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The Development of Metal Catalyzed Benzannulation Protocols for the Synthesis of Aromatic Boronic Esters

By

Anne-Laure Auvinet

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

University of Sheffield

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In memory of my colleague and dear friend Dr Jérôme Vivat

"Patience et longueur de temps font plus que force ni que rage"

-Jean De La Fontaine-

The Development of Metal Catalyzed Benzannulation Protocols for the Synthesis of Aromatic Boronic Esters

Anne-Laure Auvinet

Abstract

A transition metal catalyzed benzannulation of alkynylboronates and dienes/diene equivalents has been developed for the synthesis of aromatic boronic esters. Alkynylboronates participate in a regioselective cycloaddition with 1,3-butadiene derivatives, under ambient conditions in the presence of a cobalt catalyst. The methodology provides a convenient and general route to access 1,2-*di*-substituted, 1,2,3- or 1,3,4-*tri*-substituted and 1,2,3,4-*tetra*-substituted benzene based systems incorporating a boronate moiety. The newly formed aromatic boronic esters can undergo a Suzuki cross-coupling to afford functionalized aminopyridine derivatives.

In addition, alkynylboronates participate in benzannulation reactions with cyclobutenones, at room temperature under nickel catalysis. The strategy provides an easy access to highly (*tetra*/*penta*) substituted phenol boronic ester derivatives in a remarkably regioselective manner. This chemistry offers an efficient route to quinone boronic esters, as well as the opportunity to carry out benzannulation and cross-coupling reactions in one-pot with a single pre-catalyst.

To extend the general strategy, an alternative sequence that employs a palladium catalyzed cyclisation process involving *o*-alkynylanilines is terminated by a boration reaction to furnish the corresponding indole boronic ester derivatives.

Acknowlegements

Waahoo... I can't believe that my time in Sheffield is coming to an end! Surely, a lot has happened in these last three years…What A life experience!

I would like to thank the University of Sheffield and all the people involved @ the university for providing such a good service, EPSRC for funding and everyone I have been fortunate to meet in the arena…

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What a feeling! Oli, we met by a trick of fate few years ago and starred @ the stars (don't remember exactly why) but I guess, there, our friendship began. We met again & again in unexpectable places. You are an outstanding friend and confident and I am really lucky to have met you. Thank you so much Olivier Rannou ;)

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Yo Calum, what a character ! Thanks for bringing the scottish touch in he lab… It was fun to work next to you ;) Thank you champion for introducing me to guitar hero. Hope you managed to get your uzi 9mm ☺ Get your Axxx to Mars ;)

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I wish you all the best down under Dr. Have fun and keep in touch xxx

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With love from E26 ☺ xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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Au cours des experiences de la vie nous devons nous assagir. En avançant, le temps nous est compté mais nous nous devons de lui faire confiance… ***"Akuna matata"***

Never forget where you are coming from & Don't stop believing... ☺

Anne-Laure Auvinet
Septembre 2011

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Abbreviations

Å	Ångstroms (10^{-10}m)
Ac	acetyl
acac	acetylacetonate
ACN	acetonitrile
AmOH	amyl alcohol
Aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'binaphthyl
Bu/^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
Bn	benzyl
br	broad
cat	catechol
cat.	catalyst
calcd	calculated
COD/cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	dichlorobenzene
DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL/DIBAL-H	diisobutylaluminium hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate

DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMG	Directed Metalation Group
DMSO	dimethyl sulfoxide
DPPE/dppe	ethylenebis(diphenylphosphine)
DPPP/dppp	1,3-bis(diphenylphosphino)propane
Dtby	4,4'-di-*tert*-butyl-2,2'-bipyridine
EI	electron impact
eq	equivalents
EtOAc	ethyl acetate
FTIR	Fourier Transform Infrared
g	gram
GCMS	Gas chromatography Mass Spectrometry
Hz	hertz
HRMS	High-Resolution Mass Spectrum
h	hour
IPA	propan-2-ol
Pr/^{n}Pr	*normal*-propyl
^{i}Pr	*iso*-propyl
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
KR	Kinetic Resolution
L	litre
L/Ln	ligand
LA	Lewis Acid
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	milli, medium (FTIR), multiplet (NMR)
M	mega or metal or molar
mmHg	millimetres of mercury
MAD	methylaluminium bis(2,6-di-tert-butyl-4-methylphenoxide)
MAO	methylaluminoxane

Me	methyl
Mes	mesityl
Ms	mesyl
MS	Mass Spectrometry or Molecular Sieves
μ	micro
min	minute
m	milli or medium or multiplet
m	meta
mol	moles
M.pt	Melting Point
MW	microwave
NCS	*N*-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
o	ortho
p	para
PEPPSI	Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation
Ph	phenyl
PIFA	phenyl iodine bis(trifluoroacetate)
Pin	pinacol structure
ppm	parts per million
PTSAA	*para*-Toluenesulfonic anhydride
Py	pyridyl/pyridine
q	quartet
R	alkyl group
RT or rt	room temperature
s	singlet (NMR), strong (FTIR)
sat.	saturated
SM	starting material
SN_{Ar}	Nucleophilic Substitution Aromatic
t	triplet
TBS/TBDMS	*tert*-Butyldimethylsilyl
TDMPP	tris(2,6-dimethoxyphenyl)phosphine

Tf	triflate/trifluoromethanesulfonate
TFP	tri-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl
Tp	tris(1-pyrazolyl)borate
TsOH	*para*-Toluenesulfonic acid monohydrate
w	weak
Xn	ligand
X	directing group, leaving group

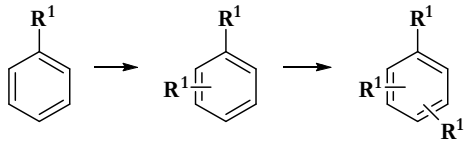
CHAPTER I

Overview of transition metal catalyzed benzannulation reactions

---

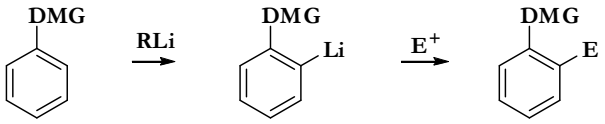
1.0 Introduction

Studies on the structure, reactions and synthesis of aromatic compounds are steeped in the history of organic chemistry since the time of Kekulé's dream[1] a century ago. Functionalised aromatic and heteroaromatic compounds are ubiquitous in organic chemistry, and are widely used in industry as well as in academic laboratories. Their preparation has traditionally been carried out by the stepwise introduction of substituents using well known techniques based on electrophilic aromatic substitution processes such as the Friedel-Crafts reaction[2] (**Scheme 1.1**). This is a useful method for the synthesis of polysubstituted benzene derivatives. However, high regioselectivity (and yield) can only be achieved by the careful choice of reagents and a well planned synthetic strategy.



Scheme 1.1

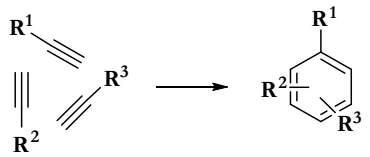
Directed *ortho* metalation techniques developed by Snieckus represent another useful synthetic method for the introduction of a substituent at the *ortho*-position of a benzene ring and in heteroaromatic systems[3] (**Scheme 1.2**). However, the scope of this reaction is clearly restricted by its nature. There remain a number of potential drawbacks to approaches that involve the direct functionalisation of an aromatic ring including regiocontrol and functional group compatibility, not to mention the question of availability of the aromatic precursor itself. For these reasons, transition metal-catalyzed benzannulation methods are promising alternatives for the synthesis of benzene derivatives.



DMG = Directed Metalating Group

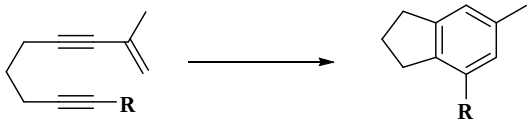
Scheme 1.2

With respect to alkyne cycloaddition strategies, one of the premier synthetic methods for accessing substituted benzene derivatives is the transition metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes, first discovered by Reppe.[4] This reaction allows the formation of three C-C bonds in one step (**Scheme 1.3**).



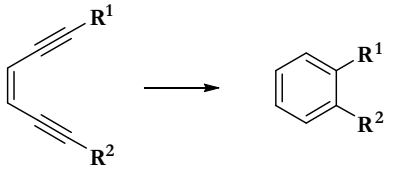
Scheme 1.3

The construction of a benzene ring by a metal catalysed [4 + 2] approach is another promising methodology. The intramolecular reaction of conjugated enynes with alkynes in the presence of Lewis acid or under thermal conditions has been reported[5] (**Scheme 1.4**).



Scheme 1.4

Related studies have shown that the benzene ring can also be formed by cyclisation of dienynes or endiynes[6] (**Scheme 1.5**). While the thermal benzannulation of these compounds, for example using the Bergman cyclisation, has been extensively studied and reviewed, there are relatively few examples of transition metal catalysed variants[7].



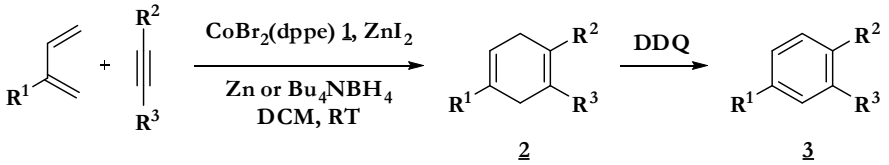
Scheme 1.5

This review will cover some key metal catalysed benzannulation processes, and is organised with respect to the transition metal employed.

1.1 Cobalt-Catalysis

Most Diels-Alder reactions are conducted between 1,3-dienes and dienophiles that exhibit activating electronic properties or that bear substituents that allow Lewis acid coordination and thus provide a means for promoting the reaction under mild conditions. Problems arise when electronically neutral substrates without coordinating groups, such as pure hydrocarbons, are used. Drastic conditions are often required to force these substrates to react, consequently leading to an increase in the number of side reactions such as starting material polymerisation. To circumvent this problem, π-coordinating metal catalysts can be used, and one of the most promising developments of recent years has employed a cobalt catalyst system. Originally decribed by Brunner, Lautens and Snyder, cobalt catalyst systems can be employed in homo-Diels-Alder reactions[8]. More recently, Hilt and co-workers have compiled a body of work to further analyse and develop the scope of this and other cobalt mediated processes[9]. The applied catalyst system, made up of $CoBr_2$(dppe) **1**, zinc iodide and zinc or tetrabutylammonium borohydride, is inexpensive and both easy to prepare and handle. With this catalyst, a great diversity of non-activated dienes and internal as well as terminal alkynes can be used in the neutral electron demand Diels-Alder reaction for the synthesis of dihydroaromatic compounds[10]. The resulting oxygen-sensitive cyclohexa-1,4-dienes **2** can be isolated or directly oxidised by DDQ to the corresponding benzene derivatives **3** (**Scheme 1.6**) in good to excellent yield. The reaction proceeds with

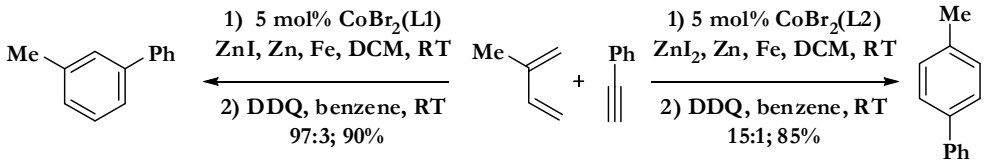
regioselectivities in the range of 80:20 to 98:2 for the *para*-product depending on the steric bulk of the substituents.



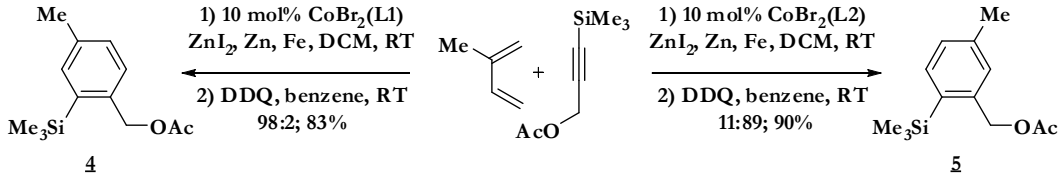
Scheme 1.6

Recently, Hilt reported a catalyst system for the regioselective synthesis of *meta*-substituted benzenes. They found that by changing the ligand on cobalt from a bidendate phosphine ligand (dppe) **L2** to Schiff base type ligands **L1**, one could alter the regioselectivity of the cyclisation process[11] (**Scheme 1.7**). The extraordinary dependency of the regioselectivity has been rationalised by theoretical investigations reported by Hilt and Frenking[12]. The calculations concur with the experimental finding that the *para*-product is kinetically favoured when L = dppe (**L2**) while the meta product is favoured kinetically when L = imine (**L1**). In addition, more recently Hilt[13] reported a simple and flexible approach for the synthesis of silicon-functionalized compounds. Indeed, the cobalt catalyzed Diels-Alder reactions lead to the generation of both possible regioisomers from an alkyne and a 1,3-diene by simply altering the ligands of the cobalt complex (**Figure 1.1**). Therefore, the two catalyst systems were able to convert the silyl-functionalized alkynes in very good yields and with complementary regioselectivity to the desired *meta*-substituted cycloadduct **4** using ($CoBr_2$(**L1**)) as a catalyst and to the *para*-substituted product using **5** ($CoBr_2$(**L2**)) (**Scheme 1.8**).

Figure 1.1

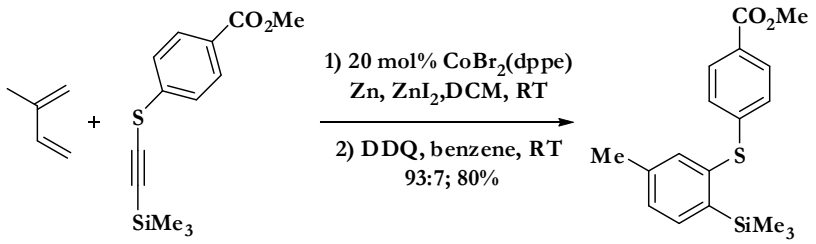


Scheme 1.7



Scheme 1.8

The scope and utility of these cobalt catalysed Diels-Alder reactions was demonstrated by their application to a range of heteroatom-substituted substrates for the synthesis of valuable building blocks for organic synthesis. The successful use of alkynyl sulfides in the cobalt catalysed Diels-Alder reaction for the construction of highly functionalised diaryl sulfides is notable and significantly broadens the scope of this reaction[14] (**Scheme 1.9**).

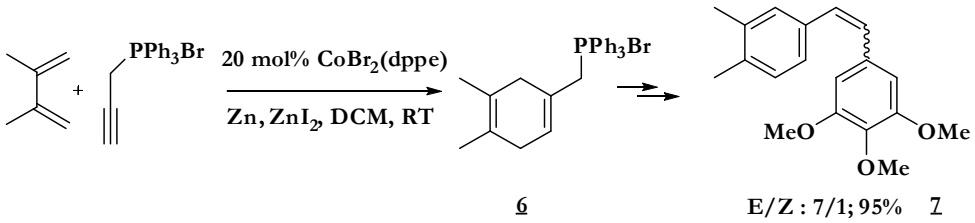


Scheme 1.9

A range of aryl-substituted alkynylsulfides were investigated in this reaction and the desired products were obtained in good to excellent yields. One drawback to this particular method is the ability of sulphur-containing compounds to poison the cobalt catalyst, resulting in the requirement for higher catalyst loadings.

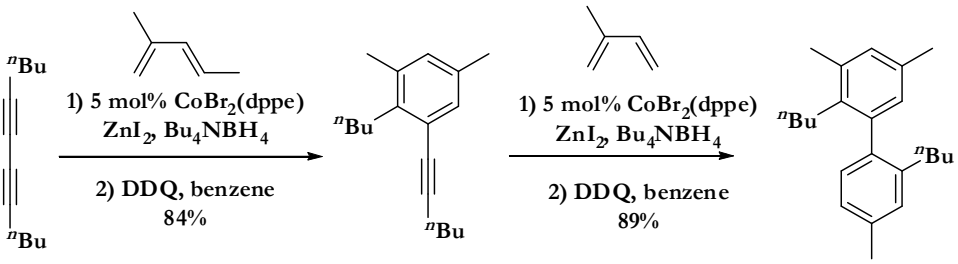
Additionally, alkynyl phosphonium salts have been applied in cobalt-catalysed Diels-Alder reactions (**Scheme 1.10**). The intermediate phosphonium salts **6**

were not isolated but directly used in a Wittig reaction and subsequently oxidised with DDQ into stilbenes **7**[15]. Notably, both E/Z mixtures and regioisomeric mixtures were obtained when unsymmetrically substituted 1,3-dienes were employed.



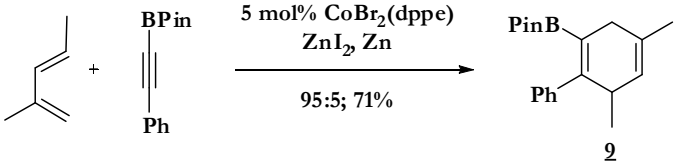
Scheme 1.10

Also, symmetrical as well as unsymmetrical 1,3-diynes can be used in a two-step procedure for the construction of highly substituted biphenyls[16] (**Scheme 1.11**). The products were obtained in high yields and as single regioisomers.



Scheme 1.11

The use of boron-substituted alkyne substrates in the cobalt-catalysed Diels-Alder reaction has been studied by Hilt. Alkynylboronic esters reacted slowly in thermal Diels-Alder reactions, resulting in rather harsh reaction conditions for their efficient use. In contrast, they smoothly participate in cycloadditions under the mild conditions of the cobalt-catalysed reaction, affording the boron-substituted cyclohexadienes **8** in excellent yield[17]. When 2-substituted 1,3-dienes such as isoprene were used, the regioisomer formed was the one in which the boron functionality and the substituent from the 1,3-diene emerged in a *meta*-relationship to each other (**Scheme 1.12**).



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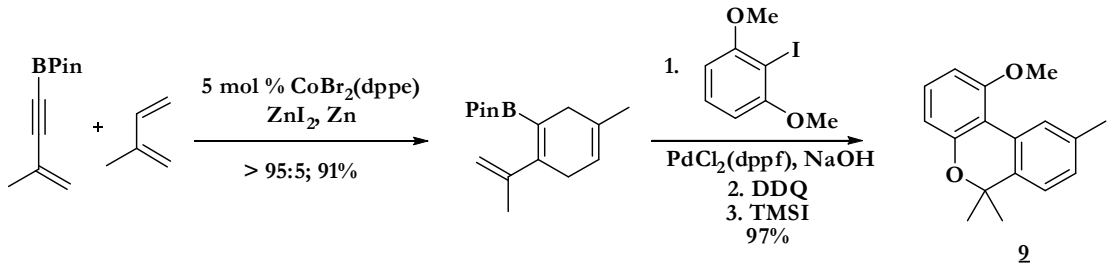
Scheme 1.12

The utility of boron-substituted cyclohexadienes was demonstrated by a palladium-catalysed Suzuki reaction to ultimately form the framework of the cannabinoid family of natural products **9**[17] (**Scheme 1.13**).



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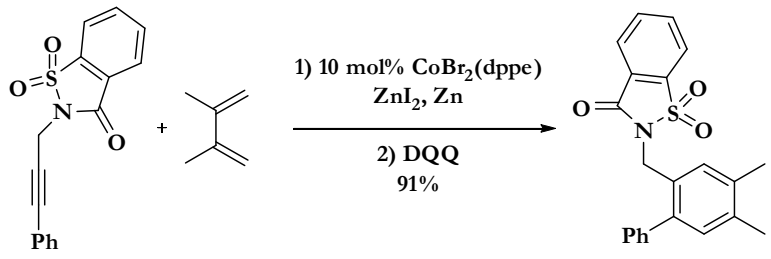
Scheme 1.13

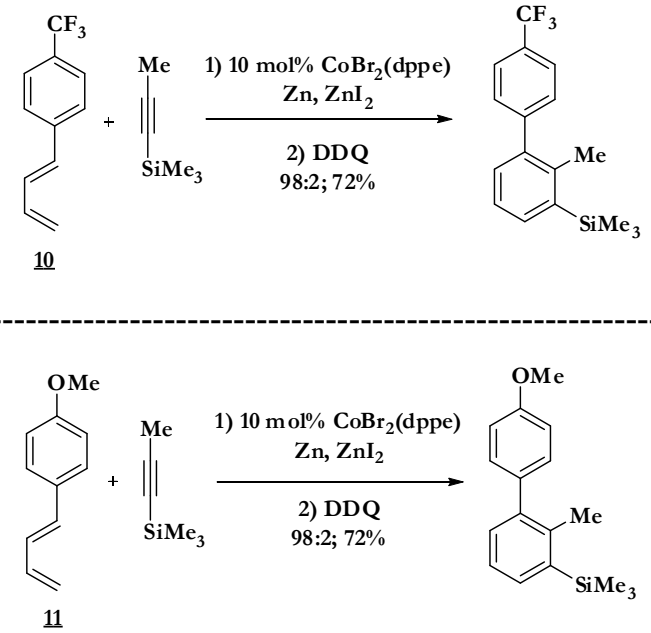
The cobalt-catalysed Diels-Alder reaction tolerates a variety of functional groups and is broadly applicable. However, free amines are not tolerated because of their ability to coordinate to the cobalt catalyst. Nevertheless, their protected counterparts can be successfully applied in the reaction for the construction of protected benzylic imides and sulfonamides[18] (**Scheme 1.14**).



Scheme 1.14

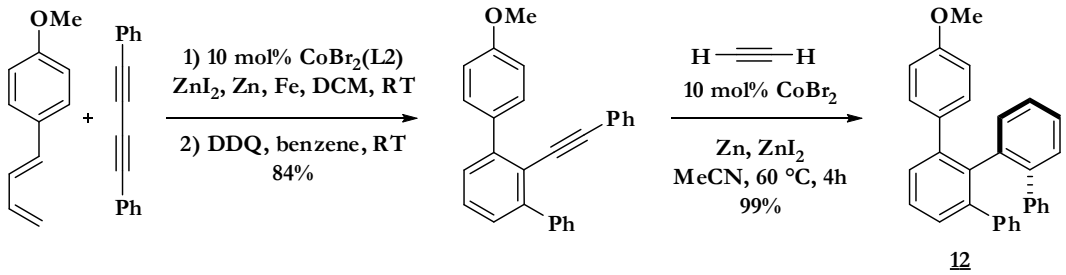
Hilt[19] also reported a regioselective cobalt-catalysed Diels-Alder reaction towards polyfunctionalised benzene derivatives. Dienes containing both

electron withdrawing **10** and donating aromatic groups **11** yield the desired aromatic derivatives with excellent regioselectivities (**Scheme 1.15**).



Scheme 1.15

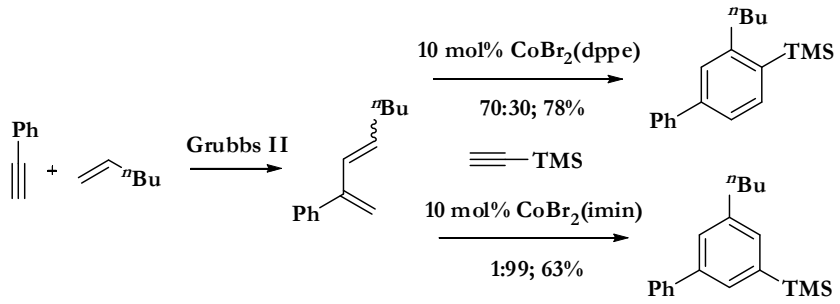
Interestingly, this methodology can be applied in combination with cobalt-catalyzed cyclotrimerisation using acetylene under atmospheric pressure to prepare axially (racemic) chiral product **12** under mild conditions[19] (**Scheme 1.16**).



Scheme 1.16

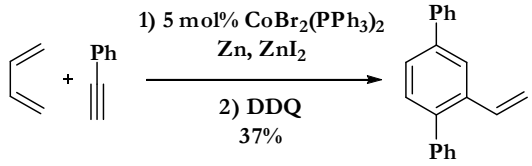
In this context Hilt[20] reported a ruthenium-catalyzed enyne metathesis reaction followed by a cobalt-catalyzed Diels-Alder reaction and oxidation of dihydroaromatic intermediate to generate the two regioisomeric aromatic products in good overall yield in a "one-pot" procedure. The regiochemestry

of the cycloaddition can be controlled by the ligand choice on the cobalt catalyst to generate the product with the 1, 3, 5- or the 1, 2, 4-substitution pattern predominantly (**Scheme 1.17**).



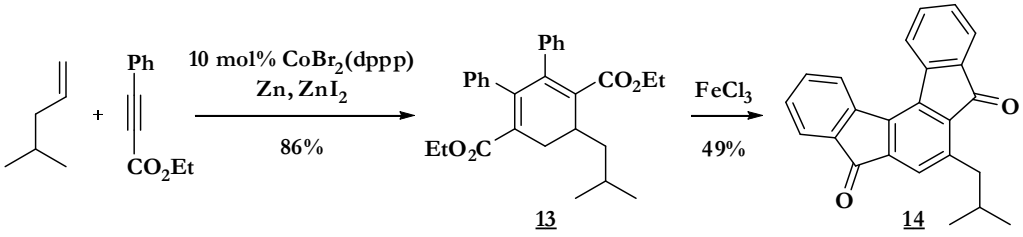
Scheme 1.17

Hilt[21] demonstrated recently that the cobalt-catalysed cycloaddition of alkynes and 1,3-dienes can be expanded to the [2 + 2 + 2] cycloaddition process leading to vinyl-substituted cyclohexa-1,3-dienes which can then be oxidised to the corresponding aromatic derivatives (**Scheme 1.18**).



