.4(2)
C(10)-N(1)-C(9)	117.3(2)
C(14)-C(1)-C(2)	119.1(2)
C(14)-C(1)-H(1)	120.5
C(2)-C(1)-H(1)	120.5
C(3)-C(2)-C(1)	120.9(3)
C(3)-C(2)-H(2)	119.6
C(1)-C(2)-H(2)	119.6
C(2)-C(3)-C(4)	120.7(2)
C(2)-C(3)-H(3)	119.6
C(4)-C(3)-H(3)	119.6
C(3)-C(4)-C(15)	117.8(2)
C(3)-C(4)-C(5)	121.7(2)
C(15)-C(4)-C(5)	120.5(2)
C(11)-C(5)-C(6)	118.3(2)
C(11)-C(5)-C(4)	118.9(2)

C(6)-C(5)-C(4)	122.8(2)
C(7)-C(6)-C(5)	118.8(2)
C(7)-C(6)-B(1)	108.0(2)
C(5)-C(6)-B(1)	133.3(2)
C(13)-C(7)-C(6)	122.4(2)
C(13)-C(7)-C(8)	129.7(2)
C(6)-C(7)-C(8)	107.9(2)
O(1)-C(8)-N(1)	117.8(2)
O(1)-C(8)-C(7)	112.5(2)
N(1)-C(8)-C(7)	129.8(2)
N(1)-C(9)-H(9A)	109.5
N(1)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
N(1)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
N(1)-C(10)-H(10A)	109.5
N(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
N(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(5)	121.7(2)
C(12)-C(11)-H(11)	119.1
C(5)-C(11)-H(11)	119.1

C(11)-C(12)-C(13)	120.9(2)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(12)-C(13)-C(7)	117.8(2)
C(12)-C(13)-H(13)	121.1
C(7)-C(13)-H(13)	121.1
C(1)-C(14)-C(15)	120.4(2)
C(1)-C(14)-H(14)	119.8
C(15)-C(14)-H(14)	119.8
C(14)-C(15)-C(4)	121.2(3)
C(14)-C(15)-H(15)	119.4
C(4)-C(15)-H(15)	119.4
F(1)-B(1)-F(2)	110.5(2)
F(1)-B(1)-O(1)	107.3(2)
F(2)-B(1)-O(1)	105.43(19)
F(1)-B(1)-C(6)	116.4(2)
F(2)-B(1)-C(6)	116.0(2)
O(1)-B(1)-C(6)	99.57(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for JK471. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

F(1)	27(1)	34(1)	37(1)	6(1)	3(1)	7(1)
F(2)	28(1)	34(1)	32(1)	-4(1)	4(1)	-7(1)
O(1)	21(1)	32(1)	28(1)	-2(1)	3(1)	0(1)
N(1)	28(1)	26(1)	25(1)	-1(1)	5(1)	-2(1)
C(1)	42(2)	36(2)	24(1)	0(1)	6(1)	6(1)
C(2)	32(2)	35(2)	33(2)	0(1)	5(1)	3(1)
C(3)	28(2)	28(1)	29(2)	1(1)	4(1)	0(1)
C(4)	27(1)	22(1)	29(1)	0(1)	6(1)	3(1)
C(5)	27(2)	17(1)	31(1)	-3(1)	5(1)	-3(1)
C(6)	23(1)	16(1)	29(1)	-1(1)	3(1)	0(1)
C(7)	24(1)	20(1)	28(1)	-1(1)	2(1)	-1(1)
C(8)	26(1)	20(1)	27(1)	1(1)	2(1)	-3(1)
C(9)	33(2)	39(2)	31(2)	-3(1)	11(1)	-6(1)
C(10)	36(2)	30(1)	26(1)	1(1)	0(1)	1(1)
C(11)	27(2)	25(1)	33(2)	-2(1)	8(1)	-2(1)
C(12)	21(1)	31(1)	41(2)	0(1)	2(1)	0(1)
C(13)	27(2)	33(2)	28(1)	0(1)	2(1)	-1(1)
C(14)	43(2)	35(2)	33(2)	0(1)	14(1)	-4(1)
C(15)	29(2)	30(1)	36(2)	-5(1)	10(1)	-6(1)
B(1)	24(2)	26(2)	26(2)	0(1)	3(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{3}) for JK471.

x	y	z	U(eq)	
H(1)	873	2311	3324	40
H(2)	2545	4118	2770	40
H(3)	1921	4173	1802	34
H(9A)	3892	3386	-817	51
H(9B)	3176	1787	-1263	51
H(9C)	3975	1157	-647	51
H(10A)	-590	1322	-1103	46
H(10B)	515	2684	-1464	46
H(10C)	-581	3601	-1006	46
H(11)	-3269	2812	1188	34
H(12)	-4139	2902	235	37
H(13)	-2132	2623	-415	35
H(14)	-1503	631	2898	44
H(15)	-2223	797	1934	37