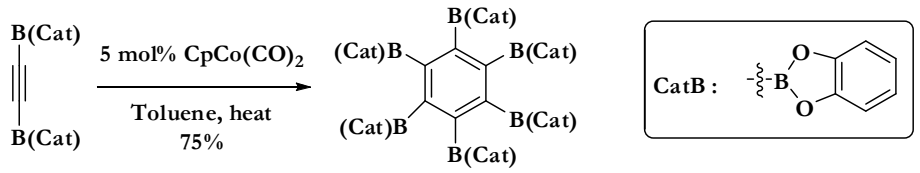
Scheme 1.18

In addition, Hilt[22] reported a highly chemo- and regioselective intramolecular variant, that allows an access to polysubstituted 1,3-cyclohexadiene derivatives **13** bearing a suitable group to promote a cyclisation to anthrone type products **14** (**Scheme 1.19**).



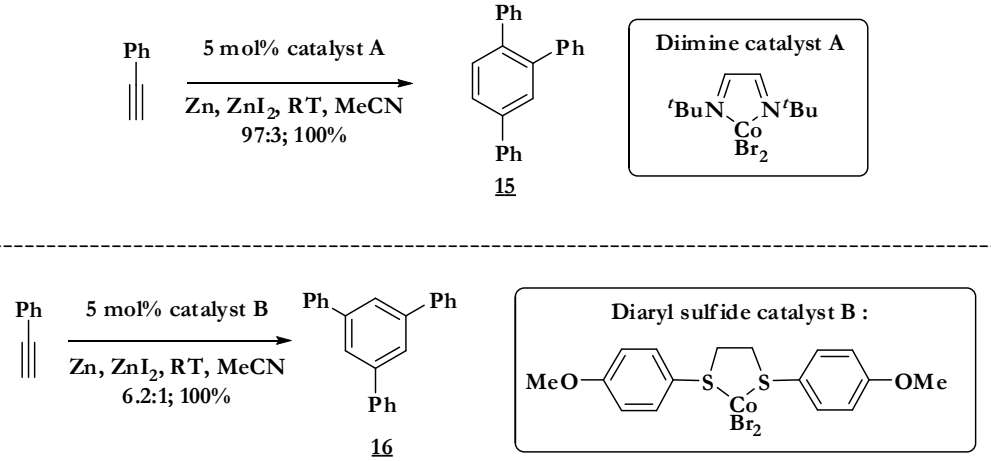
Scheme 1.19

The transition metal-catalysed cyclotrimerisation is a valuable method for the efficient and economical generation of arenes. Siebert[23] and Vollhardt[24] reported the synthesis of polyborylated aromatic compounds by this method, which are potentially versatile building blocks in organic synthesis (**Scheme 1.20**).



Scheme 1.20

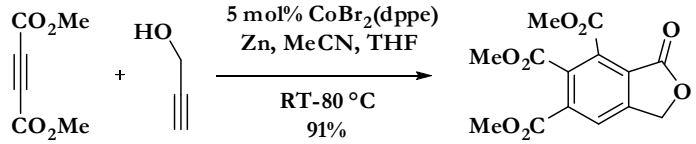
Hilt[25] investigated a simple system for the cyclotrimerisation of various terminal alkynes under mild conditions. The regioselectivity of the reaction was greatly influenced by the choice of solvent and ligand. In general, the formation of the 1,2,4-substituted isomers **15** was favoured with selectivity of up to 97:3 with diimine-based ligands. In contrast, when electron rich diaryl sulphide ligands (**Scheme 1.21**) were used, the symmetrical 1,3,5-trisubstituted product **16** (1:6.2) was obtained in high yield[26].



Scheme 1.21

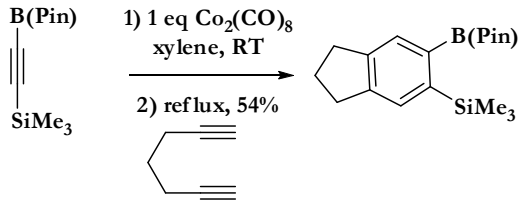
Cheng[27] reported the first chemo- and regioselective trimerisation of propiolates and propargylic alcohols in a one-pot procedure. In this reaction, a

cobalt-catalysed cyclotrimerisation is combined with a transesterification to produce bicyclic lactones in high yields (**Scheme 1.22**).



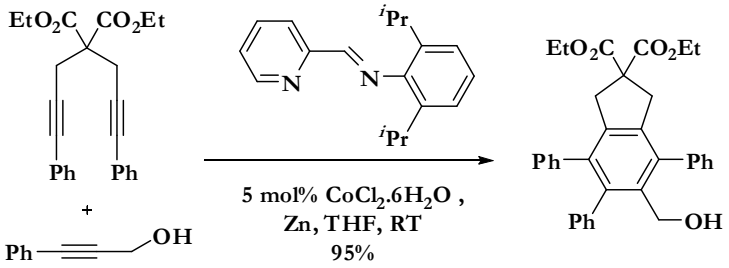
Scheme 1.22

Vollhardt[28] described the use of boron-substituted alkynes in a novel dicobalt octacarbonyl promoted reaction for the construction of arylboronic esters in moderate yield (**Scheme 1.23**). Such compounds are useful building blocks for cross coupling reactions.



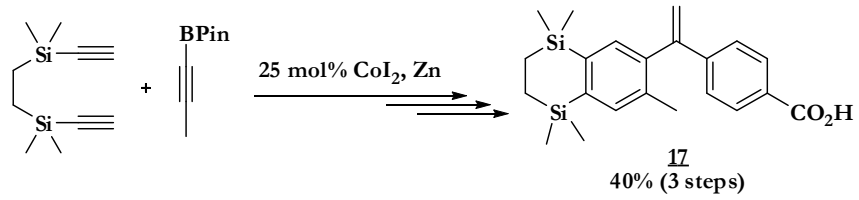
Scheme 1.23

Okamoto[29] recently described the synthesis of polysubstituted arenes using this strategy (**Scheme 1.24**). He showed that in the case of unsymmetrical diynes, the catalyst system exhibits moderate to excellent regioselectivities and the products are formed in good to excellent yields.



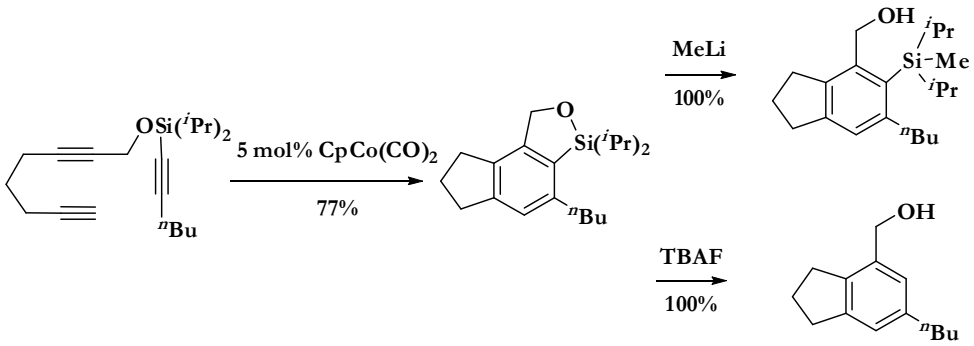
Scheme 1.24

The use of silicon-tethered diynes for the construction of 1,4-disilatetralins, 1,3-disilaindanes and 1,3-disila-1,3-dihydroisobenzofurans has been extensively investigated by Tacke.[30] The target compounds were obtained in moderate to good yield. The reaction was applied to the construction of the retinoid agonist disilahexarotene **17** (**Scheme 1.25**).



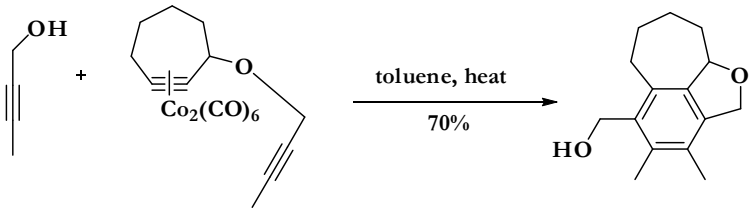
Scheme 1.25

Malacria[31] also investigated the role of silicon in the cobalt-catalysed [2 + 2 + 2] cycloaddition and developed a fully chemo- and regioselective route to form the corresponding benzene ring (**Scheme 1.26**).



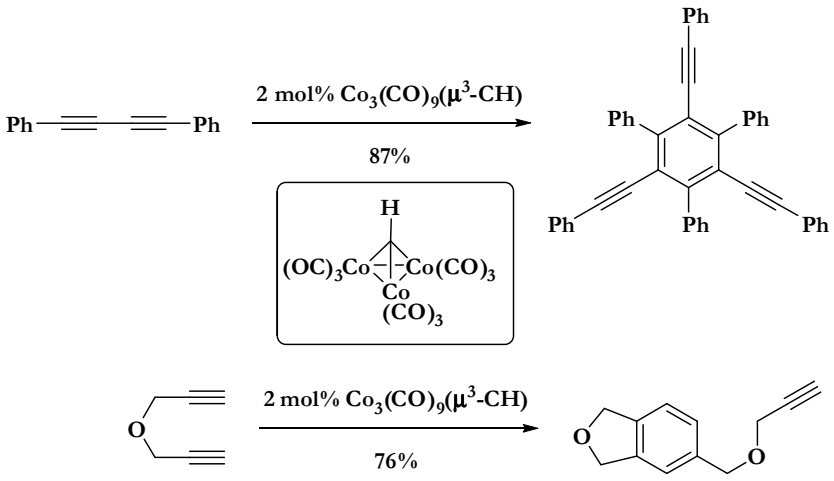
Scheme 1.26

Green[32] used a cobalt-mediated [2 + 2 +2] cycloaddition of cycloheptadiynes for the construction of fused 7,6,5-ring systems (**Scheme 1.27**).



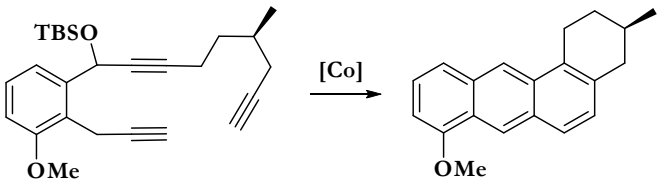
Scheme 1.27

Sugihara[33] reported a cobalt carbonyl cluster that can catalysed inter- and intramolecular cyclotrimerisation of alkynes to furnish highly substituted benzene derivatives (**Scheme 1.28**).

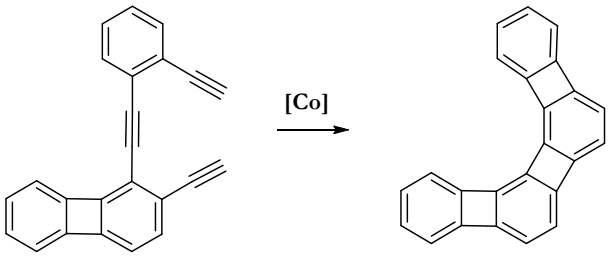


Scheme 1.28

The intramolecular cyclotrimerisation of alkynes is a powerful method for the construction of highly substituted polycyclic compounds. Nevertheless, applications in synthesis are relatively rare because of the sometimes tedious synthesis of the required triynes. Two examples are illustrated in **Scheme 1.29**.



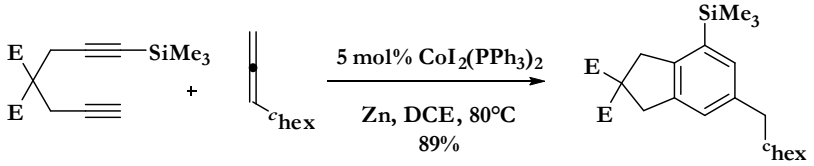
Key step towards rubiginone B2[34]



Phenylenes[35]

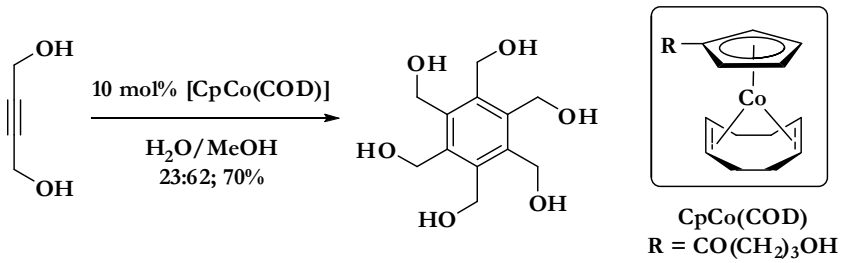
Scheme 1.29

Wu *et al.* have shown that related benzene derivatives can be accessed through a [2 + 2 + 2] cycloaddition of hepta-1,6-diynes with allenes[36] (**Scheme 1.30**).



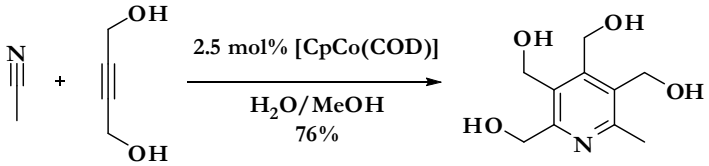
Scheme 1.30

Eaton[37] reported a cobalt-catalysed cyclotrimerisation of alkynes in aqueous solution giving a direct access to polyfunctionalised benzene derivatives (**Scheme 1.31**).



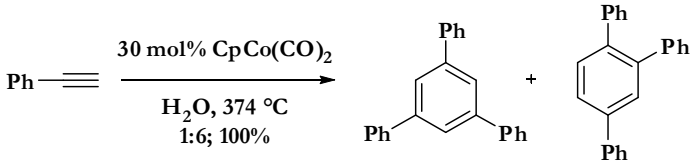
Scheme 1.31

The cyclotrimerisation concept can be expanded to include nitriles to furnish N-heterocycles[38]. This method offers the opportunity to prepare pyridine derivatives under mild conditions in good to excellent yield (**Scheme 1.32**).



Scheme 1.32

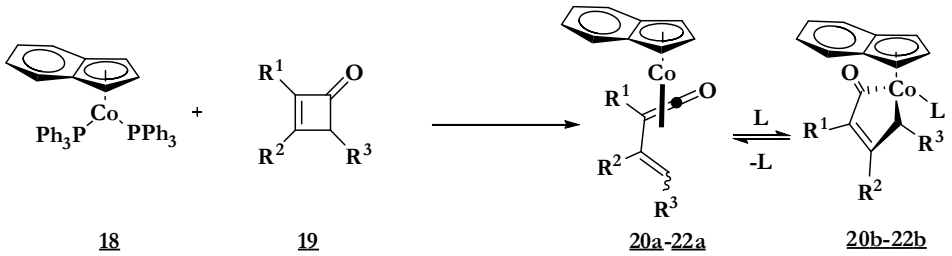
Finally, Parsons[39] demonstrated that cobalt-catalysed cyclotrimerisation of alkynes can be achieved in supercritical water, thereby avoiding the need for organic solvents (**Scheme 1.33**).



Scheme 1.33

* [4 + 2] *Cycloadditions involving vinyl ketene equivalent*

A few years ago, Liebeskind[40] described a cobalt catalyst that leads to functionalised phenol derivatives. The reaction required an electron-rich cobalt catalyst (η^5-C_9H_7)$Co(PPh_3)_2$ **18** that undergoes insertion into cyclobutenones **19** to form complexes **20**-**22** (**Table 1.1**) that subsequently undergo a cycloaddition with alkynes to provide the corresponding oxygenated aromatic compounds **23** & **24** (**Table 1.2**).



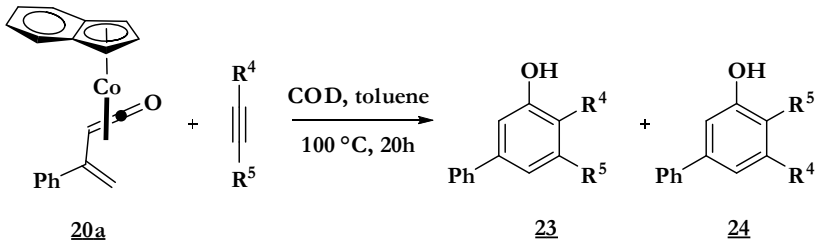
18 **19** **20a-22a** **20b-22b**

Entry	R^1	R^2	R^3	Yield (%)	Product
1	H	Ph	H	32	**20a**
2	H	OEt	H	25	**21b**
3	Et	Et	H	0	-
4	H	Ph	Me	80	**22a**
5	Et	Et	Me	0	-

Table 1.1

However, the insertion of cobalt was difficult with some 3-substituted cyclobutenones (**Table 1.1**, entry 1 & 2) but could be quite efficient with some 3,4-disubstituted cyclobutenones (**Table 1.1**, entry 4). 2,3- Disubstituted and 2,3,4-trisubstituted cyclobutenones prevented the reaction from occurring altogether (**Table 1.1**, entry 3 & 5). The complex **22** was found to be unreactive toward alkyl-substituted alkynes. Only, DMAD **25** gave a significant

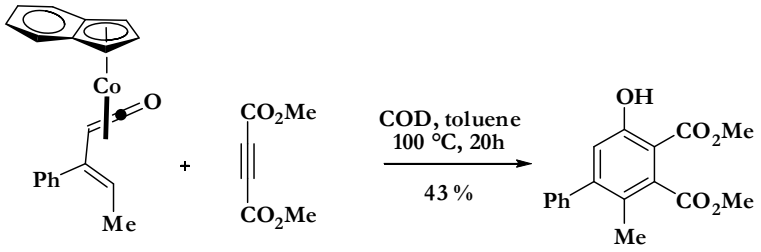
yield of phenol **26** (**Scheme 1.34**). Cobalt complex **20a** undergoes a cycloaddition with alkynes to provide the corresponding phenol derivatives **23**, **24** in good yields but with low levels of regiocontrol (**Table 1.2**, entry 1 & 2).



20a **23** **24**

Entry	R^4	R^5	Ratio 23:24	Yield (%)
1	H	Bu	71:29	63
2	CO_2Et	Me	46:54	92

Table 1.2

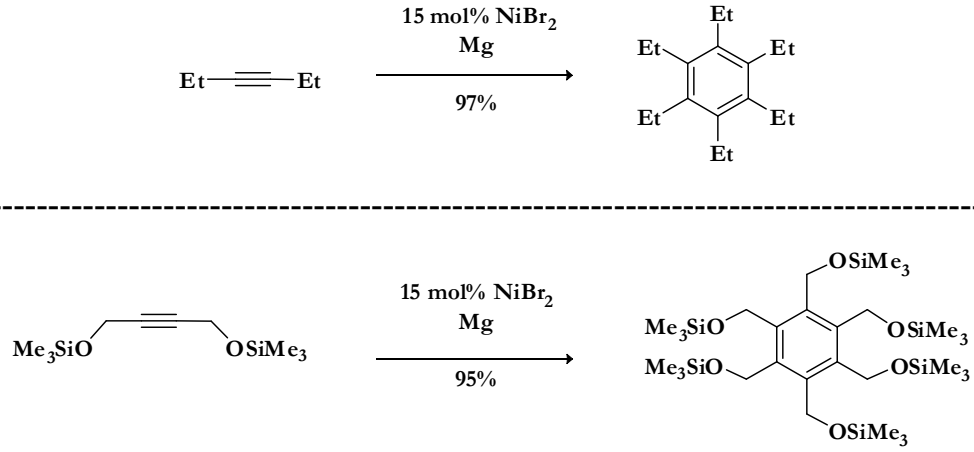


22 **25** **26**

Scheme 1.34

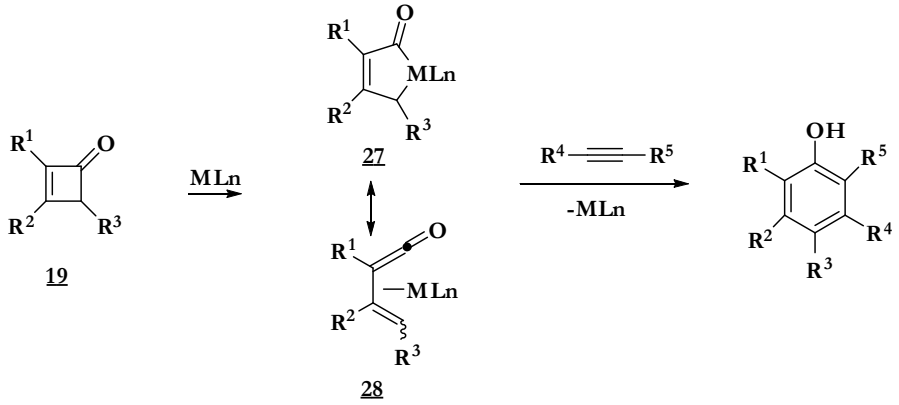
1.2 Nickel Catalysis

Alphonse[41] and co-workers have reported the nickel catalysed cyclotrimerisation of alkynes (**Scheme 1.35**). The benzannulation occurs with a variety of alkynes, however the process is most effective when an acceptor group is incorporated in the propargylic position. Notably, no cyclisation was observed when bulky groups where appended to the triple bond.



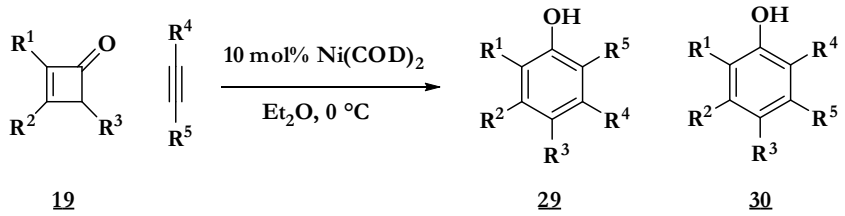
Scheme 1.35

The convergent synthesis of substituted phenols is possible by a nickel(0)-catalysed ring opening cycloaddition of cyclobutenones with alkynes[42]. The reaction is proposed to proceed *via* η^2-vinylketene **27** or η^4-vinylketene **28** intermediates (**Scheme 1.36**).



Scheme 1.36

Liebeskind[42] showed that nickel(0) can catalyse the coupling of cyclobutenones with alkynes in a direct way providing substituted phenols under mild conditions (**Scheme 1.37**).



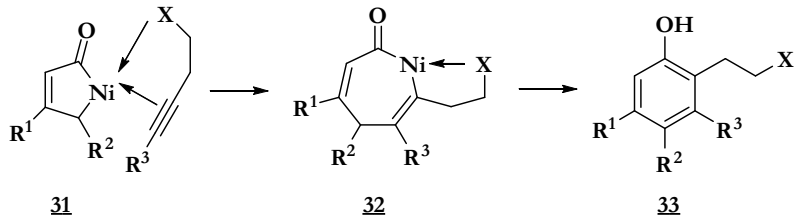
19 **29** **30**

Scheme 1.37

Entry	R^1	R^2	R^3	R^4	R^5	Ratio 29:30	Yield (%)
1	H	^{n}Bu	H	Me	$(CH_2)_2$OTBDMS	75:25	59
2	H	^{n}Bu	H	Me	$(CH_2)_3$OTBDMS	50:50	67
3	H	^{n}Bu	H	Me	$(CH_2)_2$OTHP	65:35	47
4	H	Ph	H	Et	$(CH_2)_2$Cl	72:28	64
5	H	Ph	H	Et	$(CH_2)_3$Cl	58:42	57

Table 1.3

Regioselectivity appears to be controlled by the size of alkyne substituents. Alkynes bearing heteroatom-substituted side chains did show a modest selectivity which was greater with two carbon-containing tethers (**Table 1.3**, entry 1, 3 & 4) than three carbon-containing tethers (**Table 1.3**, entry 2 & 5). In all cases, the major product bears the heterosubstituted chain *ortho*-to the phenol. These observations can be explained by the mechanism outlined in **Scheme 1.38**. The alkyne inserts preferentially into the metal-C4 bond of the vinylketene complex **31** followed by chelation of nickel with a heteroatom-substituted alkyne **32** and reductive elimination furnishes the observed phenol derivatives **33**.

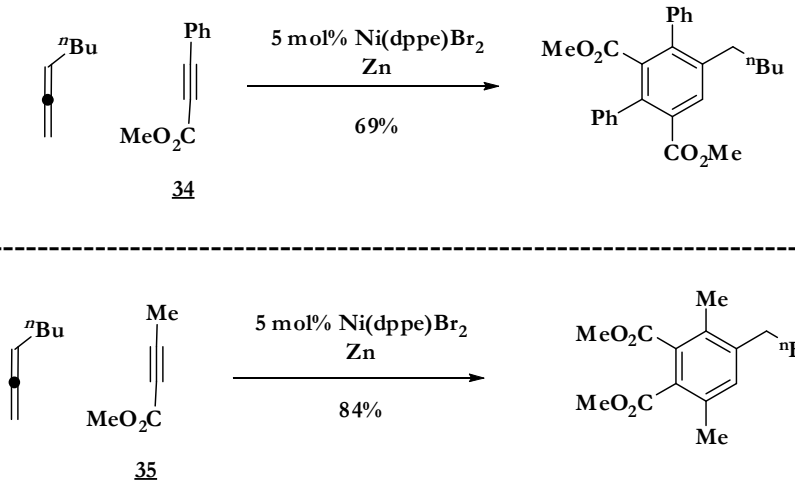


31 **32** **33**

Scheme 1.38

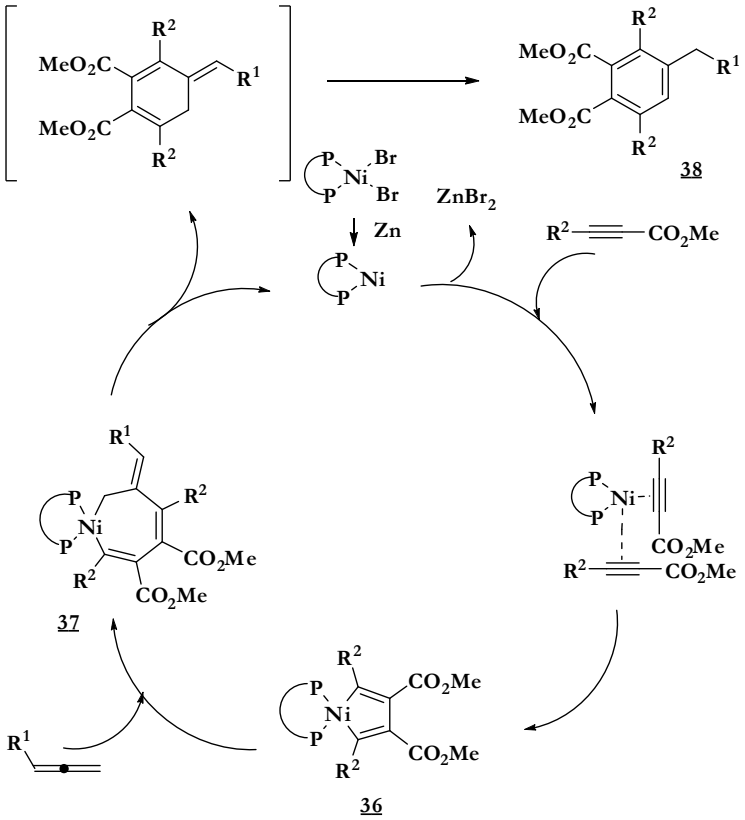
Cheng[43] reported a highly regio- and chemoselective cyclotrimerisation of propiolates with allenes to generate polysubstituted benzene derivatives.

Interestingly, phenyl-substituted propiolate **34** and the corresponding methyl-substituted analogue **35** provided complementary regioisomers (**Scheme 1.39**).



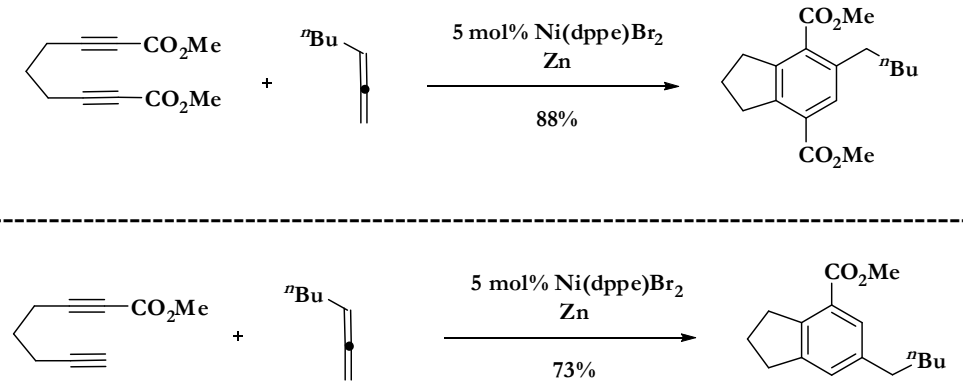
Scheme 1.39

With regard to the reactions outlined in **Scheme 1.39**, the first step of the proposed mechanism is the reduction of Ni(II) species by Zn metal which initiates the catalytic reaction. Two molecules of alkyne then coordinate to the metal centre and a regioselective head-to-head oxidative cyclometalation takes place, furnishing the nickelacyclopentadiene **36**. Coordination of the allene and subsequent insertion of this molecule into a Ni(II)-carbon bond gives nickelacycloheptadiene intermediate **37**. Subsequent reductive elimination and isomerisation affords the observed benzene derivative **38** and regenerates the Ni(0) catalyst (**Scheme 1.40**). For the reaction of methyl phenyl propiolate, apparently a head-to-tail oxidative cyclometalation occurs and this produces the other regioisomer.



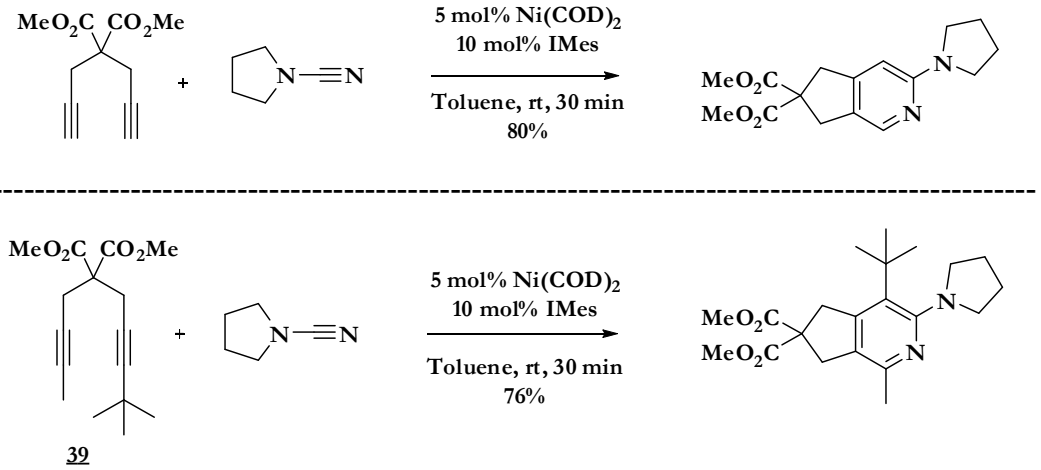
Scheme 1.40

Cheng[44] investigated the [2 + 2 + 2] cycloaddition of electron deficient diynes with allenes and developed a novel and highly regio- and chemoselective route to polysubstituted benzene derivatives. This strategy is compatible with symmetrical and unsymmetrical alkynes (**Scheme 1.41**). Allenes are synthetically equivalent to monosubstituted alkynes but they are superior to them in terms of reactivity and selectivity.



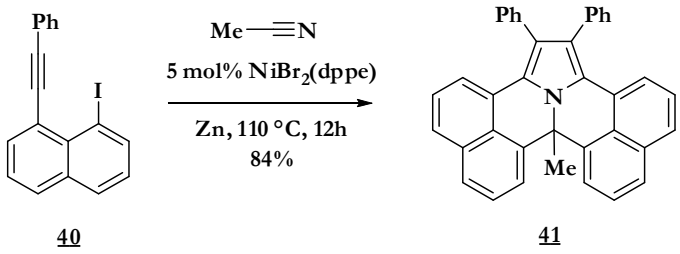
Scheme 1.41

Recently, Louie[45] demonstrated that diynes undergo [2 + 2 + 2] cycloaddition reactions with cyanamides in the presence of a Ni-catalyst to generate *N,N*-disubstituted 2-aminopyridines in good yield (**Scheme 1.42**). This strategy is compatible with internal as well as with terminal diynes with a large range of cyanamides and provides excellent levels of regiocontrol with unsymmetrical diyne **39**.



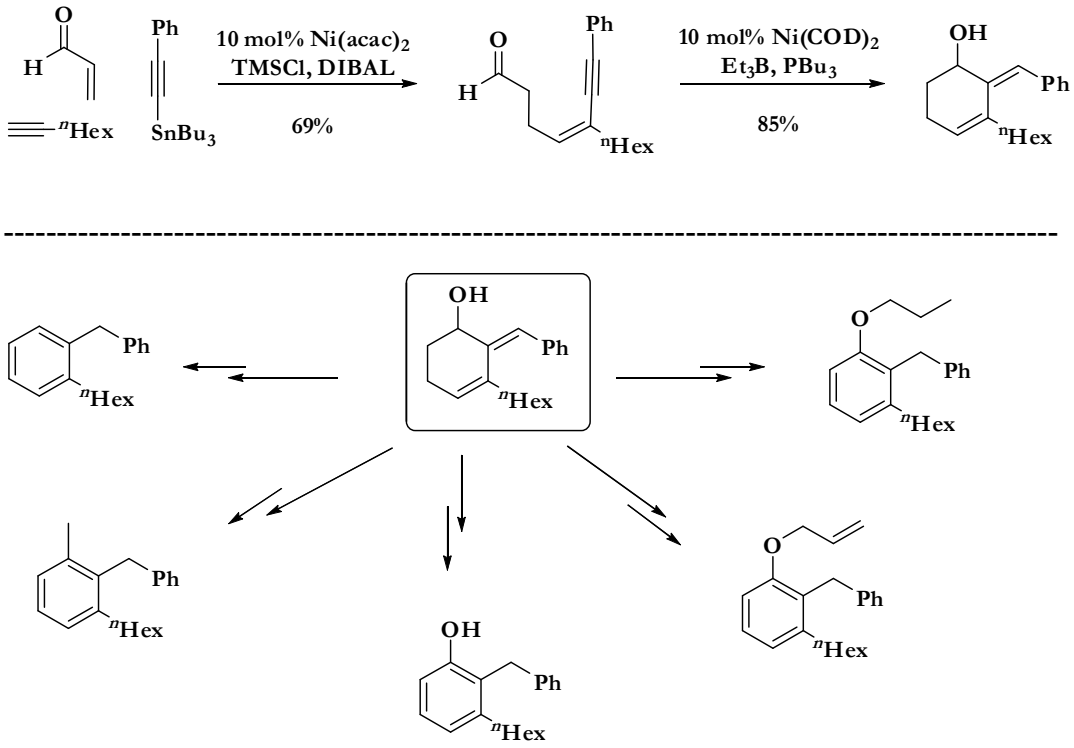
Scheme 1.42

Wu[46] investigated a Ni-catalyzed cascade cycloaddition of 1-ethynylhalonaphthalene **40** with nitriles to prepare pyrroloarenes **41**. The strategy is efficient as the C-N triple bond of the nitrile is activated twice. Accordingly, five new bonds are formed in a one-pot transformation furnishing a pyrrole ring and two six membered rings in the same pot (**Scheme 1.43**).



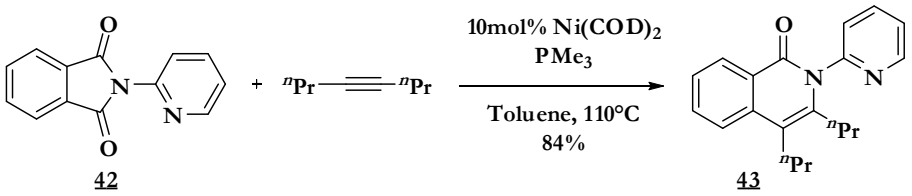
Scheme 1.43

Montgomery[47] has developed a multicomponent approach to highly substituted benzene derivatives involving sequential nickel-catalyzed reactions. This strategy gives access to a variety of substrates (benzene derivatives, phenols or aryl ethers) depending on the aromatisation sequence (**Scheme 1.44**).



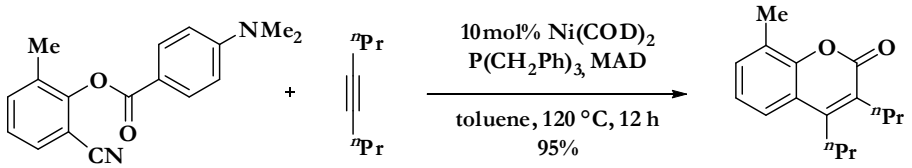
Scheme 1.44

Matsubara and Kurahashi[48] reported a nickel-catalyzed decarbonylative addition of phthalimides to alkynes. The reaction between *N*-phenylphthalimide possessing an electron withdrawing group gives a better yield compared to *N*-phenylphthalimide with an electron donating group. For example, the electron deficient *N*-pyridinylphthalimide **42** reacted with 4-octyne to give the corresponding isoquinolone **43** (**Scheme 1.45**).



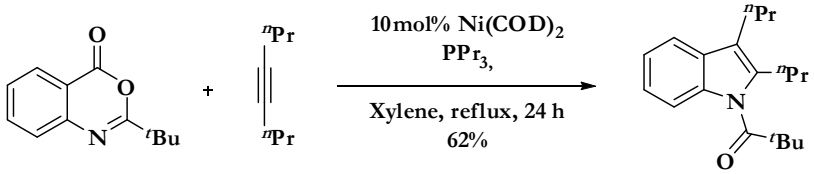
Scheme 1.45

Matsubara[49] described the cycloaddition of *o*-arylcarboxybenzonitriles and alkynes to provide coumarins. The reaction is promoted by a nickel catalyst and proceeds *via* unusual cleavage of two carbon-carbon σ bonds and the insertion of the alkyne to form two new carbon-carbon σ bonds. The strategy is quite remarkable as σ bonds are challenging to break using conventional synthetic methods (**Scheme 1.46**).



Scheme 1.46

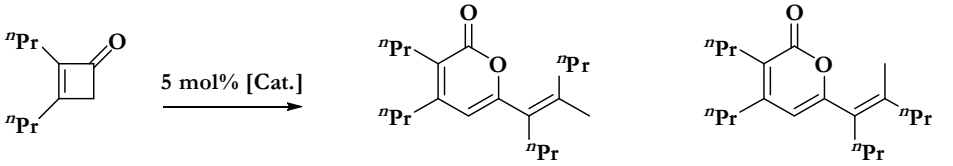
In the same context, Matsubara[50] developed an elegant strategy to access indoles from readily available anthranilic acids and alkynes (**Scheme 1.47**).



Scheme 1.47

1.3 Rhodium and Ruthenium Catalysis

Other catalyst systems have been shown to be remarkably efficient for the synthesis of polysubstituted benzene derivatives. For example, Kondo and Mitsudo[51] reported an interesting and novel ruthenium and rhodium-catalysed ring opening dimerization of cyclobutenones to furnish 2-pyranones. The dimerisation of the cyclobutenone bearing two *n*-propyl groups in the presence of a ruthenium catalyst gave both (*E*)- and (*Z*)-6-alkenyl-2-pyranones with the (*Z*)-isomer as the major product (**Scheme 1.48**). Interestingly, changing the metal to rhodium was found to give exclusively the (*E*)-isomer. However, several combinations of catalyst were analysed but [{$RuCl_2(CO)_3$}$_2$] showed the highest catalytic activity and [{$RhCl(CO)_2$}$_2$] was the only efficient Rh-based catalyst for this reaction.

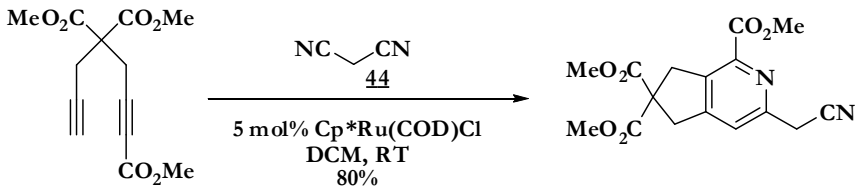


[{$RuCl_2(CO)_3$}$_2$] 81% E/Z : 22/78

[{$RhCl(CO)_2$}$_2$] 75% E/Z : 100/0

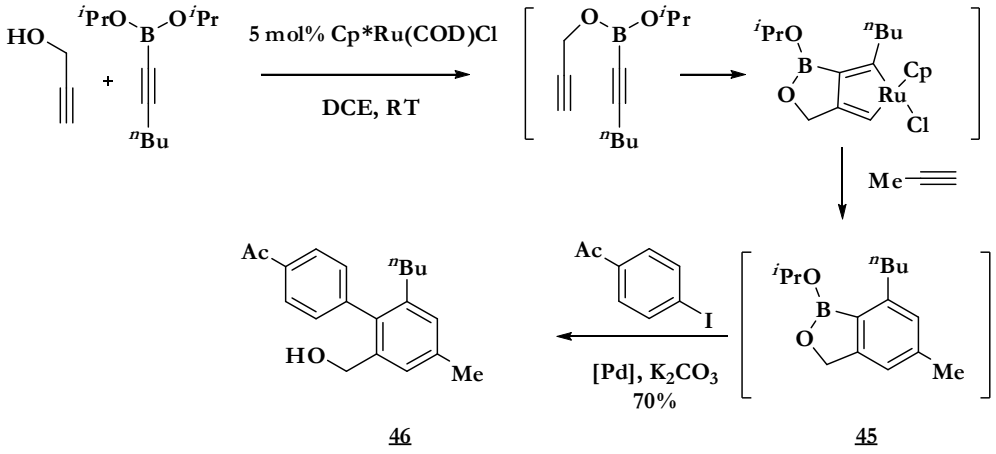
Scheme 1.48

Yamamoto[52] investigated a Ru-catalysed [2 +2 + 2] cycloaddition approach for the formation of bicyclic pyridines from 1,6-diynes and malonitrile **44** (**Scheme 1.49**). Malonitrile plays an important role in the reaction by avoiding the undesired cyclotrimerisation of the 1,6-diynes. This process shows significant chemo- and regioselectivities and proceeds under mild conditions.



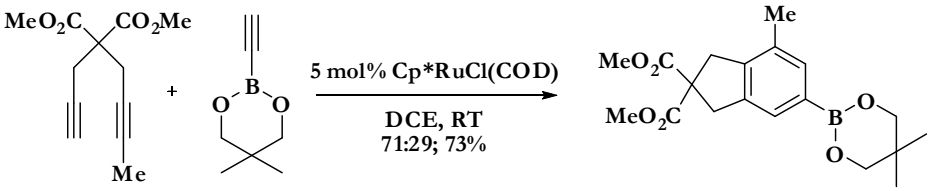
Scheme 1.49

The same group reported a few years later on the cyclotrimerization of three different unsymmetrical alkynes catalysed by Ru through a temporary boron linkage with excellent chemo- and regioselectivity[53] (**Scheme 1.50**). The intermediate **45** could not be isolated but was subjected *in situ* to a Suzuki-Miyaura cross coupling to afford the biaryl derivative **46**.



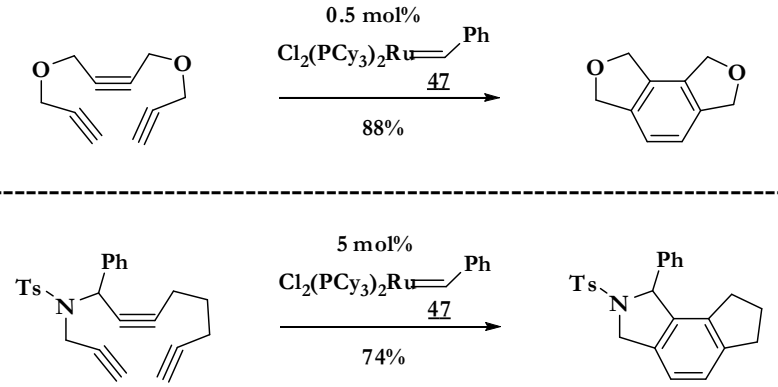
Scheme 1.50

Yamamoto[54] also published a ruthenium catalyst system which allows the synthesis of bicyclic arylboronates with moderate regioselectivity (**Scheme 1.51**).



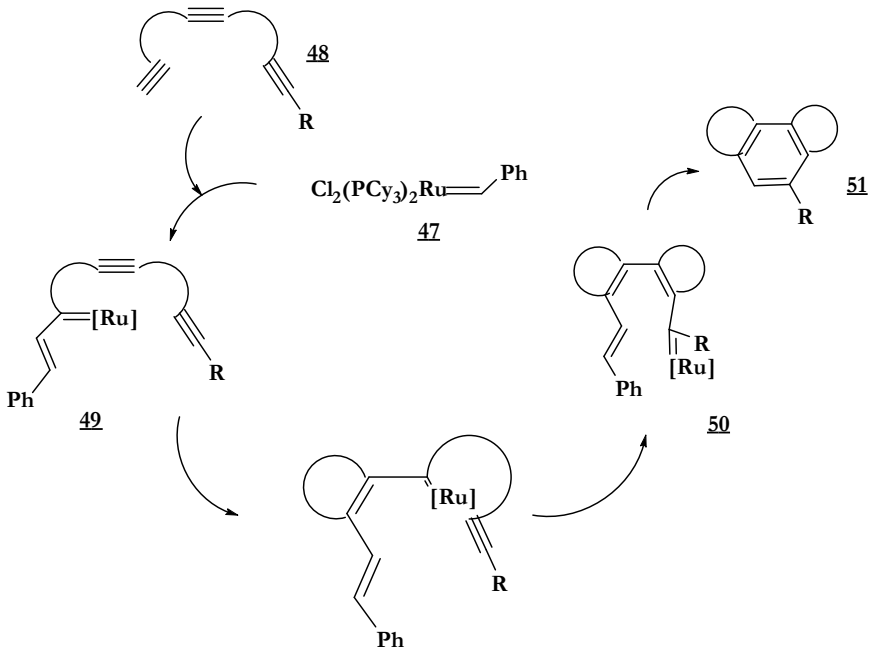
Scheme 1.51

Blechert[55] developed a novel metathesis cascade allowing the conversion of triynes to polycyclic benzene derivatives. The employment of Grubbs' Ru-catalyst allows this approach to be tolerant of a wide range of functionalities (**Scheme 1.52**).



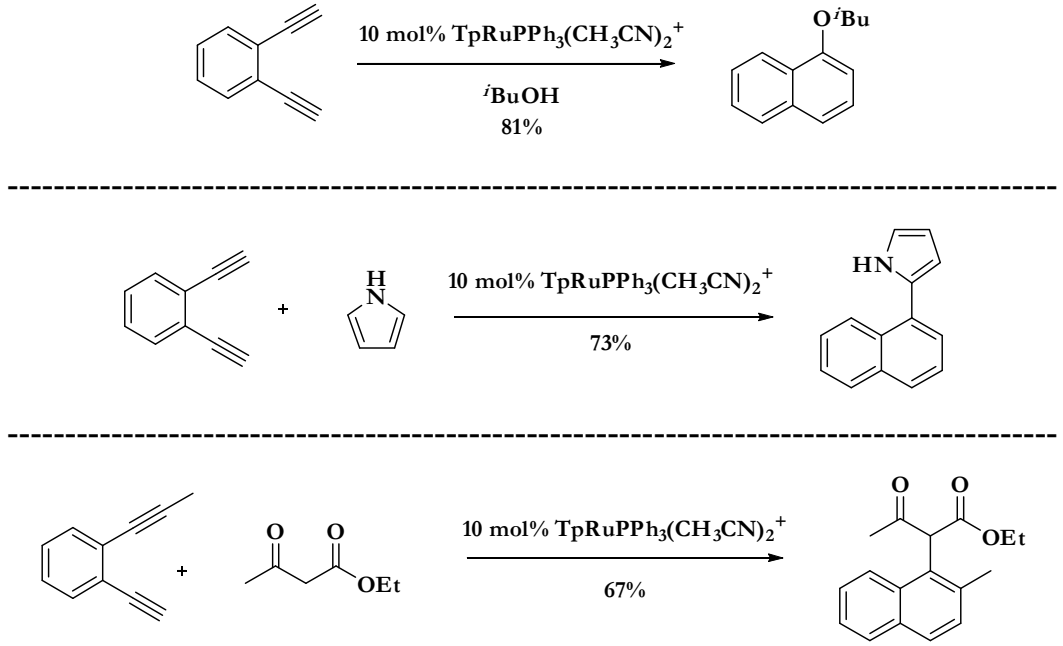
Scheme 1.52

In an initial intermolecular reaction, the ruthenium benzylidene complex **47** adds to the least hindered triple bond of the triyne **48**. The resulting vinyl carbene complex **49** undergoes a ring closing metathesis reaction to produce a conjugated carbene complex **50** with two newly formed double bonds embedded in a ring structure, thereby forcing the (*Z*)-stereochemistry. This is a prerequisite for the final ring closing olefin metathesis step which releases benzylidene complex **47** and the aromatic product **51**. The formation of an aromatic system provides a strong driving force for the overall reaction cascade (**Scheme 1.53**).



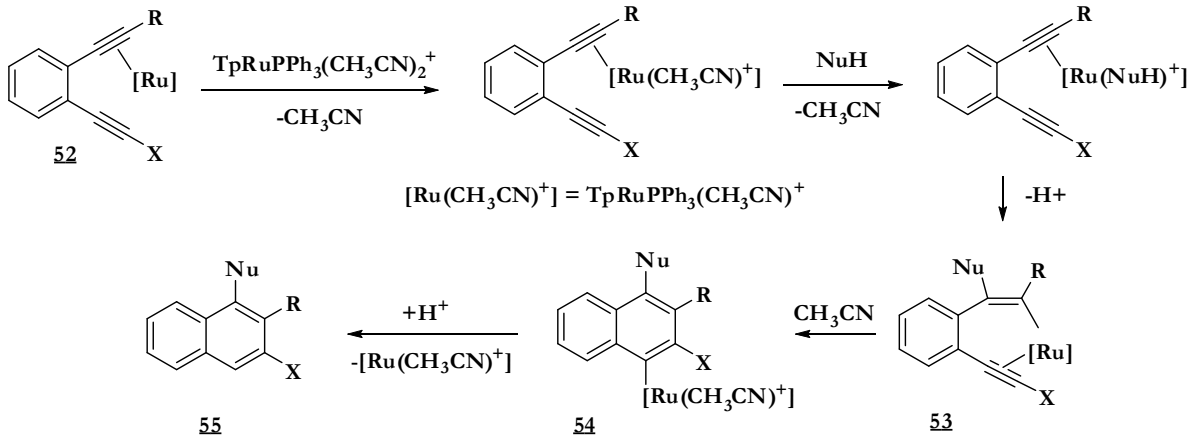
Scheme 1.53

Liu[56] has reported a ruthenium catalysed aromatisation of enediynes *via* nucleophilic addition leading to benzene derivatives in a highly regioselective fashion. A broad range of nucleophiles are tolerated including water, alcohols, aniline, acetylacetone, pyrroles and dimethyl malonate. These nucleophiles attack the internal C1 of the alkyne of the enediynes to give the desired aromatic derivatives as a single regioisomer (**Scheme 1.54**).