References

[1] *Boronic Acids* (Ed.: Hall, D. G.), Wiley-VCH, Weinheim, **2005**.
[2] Gilman, H.; Moore, L. O. *J. Am. Chem. Soc*., **1958**, *80*, 3609.
[3] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.*, **1995,** *60*, 7508.
[4] Cho, J. -Y.; Iverson, C. N.; Smith III, M. R. *J. Am. Chem. Soc*., **2000**, 12868.
[5] Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2168.
[6] Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392.
[7] Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.*, **2005**, 3389.
[8] Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.*, **2006** , 4278.
[9] Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *J. Am. Chem. Soc.*, **2007**, 2691.
[10] Vivat, J. F.; Adams, H.; Harrity, J. P. A. *Org. Lett.* **2010**, 160.
[11] Patrick Delaney, PhD Thesis, University of Sheffield, **2007**.
[12] Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.*, **2006,** 3323.
[13] Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron*, **2008**, *64*, 866.
[14] Browne, D. L.; Helm, M. D.; Plant, A.; Harrity J. P. A. *Angew. Chem., Int. Ed.*, **2007**, 8656.
[15] Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E; Harrity, J. P. A. *J. Am. Chem. Soc*., **2009**, 7762.
[16] Matteson, D. *J. Am. Chem. Soc.*, **1960**, *82*, 5759.
[17] Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.
[18] Blanchard, C.; Framery, E.; Vaultier, M. *Synthesis*, **1996**, 45.
[19] Yamamoto, Y.; Hattori, K.; Ishii, J. -I.; Nishiyama, H. *Tetrahedron*, **2006**, *62*, 4294.
[20] Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, **1978**, p 285.
[21] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 4467 (b) Cassar, L. *J. Organomet. Chem*. **1975**, *93*, 253 (c) Dieck, H. A., Heck, R. F. *J. Organomet. Chem*. **1975**, *93*, 259.
[22] Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513.
[23] Oh, C. H.; Reddy, V. R. *Tetrahedron Lett.* **2004**, *45*, 8545.
[24] Oh, C. H.; Reddy, V. R. *Tetrahedron Lett.* **2004**, *45*, 5221.
[25] Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, K. *Tetrahedron Lett.* **2005**, *46*, 8661.
[26] Chen, H.; Deng, M. -Z. *J. Organomet. Chem*. **2000**, *603*, 189.
[27] Torres, G. H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.
[28] Suzuki, A. *Chem. Lett.*, **1992**, *21*, 695.
[29] Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron*, **1999**, *55*, 14233.
[30] Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.*, **2000,** *122*, 1822.
[31] Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.*, **2005**, *127*, 3244.
[32] Wu, T. R.; Chong, J. M. *Org. Lett.*, **2006**, *8*, 15.
[33] Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.*, **2006**, *128*, 3116.
[34] Micalizio, G. C.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 3272.
[35] Morita, R.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Org . Biomol. Chem.*, **2005**, *3* , 1263.
[36] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.*, **2005**, *127*, 3252.
[37] Kim, M.; Lee, D. *Org. Lett.*, **2005**, *7*, 1865.
[38] Li, H.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc*., **2008**, *130*, 3521.
[39] Gu, Y.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.* **2001**, 373.
[40] Clayden, J.; Greeves, N.; Warren, S.; Wothers P. in *Organic Chemistry*, Oxford University Press, **2001**, 905.