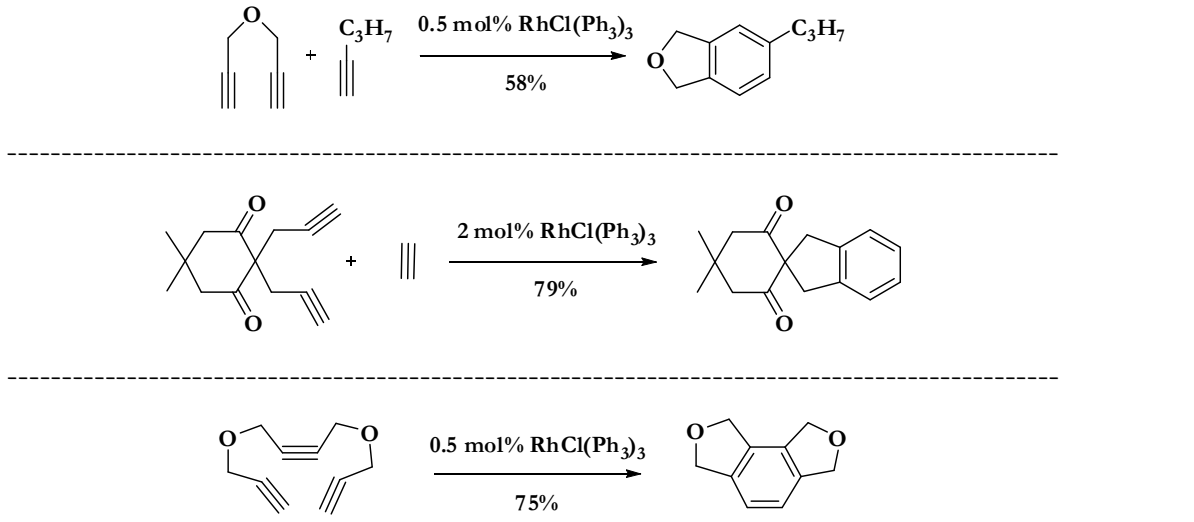
Scheme 1.54

The authors propose that, because of its cationic nature, the Ru-catalyst selectively binds to the more electron rich alkyne of the enediyne to give a ruthenium-π alkyne complex **52**. Subsequent nucleophilic displacement of the ligand followed by insertion of the Ru-NuH into the alkyne group forms a vinylruthenium species **53**. An intramolecular 6-endo-dig cyclisation gives a naphthylruthenium intermediate **54** that ultimately leads to the aromatic product **55** (**Scheme 1.55**).



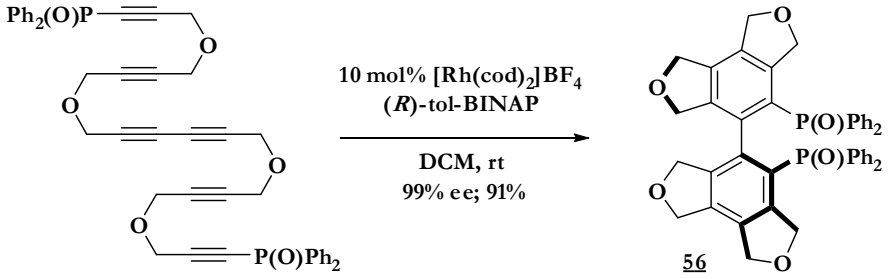
Scheme 1.55

Grigg[57] reported a rhodium catalysed [2 + 2 + 2] cycloaddition of acetylenes. In this case, Wilkinson's catalyst [$RhCl(PPh_3)_3$] proved to be effective for the trimerisation of 1,6-heptadiynes with monoacetylenes to furnish polycyclic benzene derivatives. This strategy is applicable to the synthesis of polycyclic spiro-compounds and also promotes fully intramolecular [2 + 2 + 2] cycloadditions (**Scheme 1.56**).



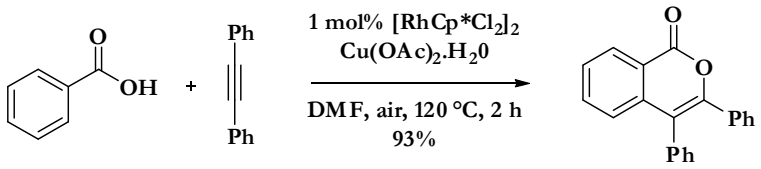
Scheme 1.56

In this context, synthesis of axially chiral biaryl diphosphine ligands such as **56**[58] can be accessed *via* rhodium catalyzed intramolecular double [2 + 2 + 2] cycloaddition (**Scheme 1.57**).



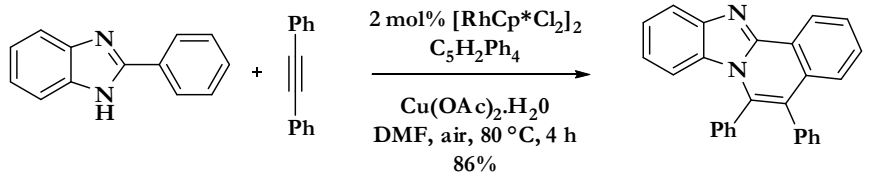
Scheme 1.57

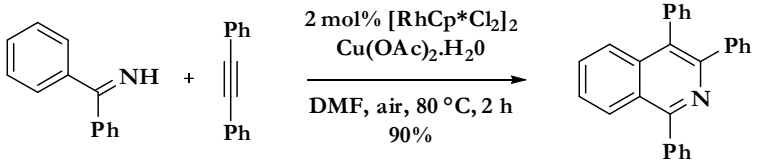
Miura and Satoh[59] recently documented that benzoic acid is able to direct aromatic C-H insertion of alkynes in the presence of a rhodium catalyst to yield isocoumarins (**Scheme 1.58**).



Scheme 1.58

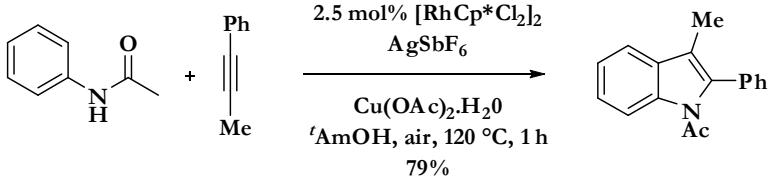
They expanded on this reactivity by using mildly acidic N-H bonds as a directing group for rhodium catalyzed C-H activation, which in the presence of alkynes results in the cyclised product from a C-H/C-N activation[60] (**Scheme 1.59**).





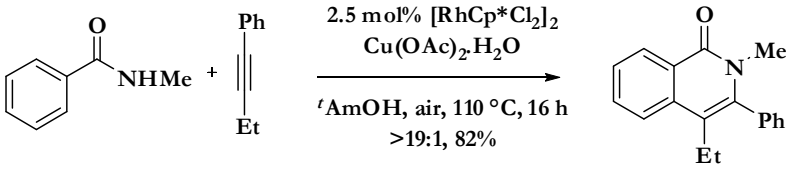
Scheme 1.59

In a remarkable application of this approach, Fagnou[61] demonstrated a regioselective indole synthesis by coupling *N*-aryl acetamides and alkynes under cationic rhodium catalyst conditions (**Scheme 1.60**).



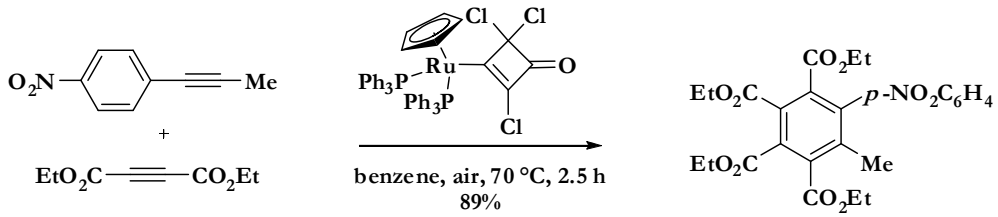
Scheme 1.60

Recently, Rovis[62] reported that amides can function as directing groups to promote selective formation of isoquinolones under rhodium catalysis. The reaction proceeds with excellent regiocontrol (**Scheme 1.61**).



Scheme 1.61

Finally, the ruthenium-catalyzed intermolecular [2 + 2 + 2] cycloaddition of dimethyl acetylenedicarboxylate (DMAD) and various internal alkynes leads to the corresponding highly substituted benzene derivatives[63] (**Scheme 1.62**).

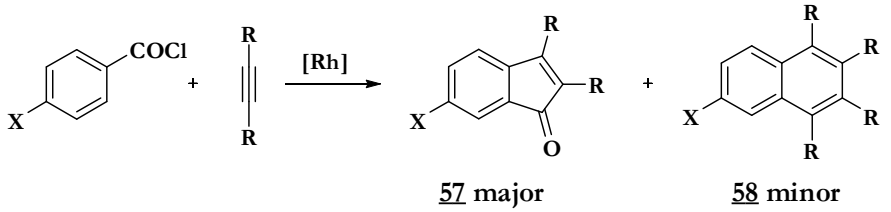


Scheme 1.62

1.4 Iridium Catalysis

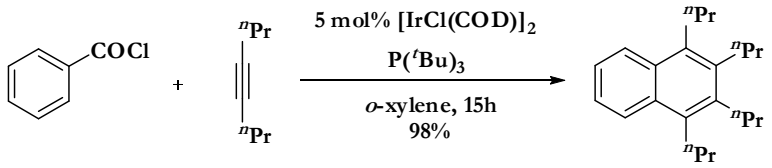
Iridium has also been used to catalyse the synthesis of novel aromatic systems. During Miura's[64] studies on the Rh-catalysed annulation reaction towards 2,3-

disubstituted indenones **57**, it was noticed that small amounts of 1,2,3,4-tetrasubstituted naphthalenes[63] **58** were also formed (**Scheme 1.63**). He then showed that these minor products could in fact be efficiently synthesised from the same starting materials by employing an iridium catalyst (**Scheme 1.64**).



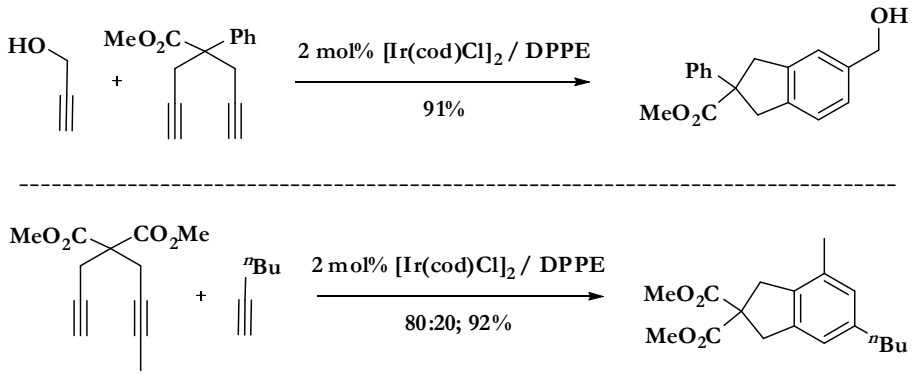
57 major **58 minor**

Scheme 1.63



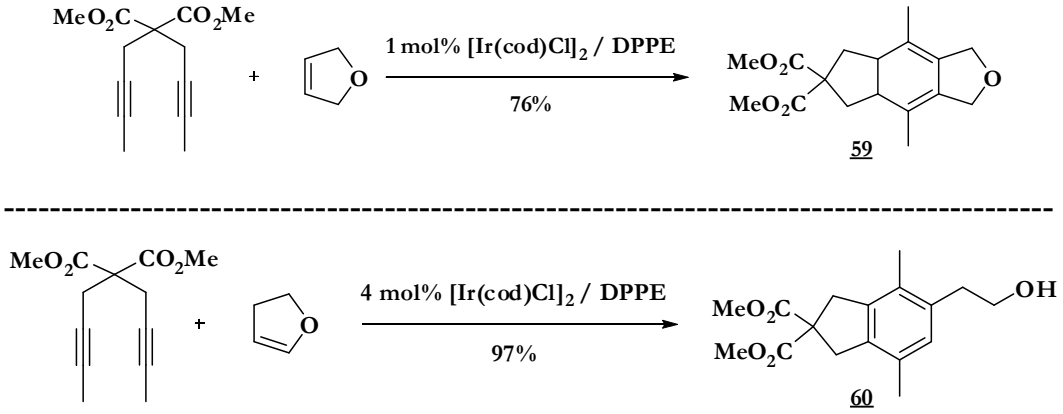
Scheme 1.64

Takeuchi[65] and co-workers have developed an iridium catalysed cycloaddition of diynes with monoynes and monoenes leading to polysubstituted benzene derivatives. The reaction proceeds under mild conditions with symmetrical and unsymmetrical diynes in the presence [Ir(COD)$_2$Cl] which is air-stable and easy to use (**Scheme 1.65**).



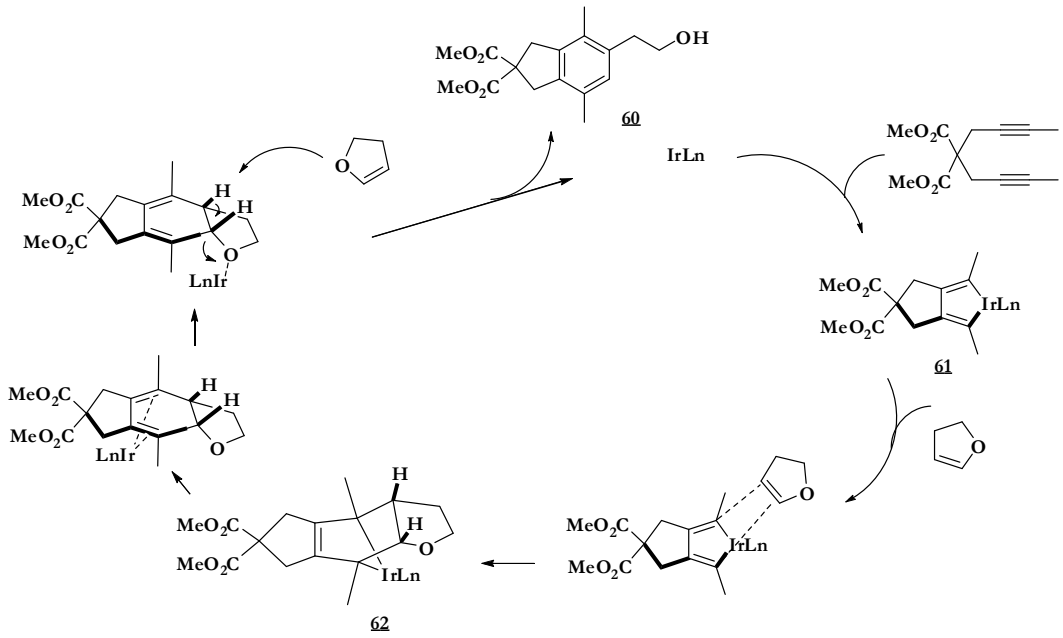
Scheme 1.65

Interestingly, the cycloaddition of a diyne and 2,5-dihydrofuran gives access to a tricyclic compound **59**. However, 2,3-dihydrofuran provides the free alcohol **60**. Both results are presented in **Scheme 1.66**.



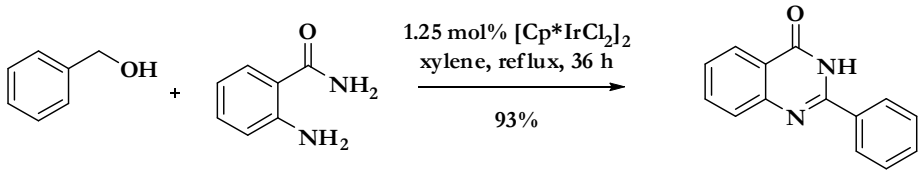
Scheme 1.66

A possible mechanism that accounts for these observations is outlined in **Scheme 1.67**. Iridacyclopentadiene **61** reacts with 2,3-dihydrofuran to give an intermediate **62** *via* a Diels-Alder type process. After reductive elimination, the iridium moiety moves to an oxygen atom and a subsequent elimination forms the desired benzannulated derivative **60**. With 2,5-dihydrofuran the elimination cannot occur, and the tricyclic compound is obtained instead of the free alcohol.



Scheme 1.67

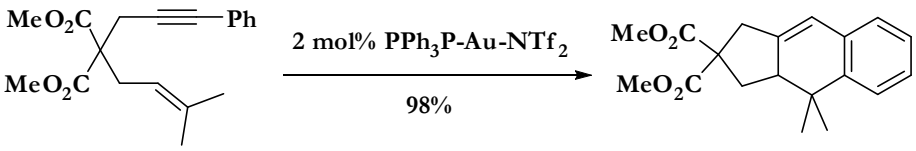
Zhou[66] demonstrated a one-pot synthesis of quinazolinones *via* an iridium-catalyzed hydrogen transfer (**Scheme 1.68**). The reaction proceeds with various alcohols and various benzamides providing the desired quinazolinones in good yields.



Scheme 1.68

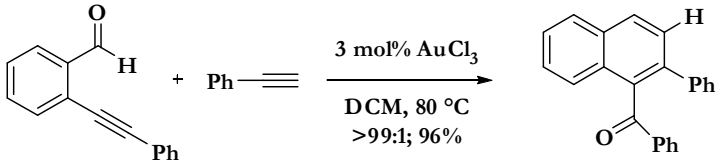
1.5 Gold and Silver Catalysis

Gagosz[67] reported a gold catalysed technique for the cyclotrimerisation of enynes. This new method involving an air stable catalyst allows facile access to polycyclic benzene derivatives (**Scheme 1.69**).



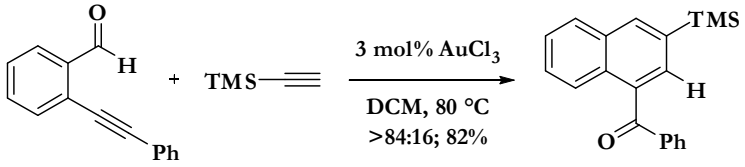
Scheme 1.69

Yamamoto[68] documented a gold catalyst system for benzannulation of α-alkynyl benzaldehydes with good regioselectivity. They found that simple gold trichloride could be used for the synthesis of naphthylaldehydes. The reaction proceeds with exquisite regioselectivity and in excellent yield (**Scheme 1.70**).



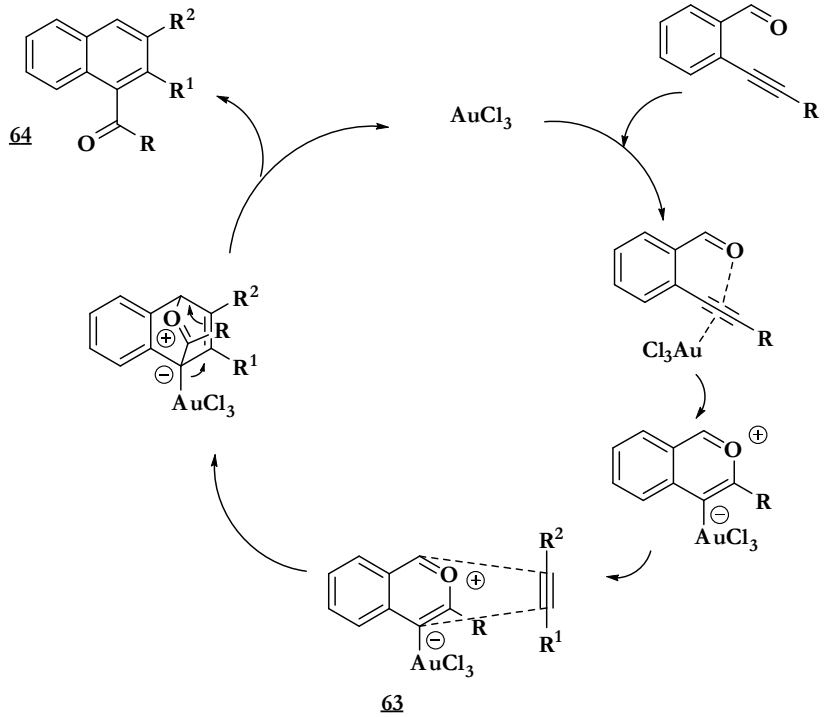
Scheme 1.70

An interesting reversal of regiochemistry was observed by using trimethylsilylacetylene in place of phenylacetylene in the presence of the *o*-phenylalkynylbenzaldehyde (**Scheme 1.70 & 1.71**).



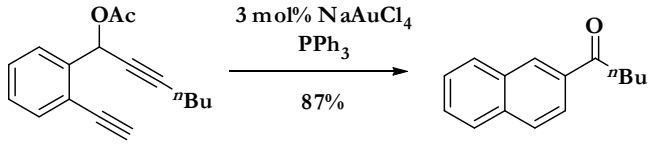
Scheme 1.71

The coordination of the triple bond to the Au-centre enhances the electrophilicity of the alkyne and the subsequent nucleophilic attack of the carbonyl oxygen to the electron deficient alkyne provides a benzopyrylium **63** intermediate that can undergo a [4 + 2] cycloaddition. The subsequent bond rearrangement affords the desired naphthalene derivative **64** and regenerates $AuCl_3$ (**Scheme 1.72**).



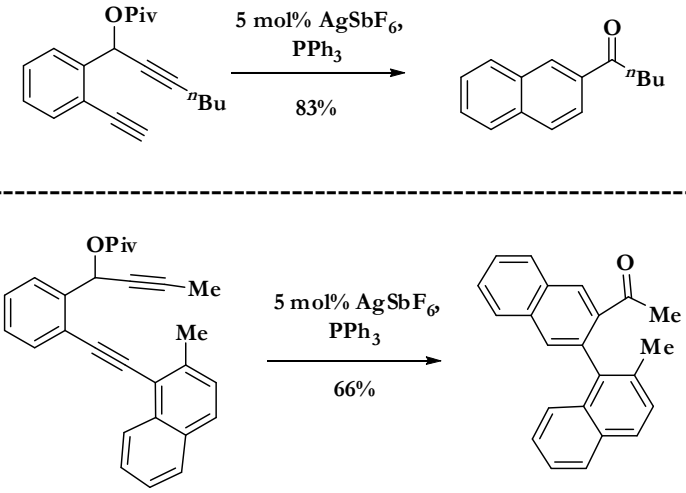
Scheme 1.72

Oh[69] described a new and highly convenient gold catalysed cyclisation of aryl-propargylic acetates that leads to 2-acyl-3-arylnaphthalene derivatives (**Scheme 1.73**).



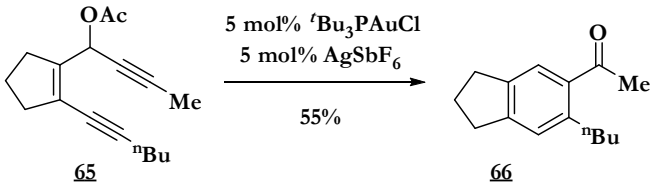
Scheme 1.73

Toste[70] reported the synthesis of aromatic ketones *via* a gold/silver-catalysed sequence. In many cases the silver-catalysed naphthyl ketone synthesis proceeds as well as or better than the analogous gold(I)-catalysed reaction (**Scheme 1.74**).



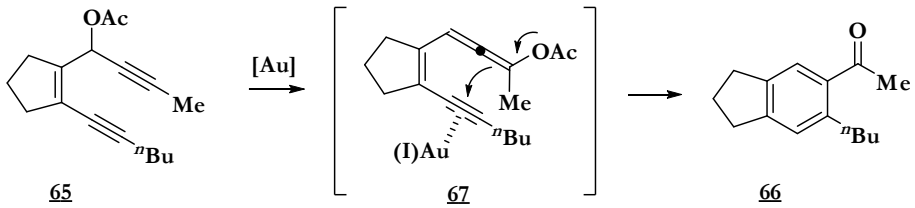
Scheme 1.74

However, gold was required to catalyse the rearrangement of enediyne **65** to produce the desired aromatic ketone **66** as all attempts with silver failed (**Scheme 1.75**).



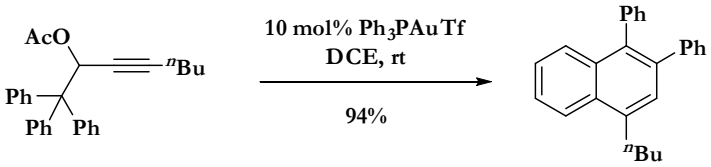
Scheme 1.75

From a mechanistic standpoint, the propargylic acetate appears to be isomerized to the corresponding yne-allenoate **67**. The Au-catalyst coordinates to the resulting triple bond thereby enhancing its electrophilicity and the cyclisation occurs to close the ring and yield the corresponding benzene derivative **66** (**Scheme 1.76**).



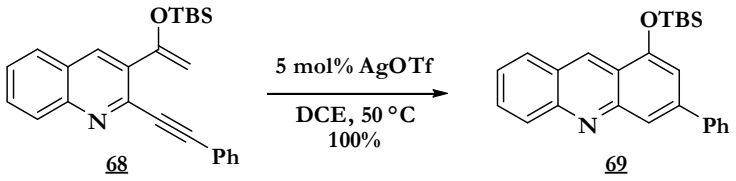
Scheme 1.76

Gevorgyan[71] developed a gold catalyzed cycloisomerization of propargylic esters leading to polysubstituted naphthalenes (**Scheme 1.77**). The cascade reaction involves a tandem sequence of 1,3- and 1,2-migrations of different migrating groups.

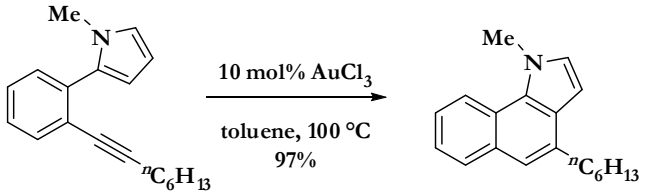


Scheme 1.77

Belmont[72] studied silver versus gold catalysis in the benzannulation reaction of electron rich enynes. Indeed, silver is able to catalyze the reaction of modified quinoline **68** to provide the corresponding acridine **69** (**Scheme 1.78**). By analogy, Dankwardt reported a similar strategy involving a gold catalyst. Both catalysts efficiently lead to polycyclic systems (**Scheme 1.79**).

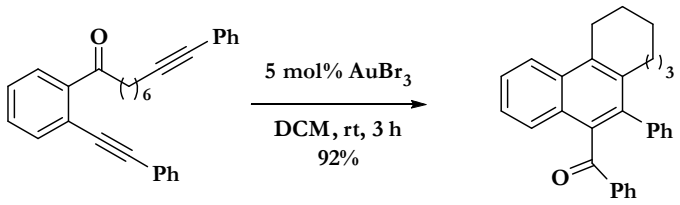


Scheme 1.78



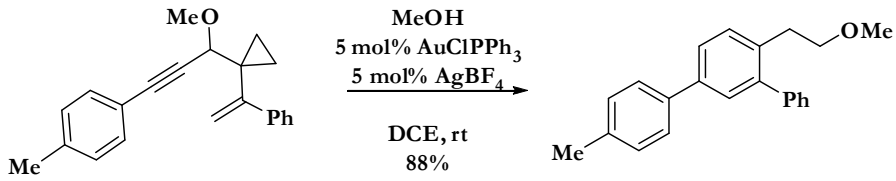
Scheme 1.79

Asao and Yamamoto[73] described an efficient intramolecular gold catalyzed benzannulation. The reaction proceeds smoothly at room temperature within 3 hours to provide the observed naphthyl ketones in good yield (**Scheme 1.80**).



Scheme 1.80

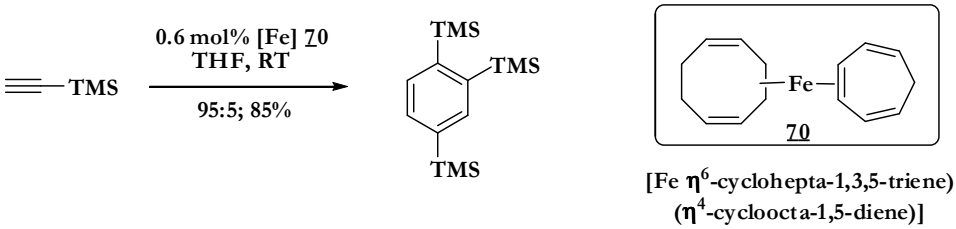
Li[74] demonstrated an efficient gold catalyzed benzannulation of 3-alkoxy-1,5-enynes bridged by a cyclopropyl ring. The process involved *in situ* trapping of the intermediate with various nucleophiles and provided a range of functionalised aromatic products under mild conditions. An example of the strategy is shown in **Scheme 1.81**.



Scheme 1.81

1.6 Iron Catalysis

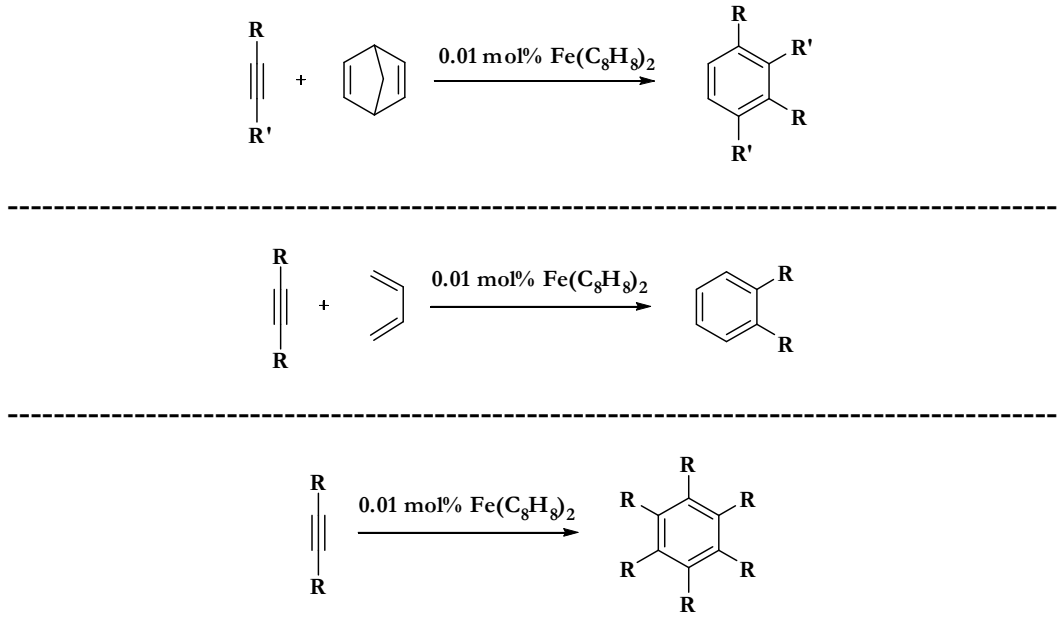
The trimerisation of trimethylsilylacetylene to form trisubstituted benzene derivatives has been catalysed by the iron complex {[Fe(η[6]-cyclohepta-1,3,5-triene)(η[4]-cycloocta-1,5-diene]} **70** and found to give good regioselectivity[75] (**Scheme 1.82**).



Scheme 1.82

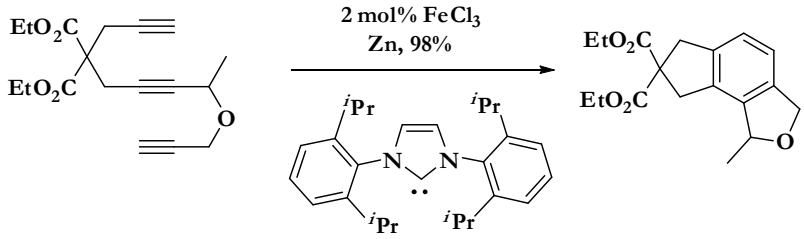
Carbonaro[76] reported an interesting catalyst system consisting of bis(cyclooctatetraene)iron(0). Such a catalyst is able to form several

polysubstituted benzene derivatives. The reaction proceeds between dienes and alkynes or via the cyclotrimerisation of alkynes in low to moderate yields (12-55%). (**Scheme 1.83**).



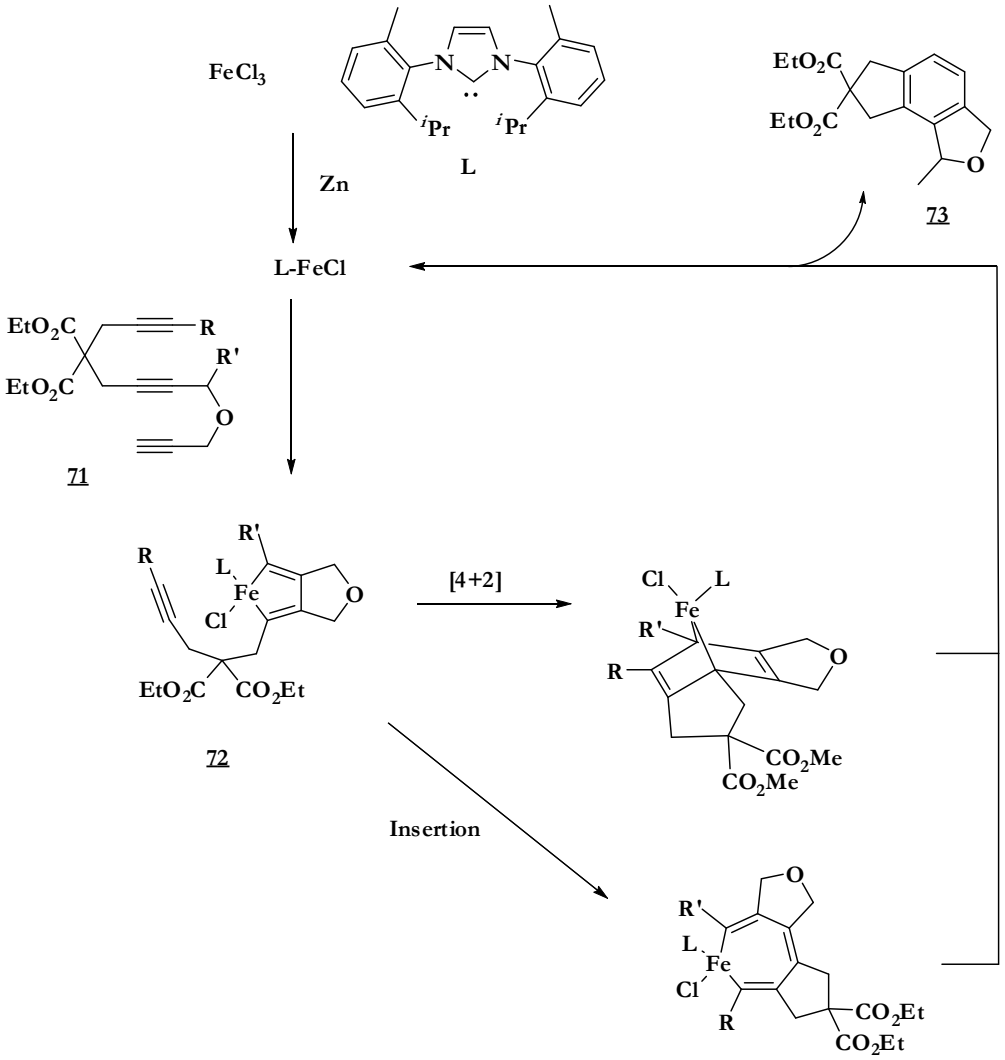
Scheme 1.83

Okamoto[77] reported an iron-catalysed intramolecular cyclotrimerisation of triynes providing polycyclic benzene derivatives (**Scheme 1.84**).



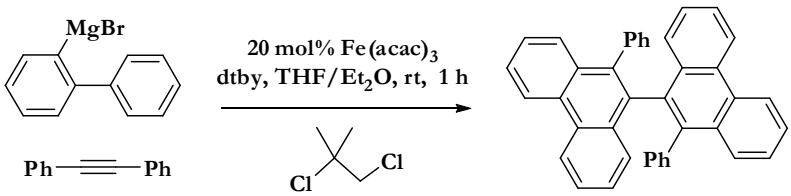
Scheme 1.84

They postulate a mechanism for this reaction. Thus, the **L**-$FeCl_3$ is proposed to be reduced by zinc. This complex may be metastable and can react quickly with triynes **71** to give metallacyclopentadiene **72** which may further be cyclised through an insertion or [4 + 2] cycloaddition. A subsequent reductive elimination furnishes the desired benzene ring derivative **73** (**Scheme 1.85**).



Scheme 1.85

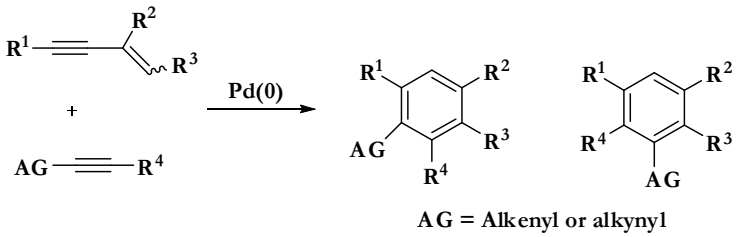
Nakamura[78] developed a new [4 + 2] benzannulation method that allows the coupling of a variety of alkynes with diaryl and related Grignard reagents. This reaction takes place under mild conditions due to the high activity of the iron-based catalyst and enables the construction of sterically congested systems (**Scheme 1.86**).



Scheme 1.86

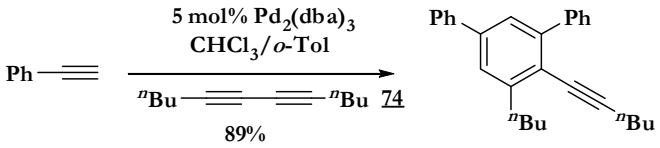
1.7 Palladium Catalysis

Palladium-catalysed benzannulation of enynes and alkynes is also a useful method for the formation of polysubstituted benzenes derivatives. In the case of substrates bearing an activating group (AG), the reaction is highly regioselective[79] (AG) (**Scheme 1.87**).



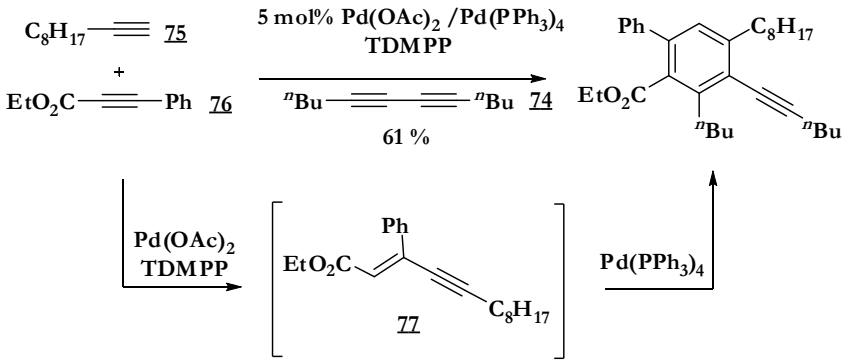
Scheme 1.87

Yamamoto[80] described a route to synthesise tetrasubstituted ethynylbenzenes regio- and chemoselectively *via* a [2 + 2 + 2] cyclotrimerisation. Phenylacetylene and 5,7-dodecadiyne **74** were heated in the presence of $Pd_2(dba)_3$, and gave only one compound in good yield (**Scheme 1.88**).



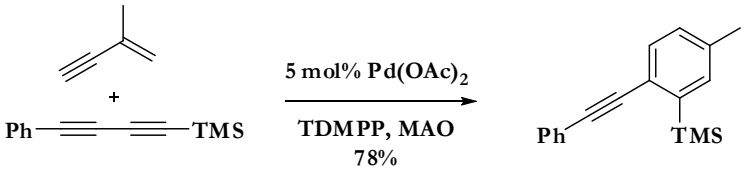
Scheme 1.88

$Pd(OAc)_2$/TDMPP efficiently catalyzed the cross-coupling of terminal alkyne **75** with activated internal alkyne **76** to provide enyne **77.** However, this catalyst system was not efficient in the [4 + 2] benzannulation reaction of **77** with diyne **74**. A combination of $Pd(OAc)_2$/$Pd(PPh_3)_4$) was required to prepare *penta*-substituted benzene derivatives (**Scheme 1.89**).



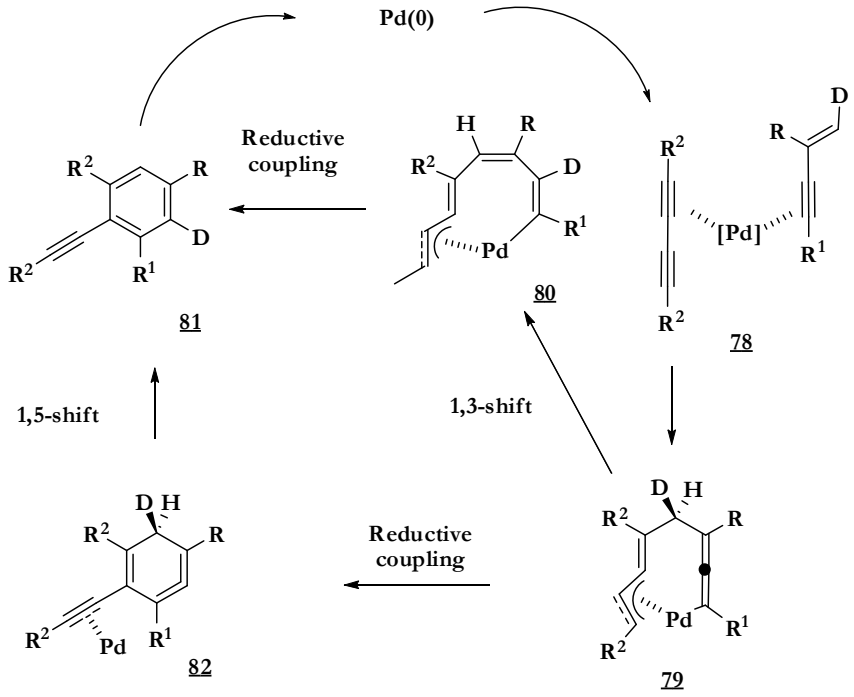
Scheme 1.89

A catalyst generated from $Pd(OAc)_2$/TDMPP in the presence of Lewis acid (MAO) has also been used for benzannulation reactions[79]. This catalyst shows the potential to control the regioselectivity of benzannulation when using unsymmetrical diynes (**Scheme 1.90**).



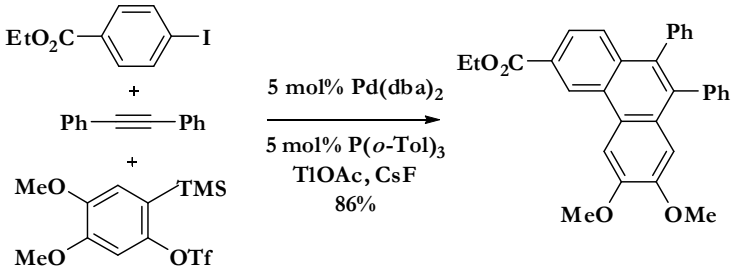
Scheme 1.90

The results of a deuterium-labelling experiment, taken together with the observation that regioselective benzannulation is possible allowed the authors to propose a rationale for this reaction as outlined in **Scheme 1.91**. The coordination of palladium with enyne and diyne would produce **78**, stabilized by the coordination of Pd with the neighbouring η^3-propargyl moiety. Then, the new allene **79** species either undergoes a 1,3-sigmatropic shift to form another metallacycle **80** which *via* reductive coupling affords the observed benzene derivatives **81** and regenerates a Pd(0) catalyst, or forms a strained cyclic cumulene **82** *via* consecutive reductive elimination processes which forms the desired aromatic ring **81** *via* 1,5-sigmatropic rearrangement.



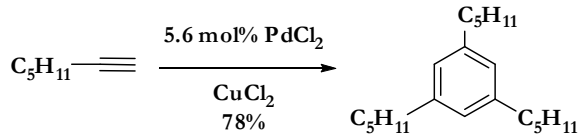
Scheme 1.91

Larock *et al.* have described an elegant benzannulation approach to phenanthrenes[81]. The process involves a palladium catalysed, sequential, three component cross coupling of aryl halides with acetylenes and arynes which affords the phenanthrene products in excellent yield (**Scheme 1.92**).



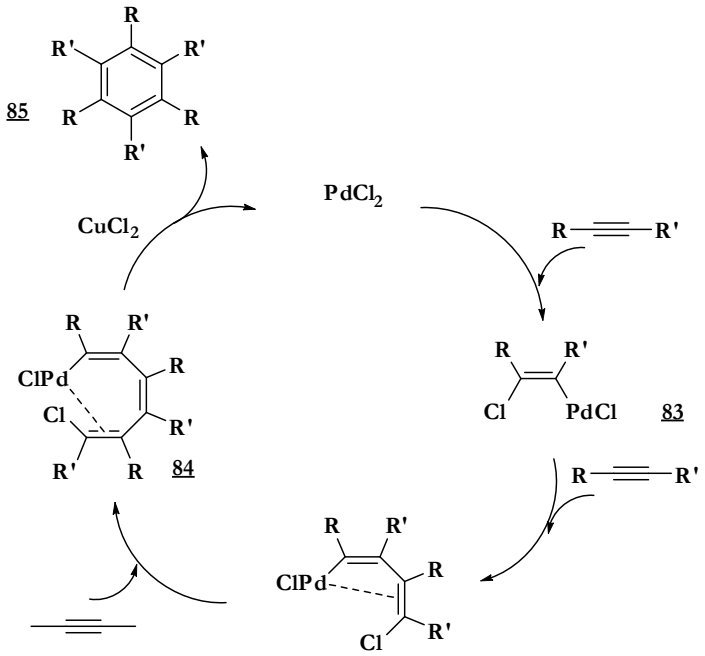
Scheme 1.92

Jiang[82] has demonstrated that copper can induce regioselectivity and reactivity in the palladium catalysed cyclotrimerisation of alkynes to benzene derivatives. Indeed, the reaction outlined in **Scheme 1.93** was unsuccessful without the presence of copper.



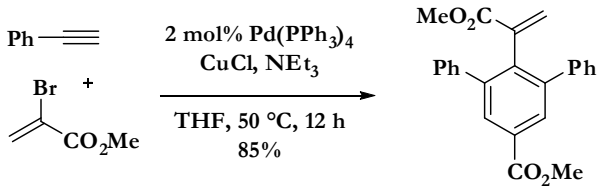
Scheme 1.93

The proposed mechanism involves a *cis*-chloropalladation **83** followed by consecutive *cis*-addition of alkynes giving a new chloropalladation intermediate **84** which then cyclises. Upon assistance of $CuCl_2$ and alcohol, the reaction gives benzene derivatives **85** and regenerates the active $PdCl_2$ (**Scheme 1.94**).



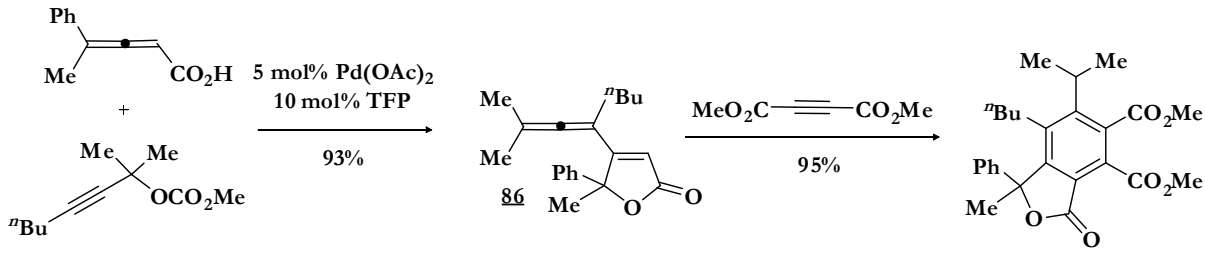
Scheme 1.94

Xi[83] reported a one-pot multicomponent coupling reaction for the highly regioselective synthesis of polysubstituted benzene derivatives using a palladium cascade of Sonogashira coupling-benzannulation reactions involving a 2-bromoacrylate and an alkyne (**Scheme 1.95**).



Scheme 1.95

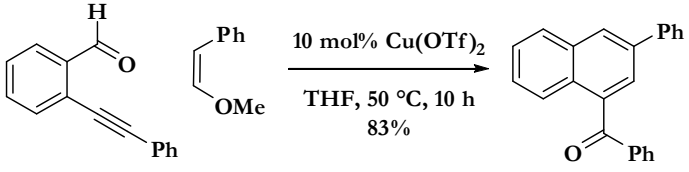
Deng[84] demonstrated that palladium catalysed coupling of 2,3-allenoic acid with propargylic carbonates forms β-allenyl butenolides such as **86** which can undergo a Diels-Alder cycloaddition to yield to the desired aromatic products[81] (**Scheme 1.96**).



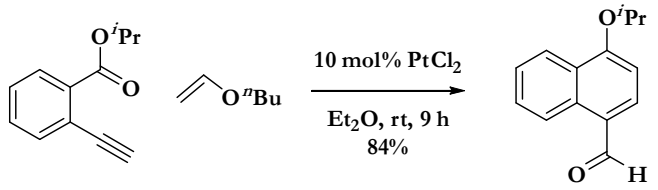
Scheme 1.96

1.8 Copper, Platinum & Indium Catalysis

Copper is often used in transition metal mediated reactions as a co-catalyst. There are also a few examples proving that copper can promote benzannulation on its own. Indeed, Asao[85] reported a copper-catalyzed reaction of enynal **87** with β-methoxy-styrene **88** to access the corresponding naphthyl ketone **89** under mild conditions in good yield (**Scheme 1.97**). Iwasawa[86] reported a similar methodology using a platinum catalyst instead (**Scheme 1.98**).

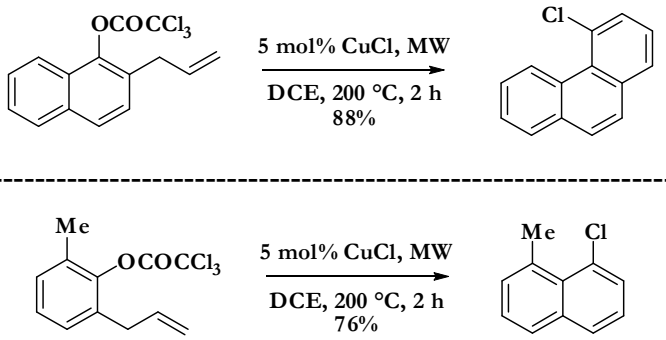


Scheme 1.97



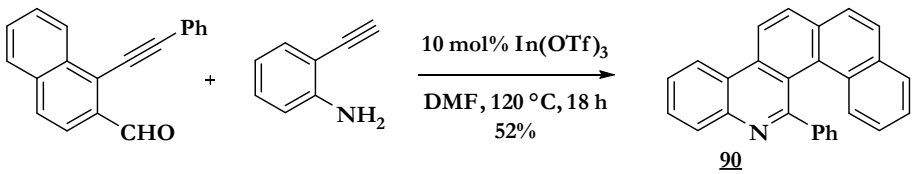
Scheme 1.98

Quayle[87] reported a simple and efficient benzannulation to access halonaphthalene derivatives under copper catalysis. The reaction proceeds with complete regiochemical control to afford aryl chlorides as single regioisomers (**Scheme 1.99**).



Scheme 1.99

A new atom-economical indium-catalyzed synthesis of ring condensed heteroaromatic compounds such as **<u>90</u>** *via* a domino intramolecular nucleophilic attack/intermolecular cycloaddition/dehydration reaction has been developed by Yanada[88] (**Scheme 1.100***).*



<u>90</u>

Scheme 1.100

1.9 Conclusion

The transition metal catalyzed benzannulation of unsaturated hydocarbons is a very useful protocol for the construction of polysubstituted benzene derivatives. The review illustrates the efficiency of the methodology through various examples. Regioselective [2 +2 +2] and [4 + 2] cycloaddition approaches have been developed including intra-and intermolecular reactions.

The wide scope of the transition-metal catalyzed reactions of benzene derivatives has been demonstrated by the facile access to natural products, sterically congested benzene based systems and other interesting compounds which cannot be easily prepared by other synthetic methods. Considering the importance of benzene derivatives in the vast field of basic and applied chemistry, these methods are highly useful in organic synthesis. However, only a few examples incorporate a boronate moiety. In this context, our target will be to focus on the development of a transition metal catalyzed benzannulation process to access aromatic boronic ester derivatives in a regioselective manner.

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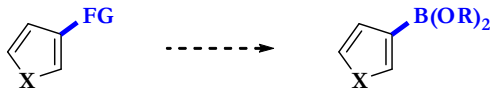
CHAPTER II

** Background to the project & Preparation of starting materials**

2.0 Introduction

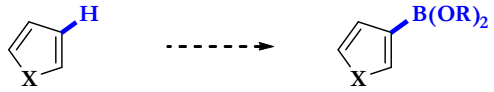
Aromatic boronic esters are one of the most valuable synthetic intermediates in modern organic synthesis. This is mainly due to their versatility, in particular with regard to their ability to form carbon-carbon bonds under mild conditions through palladium-catalyzed cross-coupling reactions[1]. They are typically prepared by functional group interconversion (**Scheme 2.1**) using Grignard reagents, organolithium species or more recently *via* palladium-catalyzed carbon-boron bond forming processes[2].