[41] Sauer, J.; Wiest, H. *Angew. Chem., Int. Ed. Engl.*, **1962**, *74*, 353.
[42] Diels, O.; Alder, K. *Ann.*, **1931**, *490*, 257.
[43] Alder, K.; Rickert, H. *Chem. Ber.*, **1937**, *70*, 1354.
[44] Seyferth, D.; White, D. *J. Organomet. Chem.*, **1971**, 119.
[45] Kyba, E. P.; Rines, S. P.; Owens, P. W.; Chou, S. –S. *Tetrahedron Lett.*, **1981**, 1875.
[46] Reed, J. A.; Schilling, C. L.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.*, **1969**, 2189.
[47] Dieter, R. K.; Balka, W. H.; Pishpaugh J. R. *Tetrahedron*, **1988**, 1915.
[48] Tolmachova, N. A.; Gerus, I. I.; Vdovenko, S. I.; Essers, M.; Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem.*, **2006**, 4704.
[49] Muzalevskiy, V. M.; Nenajdenko, V. G.; Shastin, A. V.; Balenkova, E. S.; Haufe, G. *Synthesis*, **2008**, 2899.
[50] Schmidt, J. M.; Mercure, J.; Tremblay, G. B.; Page, M.; Kalbakji, A.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. *J. Med. Chem.*, **2003**, 1408.
[51] Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.*, **1992**, *33*, 7839.
[52] Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.*, **1991**, *39*, 5295.
[53] Stefane, B.; Perdih, A.; Pevec, A.; Solmajer, T.; Kocevar, M. *Eur. J. Org. Chem.*, **2010**, 5870.
[54] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.*, **1991**, *91*, 165.
[55] (a) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122. (b) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2003**, *68*, 7158.
[56] (a) Cho, C. -G.; Park, J. -S.; Jung, I. -H.; Lee, H. *Tetrahedron Lett.* **2001**, 42, 1065. (b) Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth.* **1995**, 73, 231.
[57] (a) Kvita, V.; Sauter, H. *Helv. Chim. Acta.*, **1990**, *73*, 883. (b) Ashworth, I. W.; Bowden, M. C.; Dembofsky, B.; Levin, D.; Moss, W.; Robinson, E.; Szczur, N.; Virica, J. *Org. Process Res. Dev.* **2003**, *7*, 74.
[58] Gilman, H.; Avakian, S. *J. Am. Chem Soc.* **1945**, *67*, 349.
[59] Wittig, G. *Naturwissenschafter* **1942**, *30*, 696.
[60] Roberts, J. D.; Simmons Jr., H. E.; Carlsmith, L. A.;Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290.
[61] Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67(13)*, 348.
[62] Huisgen, R.; Knorr, R. *Tetrahedron Lett.* **1963**, 1017.
[63] Campbell, C. D.; Rees, C. W.; *J. Chem. Soc. (C)* **1969**, 742.
[64] Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tet. Lett.* **1991**, *32*, 6735.
[65] Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963,** *85*, 1792.
[66] Wittig, G.; Hoffmann, R. W. *Org. Synth., Coll. Vol. V*, *60*, **1971**.
[67] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
[68] Wu, Q. -C.; Li, B. -S.; Shi, C. -Q.; Chen, Y. -X. *Hecheng Huaxue* **2007**, *15*, 111.
[69] Atkinson, D. J.; Sperry, J.; Brimble, M. A. *Synthesis*, **2010**, 911.
[70] Cobas, A.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1997,** *62*, 4896.
[71] Pena, D.; Escudero, S.; Perez, D.; Guitian, E.; Castedo L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659.
[72] Okuma, K.; Okada, A.; Koga, Y.; Yokomori, Y. *J. Am. Chem. Soc.* **2001**, *123*, 7166.
[73] Liu, Z.; Larock, R. C. *Org. Lett.*, **2003**, 4673.
[74] Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.*, **2006**, 4689.
[75] Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.*, **2008**, 2409.
[76] Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.*, **2008**, 219.
[77] Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.*, **2005**, 15716.
[78] Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.*, **2006**, 7426.
[79] Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.*, **2007**, *9*, 5589.
[80] Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem. Int. Ed.*, **2009**, *48*, 5199.
[81] Pintori, D. G.; Greaney, M. F. *Org. Lett.*, **2010**, 168.