FG = Cl, Br, I, OTf, HgX, MgBr, Li, many other organometallic reagents[2]

Scheme 2.1

An alternative strategy is the use of a transition metal catalyst to promote C-H bond activation (**Scheme 2.2**). This approach requires expensive metal catalysts and there is often a limitation with regard to the C-H bond that is functionalised[3].



Scheme 2.2

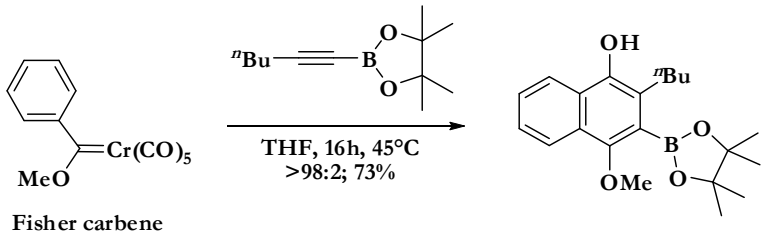
Both of these approaches provide a variety of aromatic boronic ester derivatives. However both strategies require an appropriately functionalised aromatic precursors.

A complementary strategy developed in the Harrity group is based on the cycloaddition of simple and readily available alkynylboronates, allowing the formation of the ring and the instalment of the boronate in a single step. Therefore we will focus our attention on the cycloaddition strategy (**Scheme 2.3**).

Scheme 2.3

The first route envisaged was the application of the Dötz annulation[4] reaction toward the synthesis of novel arylboronic esters. The reaction between chromium Fischer carbene complexes and alkynes has received considerable attention largely because of its ability to construct highly substituted benzene derivatives from simple starting materials in one step with a high degree of regiocontrol.

In this context, the Harrity group investigated the cycloaddition reaction between Fischer carbenes[5] and alkynylboronates[6]. The reaction proceeded in good yield and provided highly functionalised arylboronic ester derivatives with excellent levels of regioselectivity[7] **Scheme 2.4**.

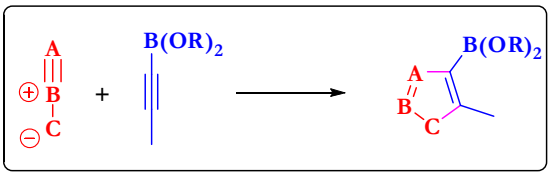


Scheme 2.4

Some drawbacks remain using the Dötz annulation due to the requirement of stoichiometric quantities of organochromium reagent. For this reason, the Harrity group focused on metal-free cycloadditions to furnish similarly highly functionalised aromatic compounds. Specifically, two different strategies have been developed for the synthesis of aromatic boronic esters through a cycloaddition process, and these will be discussed in the following sections

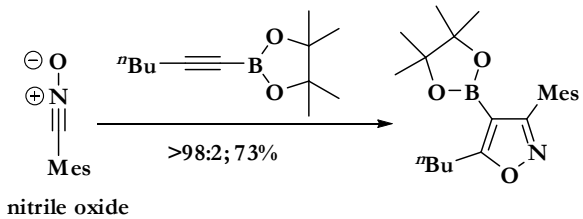
Direct [3 + 2] cycloaddition

This strategy involves the reaction of a 1,3-dipole and an alkynylboronate providing a 5-membered aromatic ring as depicted in **Scheme 2.5**.



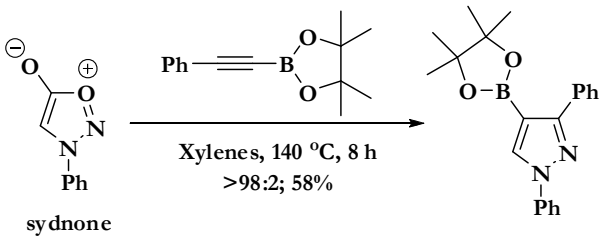
Scheme 2.5

To illustrate this strategy, the [3 + 2] cycloaddition reaction of nitrile oxides with alkynylboronates provides an approach to highly substituted isoxazoles in good yield with excellent regioselectivity[8] (**Scheme 2.6**).



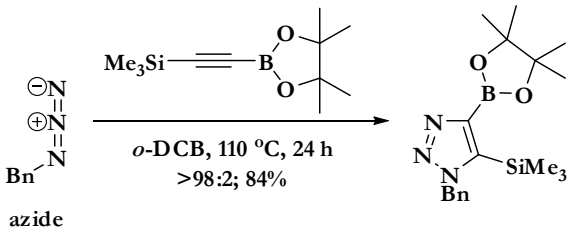
Scheme 2.6

Changing the dipole for a sydnone, the [3 + 2] cycloaddition with alkynylboronate yields the desired pyrazole with excellent regioselectivity[9] (**Scheme 2.7**)



Scheme 2.7

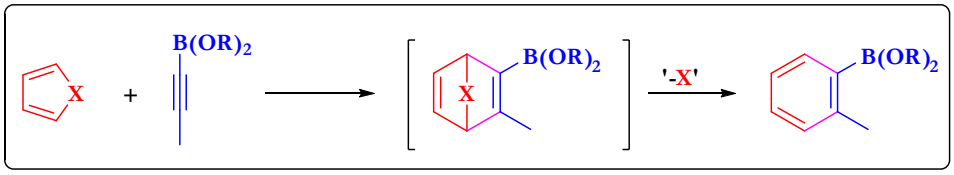
Another interesting example is the [3 + 2] cycloaddition between an azide and an alkynylboronate, providing the corresponding triazole in good yield and excellent regioselectivity[10] (**Scheme 2.8**).



Scheme 2.8

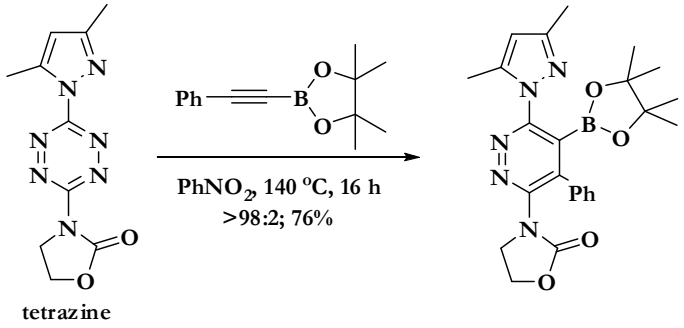
[4 + 2] cycloaddition-retrocycloaddition

This strategy involves the reaction of a 1,3-diene and an alkynylboronate forming a bridged bicyclic intermediate which can give the desired 6-membered ring aromatic boronic ester after releasing a small molecule **X** such as carbon dioxide (CO_2) or nitrogen (N_2) (**Scheme 2.9**).



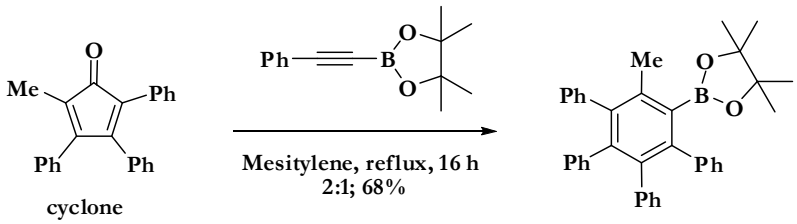
Scheme 2.9

For example, as shown in **Scheme 2.10** the [4 + 2] cycloaddition of a tetrazine and an alkynylboronate furnishes the corresponding pyridazine in good yield with excellent regioselectivities.[11]



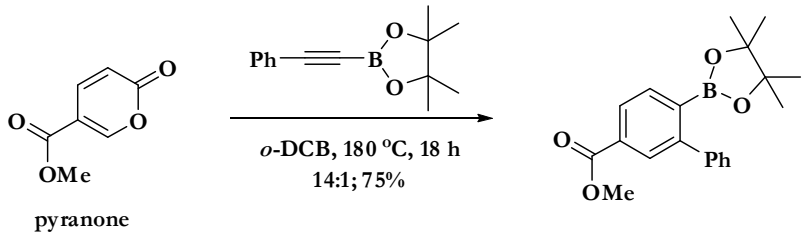
Scheme 2.10

In order to form highly functionalised benzene ring derivatives, the cycloaddition of a cyclone and an alkynylboronate has been shown to lead to the desired aromatic boronic ester in good yield but with poor levels of regiocontrol[12] (**Scheme 2.11**).



Scheme 2.11

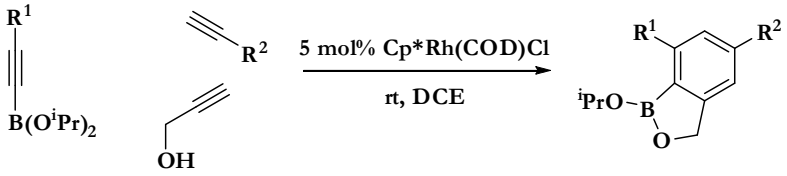
Pyranones have been investigated in the cycloaddition in order to gain access to highly functionalised aromatic boronic esters with high levels of regiocontrol. As shown in **Scheme 2.12**, the [4 + 2] cycloaddition of a pyranone and an alkynylboronate furnishes the corresponding benzene ring in good yield and with good regioselectivity.[13]



Scheme 2.12

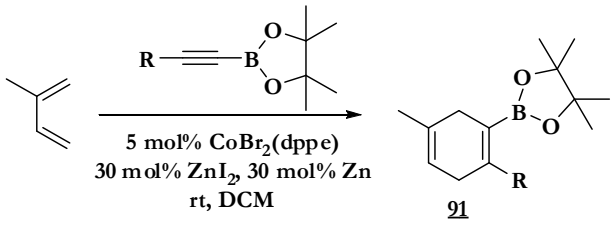
Despite the successes achieved with the [3 + 2] and [4 + 2] cycloaddition strategies towards aromatic and heteroaromatic boronic esters, all of these methods require high temperatures. Therefore, we wanted to investigate the possibility of performing these kind of cycloadditions at lower temperature, while maintaining high efficiency and useful levels of regiocontrol.

A search of the literature showed that Yamamoto[14] has reported a rhodium catalysed [2 + 2 +2] cycloaddition between an alkynylboronate, a propargylic alcohol and a terminal alkyne yielding aromatic boronic esters as shown in **Scheme 2.13**.



Scheme 2.13

An alternative route has been described by Hilt[15] involving a [4 + 2] cycloaddition involving an alkynylboronate and a diene under a cobalt-catalysis providing **91** a potential precursor to an aromatic boronic ester as shown in **Scheme 2.14**. A subsequent oxidation of the ring could lead to the desired aromatic boronic ester, if it proceeds without cleavage of the labile C-B bond.

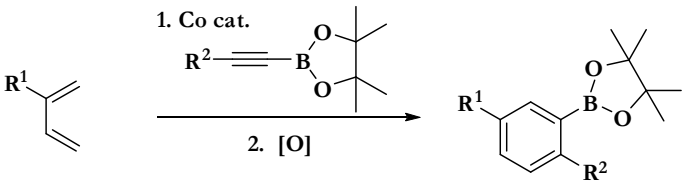


Scheme 2.14

We wished to further explore the Hilt chemistry as a means to accessing benzene boronic esters under mild conditions, and envisaged two different routes.

Cycloaddition-Oxidation

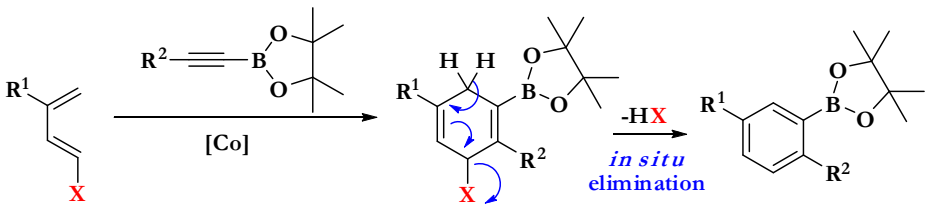
This process involves the formation of the ring and the instalment of the boronate followed by an oxidative step that would yield the desired benzene boronic ester (**Scheme 2.15**).



Scheme 2.15

Cycloaddition-elimination

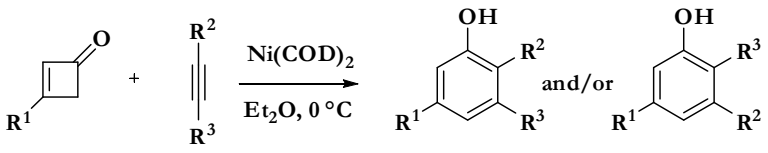
The second strategy is a one step process involving an alkynylboronate and a 1,3-diene bearing a potential leaving group **X** in C-1. We anticipated that the cycloadduct would undergo an *in situ* elimination reaction in this case to form the desired benzene boronic ester (**Scheme 2.16**).



Scheme 2.16

Ring Cleavage-cycloaddition

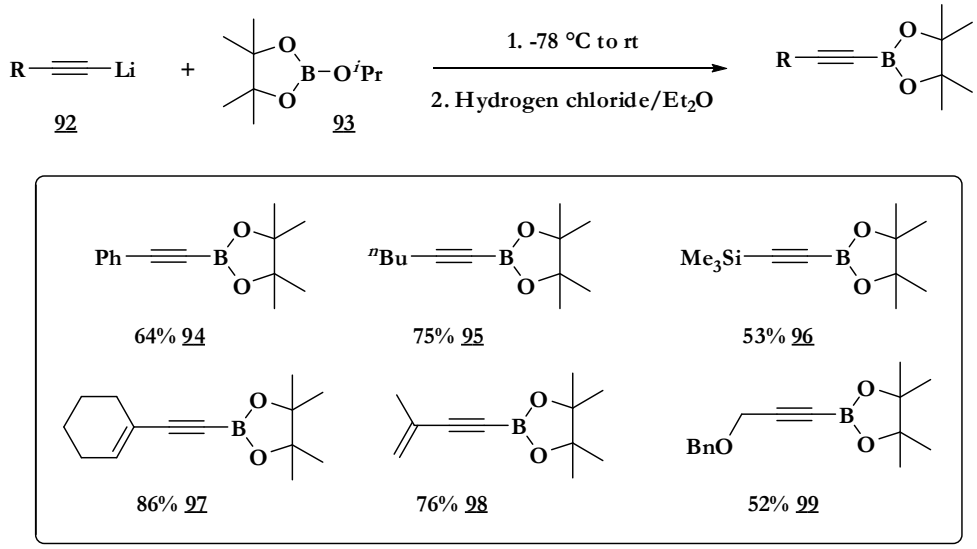
In addition to the cobalt chemistry, Liebeskind[16] reported a strategy where a nickel catalyst promotes the [4 + 2] cycloaddition of an alkyne with a cyclobutenone providing the desired phenol derivatives (**Scheme 2.17**). This methodology would be a convenient strategy to access corresponding phenol boronic esters under mild conditions.



Scheme 2.17

2.1 Synthesis of Alkynylboronates

The alkynylboronates were prepared in accordance with Brown's method[6]. Accordingly, deprotonation of the corresponding terminal alkyne with *n*butyllithium gave the lithium acetylide **92** which was quenched with isopropoxy pinacolboronate **93** providing a boronate intermediate. Further treatment with anhydrous hydrogen chloride formed the desired alkynylboronate in moderate to good yields as outlined in **Scheme 2.18**.



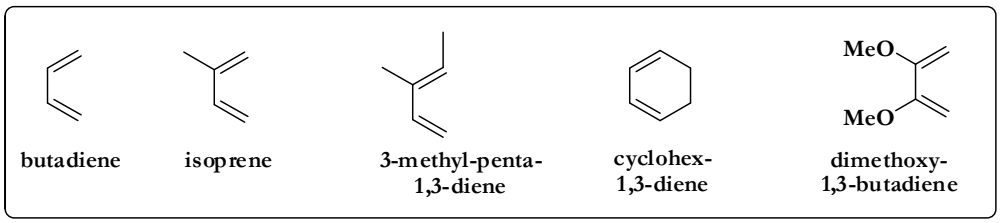
Scheme 2.18

Once formed, the alkynylboronates are quite stable and easy to handle. They can be stored in a refrigerator under an inert atmosphere. Alkynylboronates as oils **95**, **98** and **99** are easily purified by vacuum distillation, whilst the solids **94**, **96** and **97** are purified by crystallisation from petrol. However, phenylalkynylboronate **94** and cyclohexenylalkynylboronate **97** are generally more difficult to crystallise. We believe that these samples are contaminated by the corresponding parent terminal alkynes. These compounds have a relatively high boiling point (phenylacetylene, b.p. 145 °C or 1-ethynyl-cyclohexene, b.p. 154 °C) and cannot be easily removed under high vacuum. Notably, heating increases the rate of polymerisation of the alkyne that further prevents any crystallisation. Making sure small quantities of alkyne are removed, by leaving the crude mixture under high vacuum for a longer period of time. The synthesis of alkynylboronates can be performed easily on a large scale by a practical protocol.

2.2 Cobalt Chemistry-Synthesis of dienes

Synthesis of dienes-Part 1 : Cycloaddition-Oxidation strategy

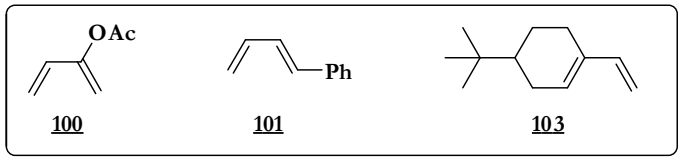
A variety of commercially available 1,3-dienes were employed in the cycloaddition-oxidation process as outlined in **Scheme 2.19**. The results of the cycloadditions of those dienes, and the analogues described below, with alkynylboronates will be discussed in chapter III.



Scheme 2.19

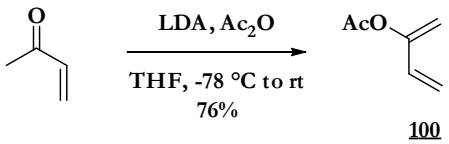
These substrates are very convenient to use as they are commercially available, moreover, they are quite volatile which allows an easy elimination of any unreacted diene at the end of the reaction.

We also wanted to investigate different substituted 1,3-dienes in the cycloaddition-oxidation process. The different dienes prepared are shown in **Scheme 2.20**.



Scheme 2.20

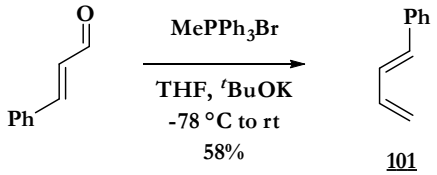
The diene **100** was prepared from methyl vinylketone in the presence of LDA and acetic anhydride[17] (**Scheme 2.21**).



Scheme 2.21

The diene was purified easily by flash column chromatography on silica gel. Unlike many of these electron rich dienes, no polymerisation was observed during the synthesis and purification steps, making this diene a potentially good substrate.

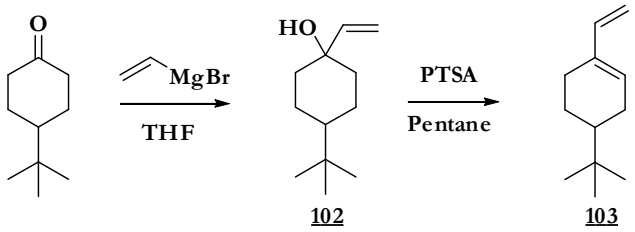
1-Phenylbuta-1,3-diene **101** was synthesized by Wittig reaction between methyl triphenyphosphonium bromide and cinnamaldehyde[18] **Scheme 2.22**



Scheme 2.22

This diene is stable and very straightforward to prepare as both starting materials are commercially available.

Finally, **103** was synthesized by vinyl Grignard addition to 4-*t*butylcyclohexanone and an acid catalysed elimination reaction[18] (**Scheme 2.23**). A 1:1 ratio of diastereoisomers was observed after Grignard addition. When the mixture of diastereoisomers was used directly in the elimination, the reaction did not go to completion and gave a complex mixture. Accordingly, the diastereoisomers were separated and subjected to the elimination individually. Interestingly, one of the diastereoisomers **102** gave the desired diene **103** in modest yield, while the other regioisomer gave a complex mixture. The identity of the alcohol diastereoisomers was not confirmed.



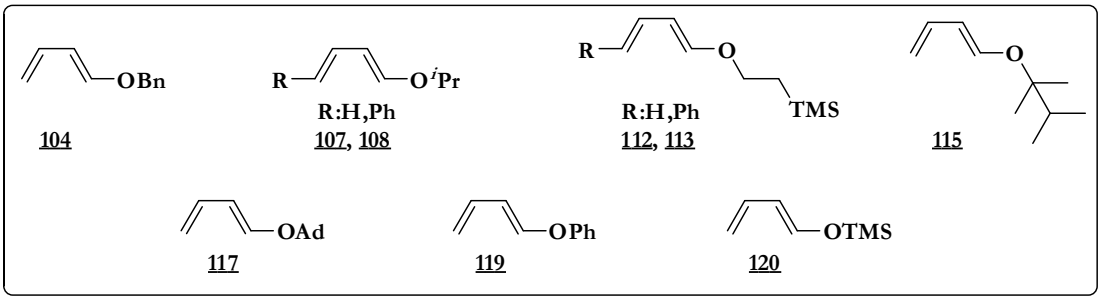
Scheme 2.23

Synthesis of dienes-Part 2 : Cycloaddition-Elimination strategy

We wanted to investigate a strategy that would allow the synthesis of aromatic boronic esters in one step. This method required the preparation of dienes bearing a potential leaving group at C1. The exploration of different 1-heteroatom substituted 1,3-butadienes (O-, S-, N-substituted) was envisaged to determine the compatibility of the expelled molecule (ROH, RSH, RNH) with the alkynylboronate substrate.

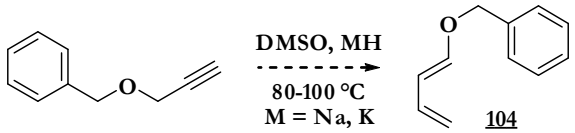
We began our studies by attempting to prepare a series of dienyl ethers. These compounds are known to be prone to polymerisation, however several examples have been reported in the literature. The following section outlines our attempts to prepare the compounds depicted in **Scheme 2.24**.

- *O-Substituted dienes*



Scheme 2.24

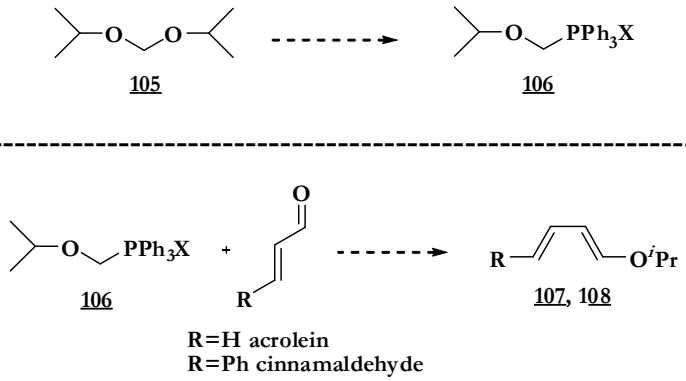
Chmielewski[19] and co-workers reported a synthesis of 1-alkoxy-1,3-butadienes from the corresponding propargyl ethers that involved the formation of an allene intermediate in presence of sodium or potassium hydride in DMSO (**Scheme 2.25**).



Scheme 2.25

It is known that propargyl ethers undergo isomerisation to the corresponding alkoxyallene at low temperature. The addition of dimsyl anion to the allene is followed by protonation of unstable carbanion by DMSO and subsequent elimination of sodium (potassium) methylsulfinate. We attempted to prepare **104** using this strategy, unfortunately, only a complex mixture was recovered. It is unclear why we were unable to repeat the literature conditions but after several attempts we chose to abandon this route.

We next focused on the synthesis of differently O-substituted 1,3-butadienes. The strategy envisaged was the formation of diene **107, 108** *via* a Wittig reaction between a phosphonium salt **106** and acrolein or cinnamaldehyde (**Scheme 2.26**). We first had to prepare the phosphonium salt **106** (**Scheme 2.26**).



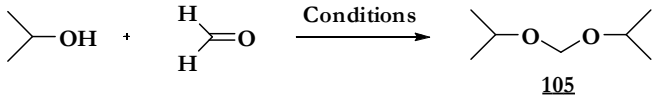
Scheme 2.26

The first strategy for the formation of acetal **105** involved the condensation of isopropanol and formaldehyde. Initial attempts involved heating paraformaldehyde in the presence of catalytic TsOH in refluxing isopropanol. The purification of the acetal **105** by distillation was unsuccessful due to the contamination of the product by paraformaldehyde which originated from the co-distillation of formaldehyde and the product **105** (**Table 2.1**, entry 1-3).

Several formaldehyde sources were investigated. The easiest method used commercial formaldehyde in aqueous solution. Unfortunately, the reaction did not proceed, likely because of aqueous hydrolysis of the product (**Table 2.1**, entry 4-6). Therefore, we had to prepare formaldehyde as a solution in a volatile organic solvent. Different strategies to achieve this were explored. An *adsorption*[20] technique whereby paraformaldehyde was heated in presence of *p*-toluene sulfonic anhydride was investigated. The vapours are carried by a slow nitrogen stream *via* cannula into a receiving flask which contains the appropriate solvent (usually Et_2O or THF). Unfortunately, when we employed this technique, we were unable to observe the presence of any traces of formaldehyde in the solution, possibly because the cannula was too small to carry sufficient formaldehyde to the solvent (**Table 2.1**, entry 7). We next explored a *co-distillation*[20] approach. In this case, the slow distillation of a paraformaldehyde solution containing *p*-toluene sulfonic anhydride allows the solvent to carry the formaldehyde over in the vapour phase as soon as it is

produced. When the collecting flask was kept at room temperature no formaldehyde was present in the solution. Only a cloudy mixture containing the solvent and paraformaldehyde was recovered. However, when the receiving flask was cooled to -78 °C or -10 °C we did observe the presence of formaldehyde (**Table 2.1**, entry 8-11).

With the method for producing formaldehyde solutions at hand, we could perform the acetal formation. Accordingly, freshly prepared formaldehyde solution was reacted with IPA. Pleasingly, the acetal was obtained, but once again it was impossible to purify because contamination with paraformaldehyde (formed from unreacted excess of formaldehyde).

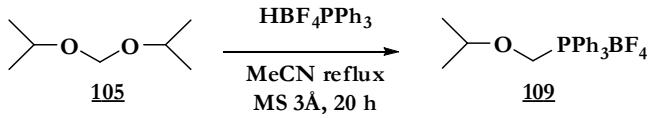


105

Entry	Formol source	T (°C)	Time	PTSAA
1	$(CH_2O)_n$	82	6h	✓
2	$(CH_2O)_n$	82	4h	✓
3	$(CH_2O)_n$	82	2h	✓
4	CH_2O solution	82	2h	✓
5	CH_2O solution	RT	2h	✓
6	CH_2O solution	-10°C	2h	✓
7	CH_2O adsorption	x	x	✓
8	CH_2O co-distillation	-78°C	2h	x
9	CH_2O co-distillation	-10°C	8h	✓
10	CH_2O co-distillation	-78°C	2h	✓
11	CH_2O co-distillation	-10°C	8h	✓

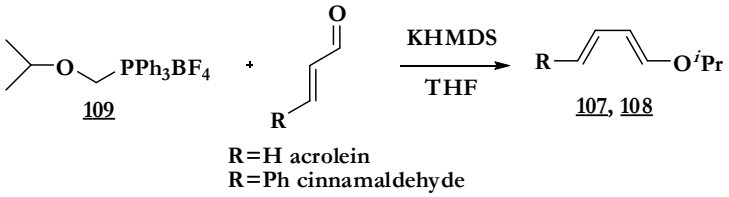
Table 2.1

We then attempted to perform the reaction with the crude acetal **105** in the presence of HBF_4PPh_3 (**Scheme 2.27**) and obtained a crude NMR spectrum of the product which seemed promising. Unfortunately, the phosphorus NMR spectrum presented several peaks.



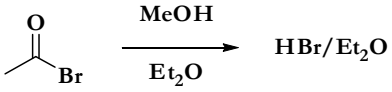
Scheme 2.27

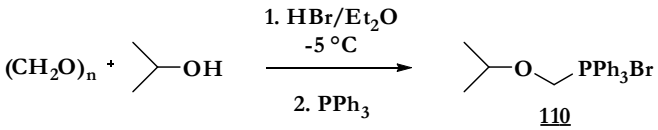
The crude phosphonium salt **109** was used in the Wittig reaction with cinnamaldehyde and acrolein as depicted in **Scheme 2.28**. Unfortunately, but not surprisingly, a complex mixture was recovered.



Scheme 2.28

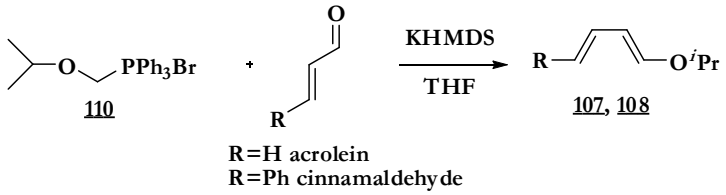
Another strategy was investigated to form a clean phosphonium salt which involved mixing paraformaldehyde, isopropanol and triphenylphosphine in the presence of HBr. A solution of HBr was prepared *in situ* starting from acetyl bromide in methanol and ether, leading to a HBr etherate solution[21]. The formation of the phosphonium salt **110** was accomplished at -5 °C[22] (**Scheme 2.29**).





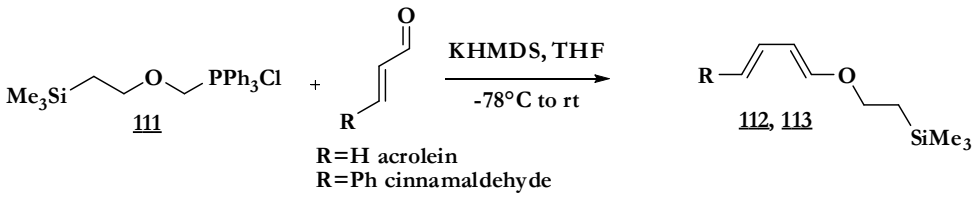
Scheme 2.29

We next tried the Wittig reaction of **110** with both cinnamaldehyde and acrolein (**Scheme 2.30**). The crude NMR spectra seemed promising in both cases. Unfortunately however, we were not able to isolate the desired dienes as the samples were destroyed during chromatography over silica or florisil.



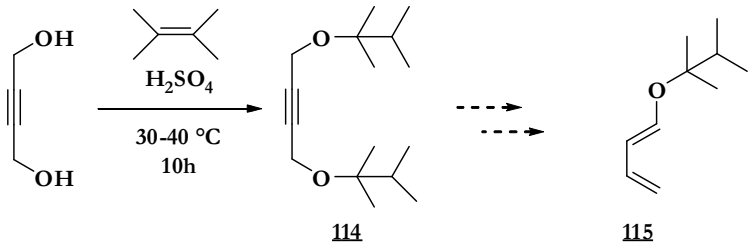
Scheme 2.30

As we did not obtain any promising results in our attempts to prepare **107** or **108**, we decided to investigate the use of an alternative commercially available phosphonium salt **111**. In the event, the attempted Wittig reaction with cinnamaldehyde or crotonaldehyde failed to provide the desired dienes **112**, **113** after chromatography on silica or florisil (**Scheme 2.31**).



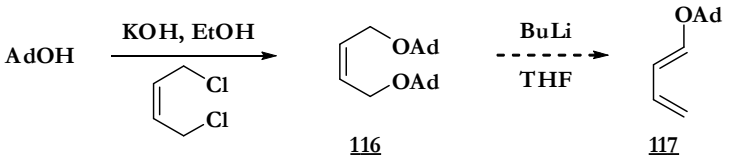
Scheme 2.31

The failure of the Wittig chemistry to generate the desired dienes prompted us to explore a different approach. In this regard, we were intrigued by a report that showed that diprotected propargylic alcohols **114** could be reduced to the corresponding alkene and then subjected to base mediated elimination to form the ether substituted diene **115**[23] (**Scheme 2.32**). The volatility of the alkene used in the first step requires that 4 equivalents were necessary to complete conversion of the starting material to **114**. With 2 equivalents of alkene only the monoprotected product was formed. In the event, we were unable to generate sufficient quantities of clean product and this route was abandoned at this point.



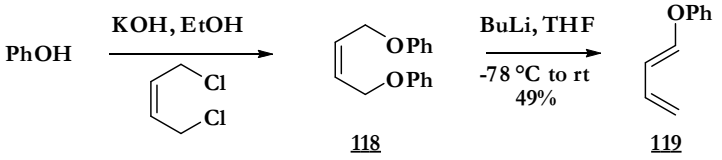
Scheme 2.32

We next looked at a related strategy[24] in which Williamson ether synthesis of dichlorobutene with adamantol, followed by elimination provides the diene **117** (**Scheme 2.33**). Unfortunately only starting materials were recovered from this route.



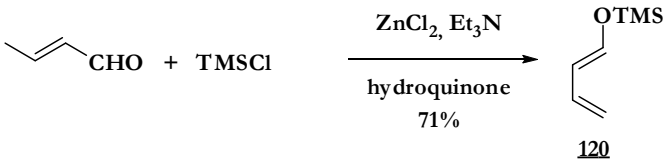
Scheme 2.33

As the adamantly group is quite hindered, we investigated the corresponding reaction with phenol. Finally, we were able to isolate our first O-substituted diene **119** in acceptable yield (**Scheme 2.34**).



Scheme 2.34

An alternative O-substituted diene was synthesised by reaction between crotonaldehyde and trimethylsilyl chloride in the presence of a Lewis acid and a base[25]. Hydroquinone was required to prevent polymerisation. In the event we were pleased to isolate **120** in good yield (**Scheme 2.35**).

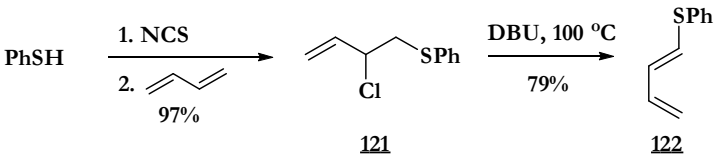


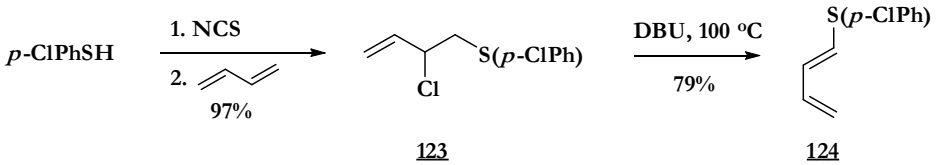
Scheme 2.35

With two representative O-substituted dienes in hand, we turned our attention to the synthesis of S-substituted dienes.

- *S-Substituted dienes*

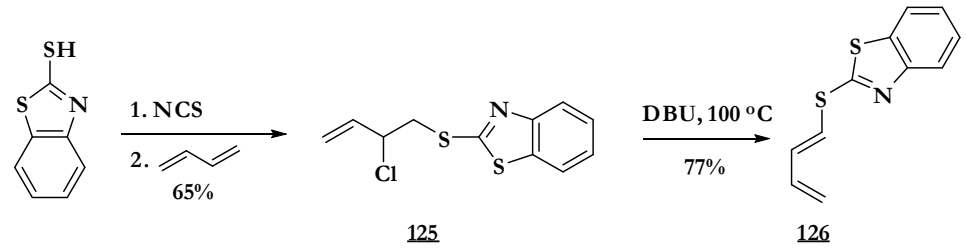
A general method for the synthesis of 1-substituted S-substituted 1,3-dienes involves the treatment of an appropriate thiol with *N*-chlorosuccinimide followed by addition of butadiene. A subsequent elimination using DBU[26] provides the products. Thiophenol derived diene **122** was obtained in good yield *via* this route. This diene can be stored in the freezer under an argon atmosphere for 2-3 weeks without significant decomposition. Surprisingly however, the *p*-chlorophenyl derivative **124** was found to be more prone to polymerisation. After storing this compound under an inert atmosphere at low temperature in the freezer for a couple of days, the diene was found to have fully polymerized (**Scheme 2.36**).





Scheme 2.36

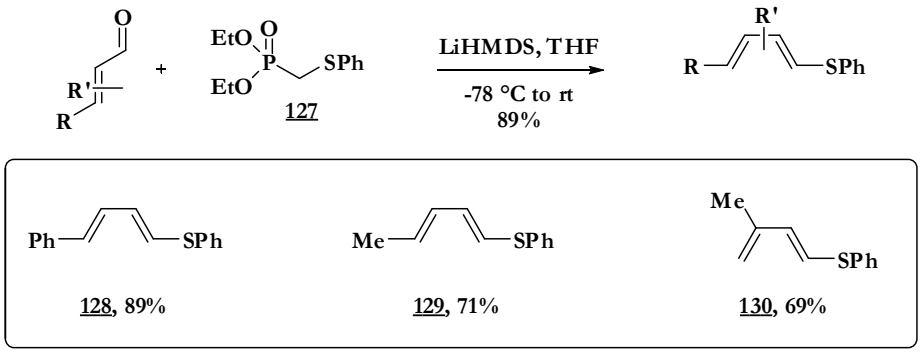
A benzothiazole derived diene **126** was also prepared in an effort to explore the cycloaddition efficiency of heteroaromatic substituted dienes (**Scheme 2.37**).



Scheme 2.37

- *Functionalised S-substituted dienes*

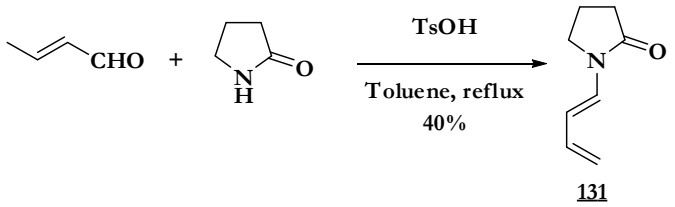
Finally, to broaden the scope of the reaction and to explore the regioselectivity of cycloadditions that generate unsymmetrical products, we wanted to investigate the cycloaddition-elimination process with some polysubstituted dienes. Accordingly, a series of S-substituted dienes were synthesized *via* Horner-Wadsworth-Emmons reactions, yielding the desired dienes in high overall yield. The reactions were carried out with commercially available aldehydes that did not require any purification before use and the S-substituted phosphonate **127**. All dienes were found to be quite easy to handle, and no polymerisation process was observed during synthesis or purification as long as they were used straight away. Polymerisation was observed however upon storage in the freezer, even under an inert atmosphere (**Scheme 2.38**).



Scheme 2.38

- *N-substituted dienes*

In order to assess the effectiveness of N-substituted dienes in the cycloaddition, a dienamide **131** was prepared *via* condensation of crotonaldehyde and 2-pyrrolidinone in the presence of an acid catalyst[27] (**Scheme 2.39**). Product **131** was stored in the freezer under inert atmosphere, however polymerisation was observed after a couple of weeks.

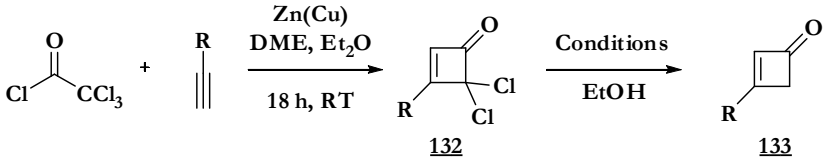


131

Scheme 2.39

2.3 Nickel Chemistry-Synthesis of cyclobutenones

The cyclobutenones were prepared *via* a [2 + 2] cycloaddition of a ketene with an alkyne. The ketene was prepared *in situ* from trichloroacetyl chloride and zinc-copper couple. The reaction took place at room temperature and provided a quantitative yield of the corresponding dichlorocyclobutenone[28] **132**. The next step was the reduction of the dichlorocyclobutenone to the desired cyclobutenone **133**. The reaction required optimisation for each cyclobutenone as their reactivity showed to be very different (**Scheme 2.40**).



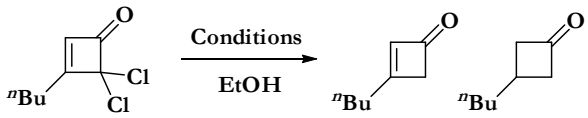
132 **133**

Scheme 2.40

- *3-Substituted cyclobutenone*

Following the procedure described by Danheiser[28], the 3-butyl dichlorocyclobutenone **134** was reduced smoothly using zinc, acetic acid (and TMEDA) in good yield providing cleanly the desired compound **135** (**Table**

2.2, entry 1). However, these conditions failed to give clean compounds in the dechlorination of substrates bearing other substituents.

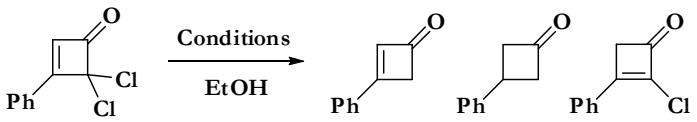


134 135 136

Entry	TMEDA	AcOH	Zn	T (°C)	Outcome
1	**6 eq**	**6 eq**	**6 eq**	**0 to RT**	**86% 135**
2	0 eq	6 eq	6 eq	0 to RT	1:1, **135**:**136**

Table 2.2

Reduction of 3-phenyldichlorocyclobutenone **137** using established conditions provided a non separable mixture (1:1) of the desired cyclobutenone **138** and the fully reduced cyclobutanone **139** (**Table 2.3**, entry 1). Performing the reaction at 0 °C did not improve the ratio (**Table 2.3**, entry 2). Cooling down the reaction to -78 °C or to -50 °C (**Table 2.3**, entry 3 & 4) prevented the reaction from taking place. A marginal improvement was observed when the temperature was maintained between -20 °C and -10 °C, as no fully reduced compound **139** was observed but compound **140** was obtained as the major compound (**Table 2.3**, entry 5). Finally, running the reaction at 0 °C without any TMEDA led to desired cyclobutenone **138** in 84% yield (**Table 2.3**, entry 6).

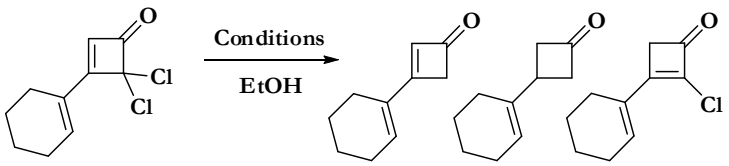


137 138 139 140

Entry	TMEDA	AcOH	Zn	T (°C)	Outcome
1	6 eq	6 eq	6 eq	0 to RT	1:1, **138**:**139**
2	6 eq	6 eq	6 eq	0	1:1, **138**:**139**
3	6 eq	6 eq	6 eq	-78	No reaction
4	6 eq	6 eq	6 eq	- 50	No reaction
5	6 eq	6 eq	6 eq	-20 to -10	1:10, **138**:**140**
6	**0 eq**	**5 eq**	**10 eq**	**0**	**84%, 138**

Table 2.3

Dechlorination 3-cyclohexenyldichlorocyclobutenone **141** using the classic conditions provided a non separable mixture (1:1) of the desired cyclobutenone **142** and the fully reduced cyclobutanone **143** (**Table 2.4**, entry 1). Under the same conditions without TMEDA, the reaction led to the fully reduced cyclobutanone **143** (**Table 2.4**, entry 2). Maintaining a reaction temperature of 0 °C did not significantly improve the ratio (**Table 2.4**, entry 3). We finally managed to isolate 44 % yield of the desired cyclobutenone **142** by reducing the amount of reagents (**Table 2.4**, entry 4). Surprisingly however, the optimal conditions required large quantities of Zn/TMEDA, and these provided 90% of the desired cyclohexenylcyclobutenone **142** (**Table 2.4**, entry 5).

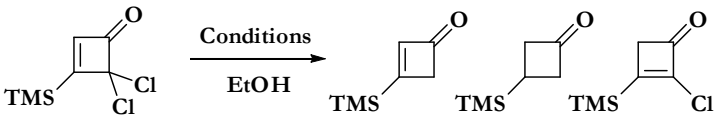


141 **142** **143** **144**

Entry	TMEDA	AcOH	Zn	T (°C)	Outcome
1	6 eq	6 eq	6 eq	0 to RT	1:1, **142**:**143**
2	0 eq	6 eq	6 eq	0 to RT	53% **143**
3	0 eq	6 eq	6 eq	0	1:3, **142**:**143**
4	2.2 eq	2.2 eq	2.2 eq	0 to -10	44% **142**; 11% **144**
5	**10 eq**	**5 eq**	**10 eq**	**0**	**90% 142**

Table 2.4

Attempts to cleanly prepare the TMS-substituted substrate failed. As seen in **Table 2.5**, we were never able to prepare cyclobutenone **146** without contamination from other by-products.



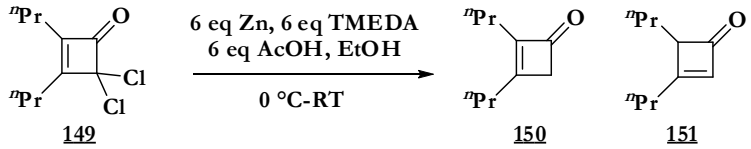
145 **146** **147** **148**

Entry	TMEDA	AcOH	Zn	T (°C)	Outcome
1	6 eq	6 eq	6 eq	0 to RT	49% **146**
2	3 eq	3 eq	3 eq	0 to RT	1:1, **146**:**147**
3	2 eq	2 eq	2 eq	0 to RT	1:5, **146**:**148**
4	2.5 eq	2.5 eq	2.5 eq	0 to RT	1.5:1, **146**:**147**
5	2.2 eq	2.2 eq	2.2 eq	0 to RT	3:1, **146**:**147**

Table 2.5

- *2,3-Disubstituted cyclobutenone*

As 2,3-di-*n*-propylcyclobutenone **149** is similar to 3-buylcyclobutenone **135**, we thought that the same conditions could be applied in the dechlorination step. However, these established conditions[28] provided a mixture of the desired compound **150** and isomerised compound **151**. Stirring for a longer time under the same set of conditions resulted in isomerisation to the most substituted isomer **150** (**Table 2.6**).



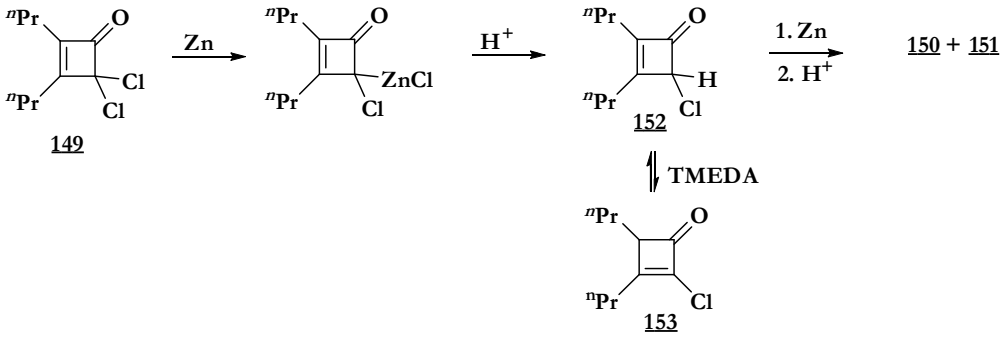
149 **150** **151**

Entry	Reaction time	Outcome
1	3 h	1:3.5, **150**:**151**
2	24 h	12.5:1, **150**:**151**; 50 % **150**

Table 2.6

A mechanistic interpretation of these results is shown in **Scheme 2.41**. The organozinc intermediate could be generated by oxidative addition without proceeding through a high-energy antiaromatic enolate intermediate. Rapid protonolysis would then provide the monochloro derivatives **152** and **153**. Only **152** can undergo further reduction. The interconversion *via* isomerisation to the deconjugated vinylchloride system **153** can happen in the presence of

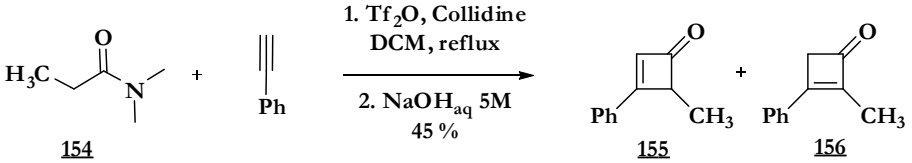
tertiary amine (TMEDA). Alternatively the interconversion can take place by addition-elimination of the tertiary amine[4].



Scheme 2.41

- *3,4-Disubstituted cyclobutenone*

The strategy we used to prepare a non-symmetrical 3,4-disubstituted cyclobutenone was different[29]. The synthesis proceeded again *via* a [2 + 2] cycloaddition. The ketene equivalent was produced *in situ* from amide **154** using triflic anhydride and collidine (**Scheme 2.42**). A basic work-up furnished a 1:1 mixture of cyclobutenone **155** and the isomerized compound **156**. We were not able to separate the isomers. In principle however, the cycloaddition should proceed using the mixture as only the 3,4-disubstituted cyclobutenone **155** is likely to react.



Scheme 2.42

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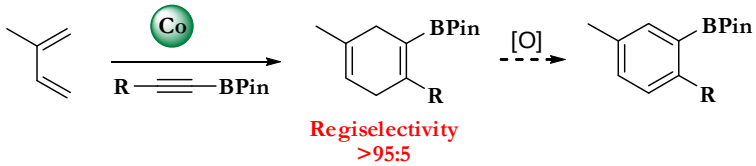
CHAPTER III

Cobalt-catalyzed cycloaddition

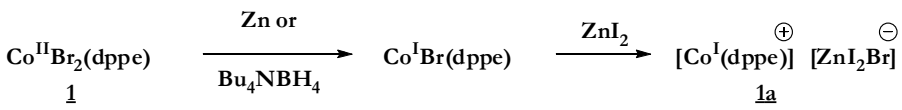
3.0 Introduction

The cobalt catalyzed [4 + 2] cycloaddition of non-activated dienes with alkynylboronates is a promising approach for the synthesis of aromatic boronic esters. Indeed, as introduced previously[1] this process provides 1,4-dienylboronic esters in high yields and with high regiocontrol, and in principle, these could be precursors to the aromatic analogues (**Scheme 3.1**). To investigate the scope of this strategy, a range of dienes have been selected and studied in the cycloaddition processes. In all cases, the reaction was performed in dichloromethane at room temperature with 10 mol% of cobalt catalyst in the presence of 20 mol% of zinc and zinc iodide.



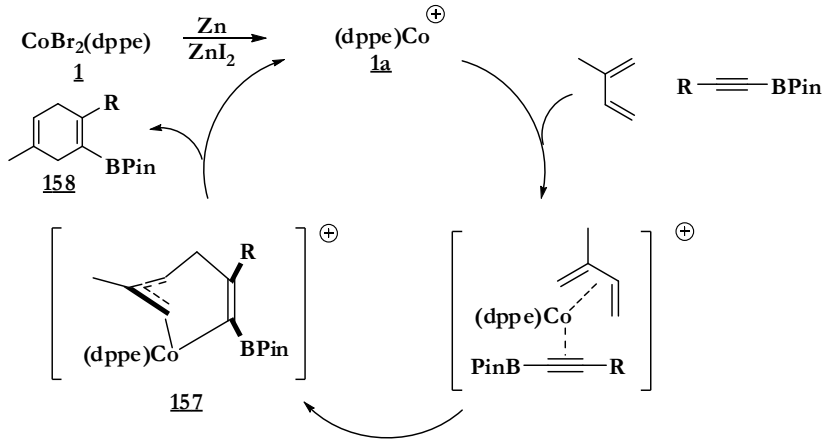
Scheme 3.1

From a mechanistic viewpoint, the first step is the formation of the active catalyst. Zinc reduces the Co^{II} to Co^{I} and in the presence of zinc iodide forms the active cationic Co^{I} catalyst (**Scheme 3.2**). This redox chemistry is accompanied by a colour change of green to brown.