[82] McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.*, **2011**, 3667.
[83] Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.*, **2005**, 5340.
[84] Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.*, **2006**, 11752.
[85] Tadross, P. M.; Virgil, S. C.; Stoltz B. M. *Org. Lett.*, **2010**, 1612.
[86] Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.*, **2008**, 1558.
[87] Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.*, **2008**, 17270.
[88] Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, 1272.
[89] Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, 1180.
[90] Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.*, **2010**, 2271.
[91] Kitamura, T.; Yamane, M. *J. Chem. Soc. Chem. Commun.*, **1995**, 983.
[92] Kitamura, T.; Wasai, K.; Todaka, M.; Fujiwara, Y. *Synlett*, **1999**, *6*, 731.
[93] Cunico, R. F.; Dexheimer, E. M. *J. Organomet. Chem.*, **1973**, *59*, 153.
[94] Crossley, J. A.; Kirkham, J. D.; Browne, D. L.; Harrity, J. P. A. *Tetrahedron Lett.* **2010**, *51*, 6608.
[95] Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860.
[96] Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.*, **2008**, *49*, 6613.
[97] Delaney, P. M.; Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Org. Lett.*, **2008**, 781.
[98] Loupy, A.; Maurel, F.; Sabatie-Gogova, A. *Tetrahedron Lett.*, **2004**, 1683.
[99] Reed, J. A.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.*, **1969**, *34*, 2188.
[100] Kranjc, K.; Kocevar, M. *Tetrahedron*, **2008**, 45.
[101] Wittig, G.; Hoffmann, R. W. *Chem. Ber.* **1962**, *95*, 2718.
[102] Escudero, S.; Perez, D.; Guitian, E.; Castedo, L. *Tetrahedron Lett.*, **1997**, *38*, 5375.
[103] Atanes, N.; Escudero, S.; Perez, D.; Guitian, E.; Castedo, L. *Tetrahedron Lett.*, **1998**, *39*, 3039.
[104] Meier, H. *Lieb. Ann. der Chemie*, **1982**, 914.
[105] Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.*, **2009**, 1007.
[106] Andrews, J. F. P.; Jackson, P. M.; Moody, C. J. *Tetrahedron*, **1993**, 7353.
[107] Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.
[108] Darses, S.; Brayer, J. -L.; Demoute, J. -P.; Genêt, J. -P. *Tetrahedron Lett.* **1997**, *38*, 4393.
[109] Darses, S.; Michaud, G.; Genêt, J. -P. *Eur. J. Org. Chem.* **1999**, 1875.
[110] Molander, G. A.; Katona, B. W.; Machrouki, F. *J. Org. Chem.* **2002**, *67*, 8416.
[111] Kabalka, G. W.; Naravane, A.; Zhao, L. L. *Tetrahedron Lett.* **2007**, *48*, 7091.
[112] Kabalka, G. W.; Dong, G.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 763.
[113] Stefani, H. A.; Cella, R.; Dorr, F. A.; Pereira, C. M. P. T.; Zenid, G.; Gomes, M. *Tetrahedron Lett.* **2005**, *46*, 563.
[114] Paixao, M. W.; Weber, M.; Braga, A. L.; de Azeredo, J. B.; Deobald, A. M.; Stefani, H. A. *Tetrahedron Lett.* **2008**, *49*, 2366.
[115] Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729.
[116] Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.*, **2004**, *45*, 1417.
[117] Kabalka, G. W.; Mereddy, A. R. *Organometallics* **2004**, *23*, 4519.
[118] Vieira, A. S.; Ferreira, F. P.; Fiorante, P. F.; Guadagnin, R. C.; Stefani, H. A. *Tetrahedron*, **2008**, *64*, 3306.
[119] (a) Bir, G.; Schacht, W.; Kaufmann, D. *J. Organomet. Chem.* **1988**, *340*, 267 (b) Billard, T.; Langois, B. R. *J. Org. Chem.*, **2002**, *67*, 997.
[120] Vieira, A. S.; Fiorante, P. F.; Hough, T. L. S.; Ferreira, F. P.; Ludtke, D. S.; Stefani, H. A. *Org. Lett.*, **2008**, *10*, 5215.
[121] Darses, S.; Genêt, J. -P. *Chem. Rev.*, **2008,** *108*, 288.
[122] Kim, W. -S.; Kim, H. -J.; Cho, C. -G. *J. Am. Chem. Soc.*, **2003**, 14288.
[123] Zhu, X. -F.; Schaffner, A. -P.; Li, R. C.; Kwon, O. *Org. Lett.*, **2005**, *7*, 2977.
[124] Bayer, M. J.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.*, **2002**, 2069.

[125] Farquharson, M. J.; Hartman, J. S. *Can. J. Chem.*, **1996**, 1309.
[126] Dunkelblum, A. *Helv. Chimica Acta.* **1970**, 2159.
[127] Tao, C. -Z.; Cui, X.; Li, J.; Liu, A. -X.; Liu, L.; Guo, Q. -X. *Tetrahedron Lett.*, **2007**, 3525.
[128] Grimes, K. D.; Gupte, A.; Aldrich, C. C. *Synthesis*, **2010**, 1441.
[129] Zimmerman, H. E.; Grunewald, G. L.; Paufler, R. M.; Sherwin, M. A. *J. Am. Chem. Soc.*, **1969,** *91*, 2330.
[130] Cho, C. G.; Kim, Y. W.; Lim, Y. W.; Park, J. S.; Lee, H.; Koo, S. *J. Org. Chem.*, **2002**, 290.
[131] Hilton, P. J.; McKinnon, W.; Gravett, E. C.; Peron, J. –M. R.; Frampton, C. M.; Nicholl, M. G.; Lord, G. *Steroids*, **2010**, 1137.
[132] Pirkle, W. H.; Dines, M. *J. Org. Chem.*, **1969,** *34*, 2239.
[133] Menke, J. L.; McMahon, R. J. *Can. J. Chem.*, **2011**, 186.
[134] Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4364.
[135] Rossi, A.; Schinz, H. *Helv. Chim. Acta.*, **1948**, 473.
[136] Metanis, N.; Keinan, E.; Dawson, P. E. *J. Am. Chem. Soc.*, **2005**, 5862.
[137] Wiley, R. H.; Hart, A. J. *J. Am. Chem. Soc.*, **1954**, 1942.