Scheme 3.2

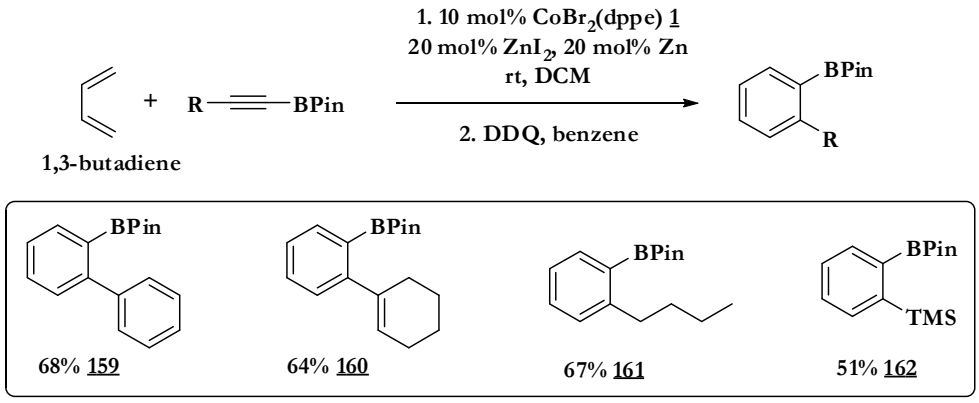
Following the mechanistic studies reported by Hilt[2], once the catalyst is formed, the diene is added, followed by the alkyne. The diene is introduced first to prevent the cyclotrimerisation of the alkyne which happens rapidly in the absence of diene. The active cobalt catalyst **1a** coordinates to both the diene and alkyne such that the large alkyne substituent **R** is orientated away from the dppe ligand, and the methyl group of the diene is incorporated at C-2 of the resulting π-allyl unit to minimise the steric interaction with the ligand. Finally, the cobaltocycloheptadiene **157** undergoes reductive elimination to yield to the desired product **158** with high regioselectivity (**Scheme 3.3**).



Scheme 3.3

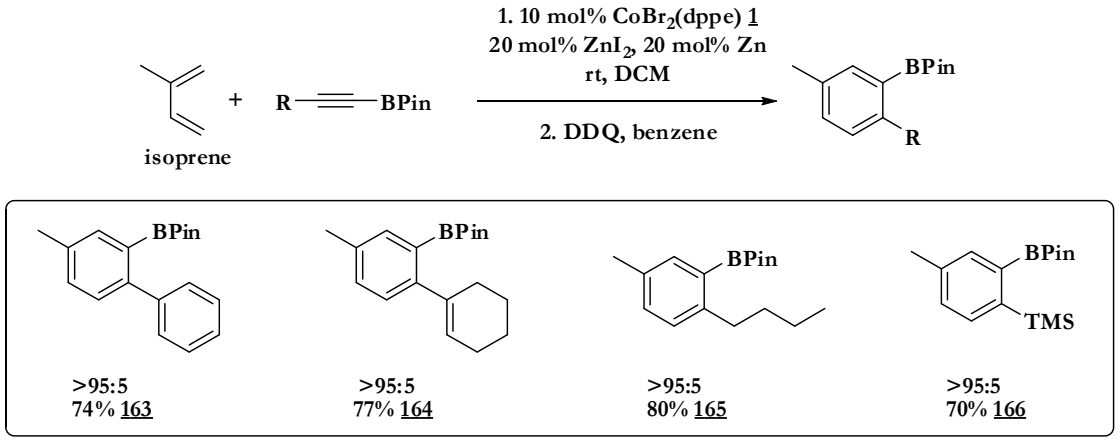
3.1 Cycloaddition-Oxidation Strategy

The cycloaddition between butadiene and an alkynylboronate provided the desired aromatic boronic esters in good yields up to 80 % as shown in **Scheme 3.4**. The scope of the chemistry is very good with respect to the alkynylboronate, and this method provides a convenient way of preparing *ortho*-substituted aromatic compounds after a mild oxidation using DDQ.



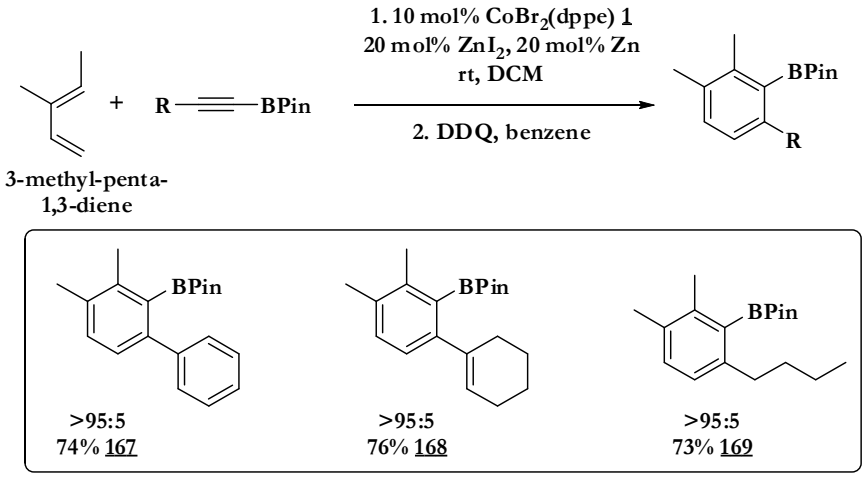
Scheme 3.4

After the use of the simplest diene, we wanted to investigate a homologue and chose readily available isoprene. The cycloaddition with isoprene and an alkynylboronate was found to proceed smoothly under mild conditions yielding the desired aromatic boronic ester in good yield and with excellent regioselectivities (>95:5) for each substrate (**Scheme 3.5**).



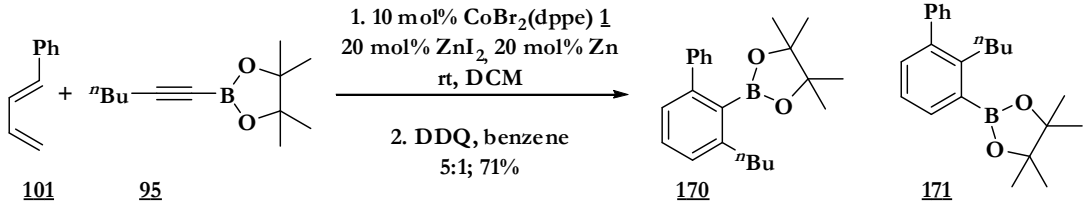
Scheme 3.5

The excellent results obtained with isoprene led us to investigate the efficiency of a disubstituted diene in the cycloaddition reaction. Pleasingly, the cycloaddition with 3-methyl-penta-1,3-diene also showed excellent regioselectivities for each substrate, as well as good yields (**Scheme 3.6**).



Scheme 3.6

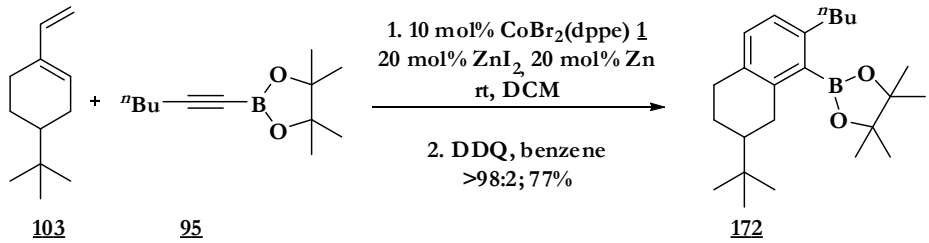
A more hindered butadiene analogue **101** bearing a phenyl group in the C1 position was also investigated. The results of the cycloaddition with *n*butylalkynylboronate **95** showed that this reaction proceeded effectively. However, we noted a drop in regioselectivity in this case; the use of **101** provided a 5:1 ratio of regioisomers **170**, **171** (**Scheme 3.7**).



Scheme 3.7

We were expecting a better regioselectivity in the reactions of substrate **101** due to the increased steric effects of phenyl compared to methyl. However, similar observations in the cycloaddition of **101** with internal alkynes have been documented by Hilt[3].

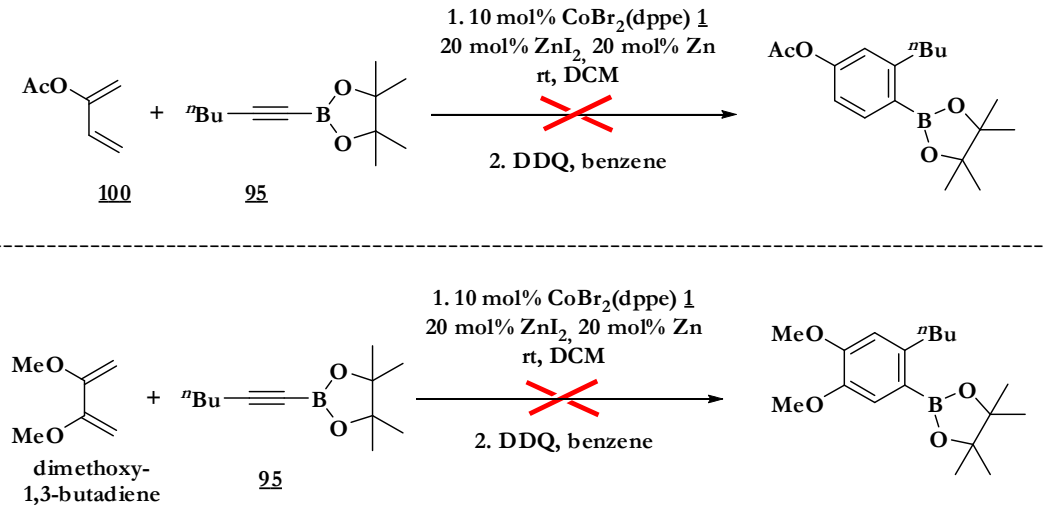
We wanted to explore more elaborate 1,2-disubstituted dienes in the cycloaddition and prepared **103**. In the event, the cycloaddition between **103** and *n*butylalkynylboronate **95** proceeded well and gave only one regioisomer **172** (**Scheme 3.8**).



103 95 172

Scheme 3.8

Finally, we turned our attention to a heteroatom functionalised diene (**Scheme 3.9**). Unfortunately the reaction with neither diene **100** nor dimethoxy-1,3-butadiene proceeded, and only starting materials were recovered with **100** and a complex mixture with dimethoxy-1,3-butadiene. In this case it is possible that Lewis base coordination to the catalyst could prevent the cycloaddition occurring or lead to unwanted reaction by-products.



100 95

dimethoxy-1,3-butadiene 95

Scheme 3.9

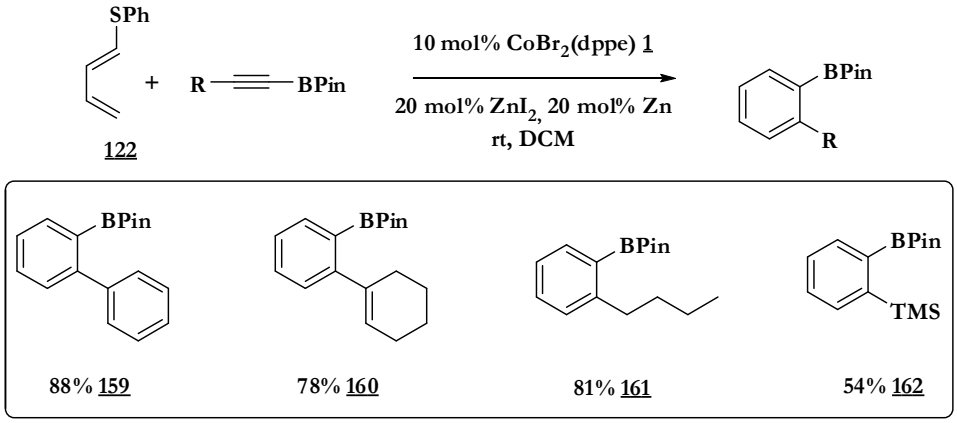
Overall, the cycloaddition-oxidation chemistry provides a reliable method for the synthesis of aromatic boronic esters bearing a wide range of substitution patterns. These processes proceed under mild conditions, at room temperature and furnish the desired benzene rings in good yields with high levels of regiocontrol.

3.2 Cycloaddition-Elimination Strategy

A second strategy based on a cycloaddition and an *in situ* elimination provides an alternative route to access aromatic boronic esters at room temperature. Several dienes were synthesised to investigate the effect of the eliminated by-product on the cycloaddition.

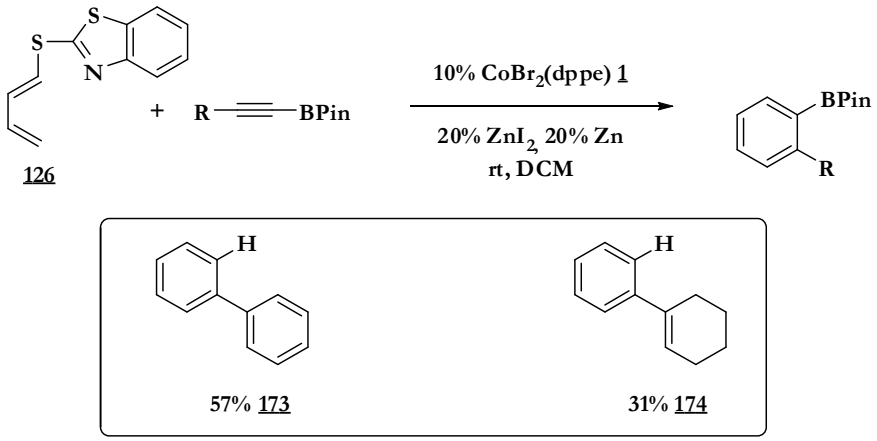
S-Substituted dienes

We began our studies in this area by investigation of **122** in the cycloaddition-elimination process. We were pleased to find that this chemistry provided the desired aromatic boronic esters in good yield (**Scheme 3.10**).



Scheme 3.10

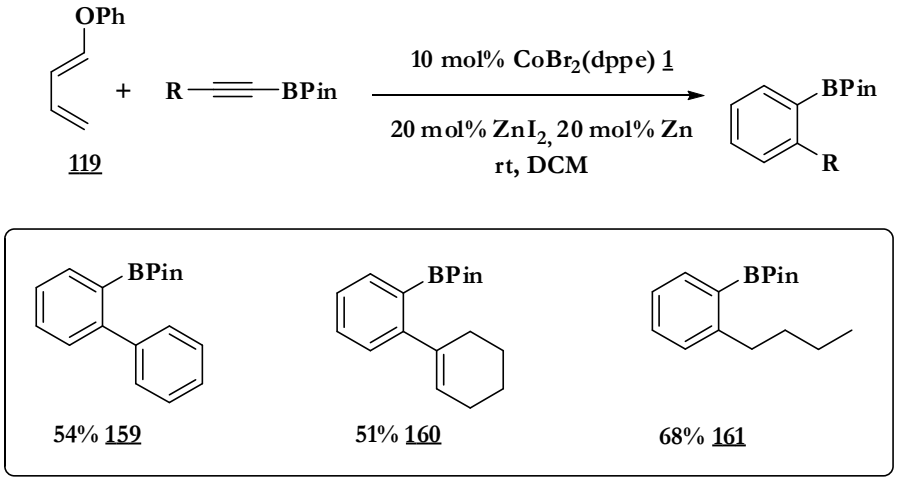
Surprisingly, the use of the benzothiazolyl analogue **126** proved to be ineffective. Whilst the cycloaddition still occurred, only deboronated cycloadducts **173** and **174** were isolated (**Scheme 3.11**). Although the moderate yield of such reaction could be attributed to the polimerisation of diene **126**, the rationale behind the deboronation of the adducts remain unclear.



Scheme 3.11

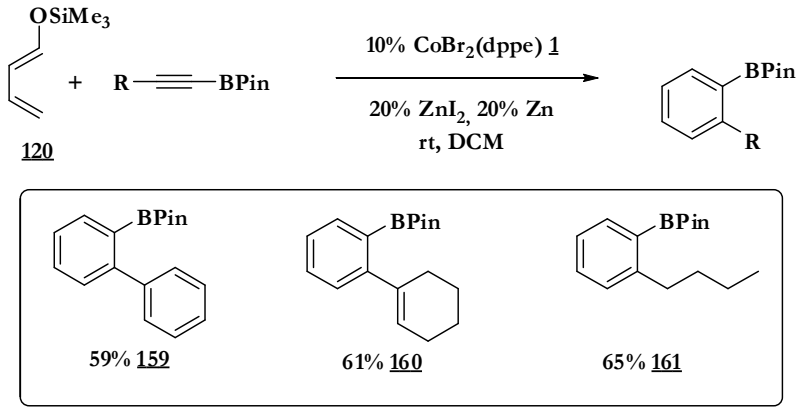
O-Substituted dienes

O-Substitued dienes **119** and **120** has been found to be the easiest to prepare and isolate. When **119** was employed in the cycloaddition process, we obtained the desired aromatic boronic esters in lower yield and with significant protodeboronation (15-30%) compared to the SPh-analog **122** (**Scheme 3.12**).



Scheme 3.12

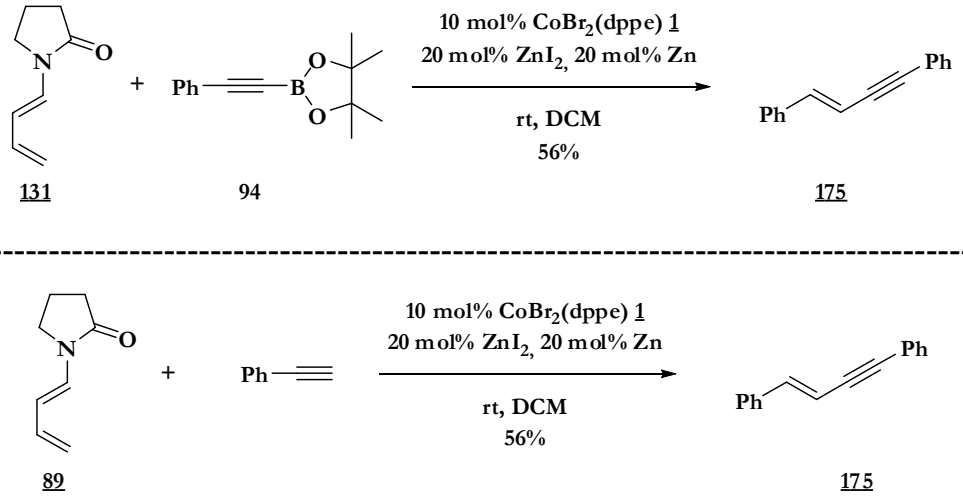
However with OTMS-diene **120**, no protodeboronation was observed but lower yields compared to the SPh-diene **122** were obtained (**Scheme 3.13**).



Scheme 3.13

N-Substituted dienes

Having had some success with S- and O-substituted dienes, we next moved on to examine the N-substituted diene **131** in the cycloaddition. Unfortunately however, these reactions failed to provide any cycloadduct. However, we did observe an enyne adduct **175** (**Scheme 3.13**). Increasing the catalyst loading, or changing the catalyst for Co(dppp)Br_2 or for pyridine based ligand[4] led only to cyclotrimerisation. The different catalysts used are presented in **Figure 3.1**. When phenylacetylene was used in this reaction instead of the alkynylboronate, the same product **175** was formed, albeit in higher yield (**Scheme 3.14**).



Scheme 3.14

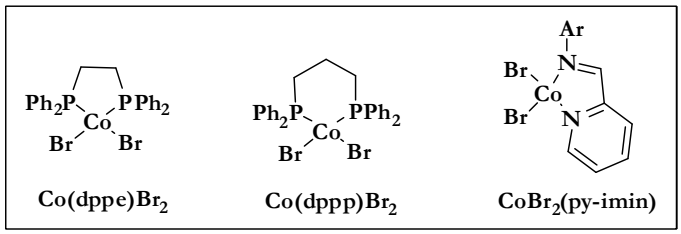
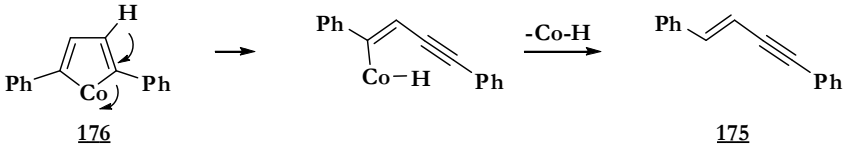


Figure 3.1

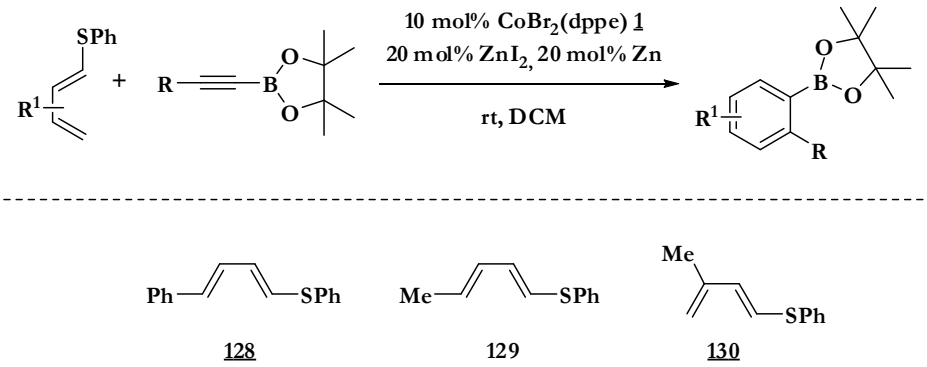
From a mechanistic viewpoint, we believe the enyne formation is the result of a β-elimination from a cobaltocyclopentadiene **176**, followed by reductive elimination of Co-H, as outlined in **Scheme 3.15**. This rationale suggests that the dienamide **131** does not participate in a reaction with the Co-catalyst.



Scheme 3.15

Functionalised S-substituted dienes

With regard to the cycloaddition-elimination reaction, the most effective substrate was the S-substituted diene **122**. We wanted to investigate the effect of incorporating substituents on the S-substituted diene on the cycloaddition process, in order to establish what regioselectivity could be achieved. In the event, treatment of C-4 substituted dienes **128** or **129** with an alkynylboronate under the cycloaddition conditions described previously, resulted in no cycloadduct being observed. The cycloaddition with C-3 substituted diene **130** did not show any better results, except that we could observe small amounts of a cycloadduct but this result was not reproducible. We assumed that the easy polymerisation of dienes prevents the cycloaddition or cleaves the C-B bond in the starting alkyne, or that they are too hindered to react (**Scheme 3.16**).



128 **129** **130**

Scheme 3.16

In conclusion, in addition to the cycloaddition-oxidation process described in this chapter, an alternative cycloaddition-elimination strategy has been developed to synthesise aromatic boronic esters under mild conditions. Both methods allow easy access to functionalised aromatic boronic ester, although the latter technique appears to be more limited.

3.3 Regiochemistry assignments

The structure of compounds **164**, **166**, **168** and **169** has been established by ^{1}H NMR nOe spectroscopy (**Figure 3.2b**, *see appendices)*. The regioselectivity of the other compounds have been inferred following the reports by Hilt and co-workers[1].

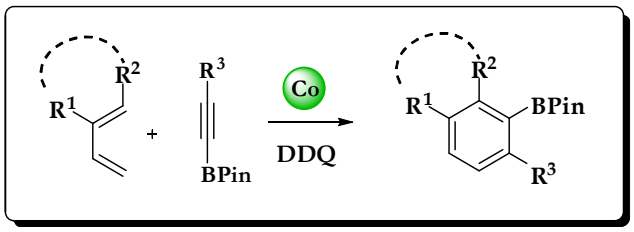


Figure 3.2a

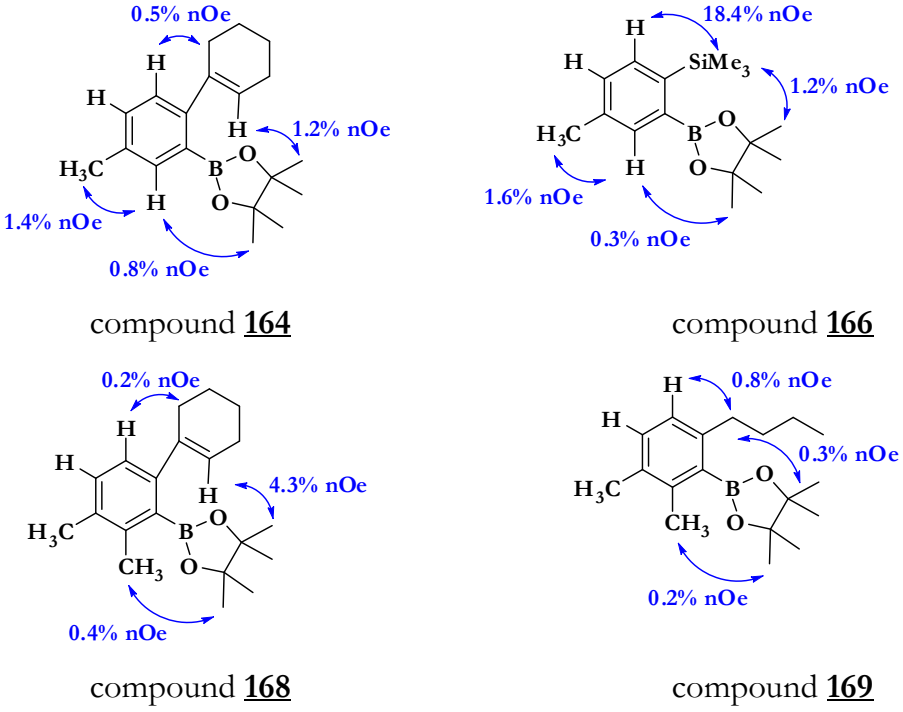
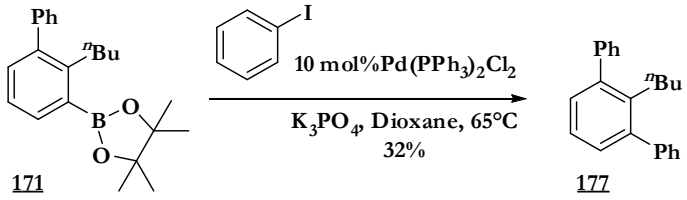


Figure 3.2b

A mixture of regioisomers was obtained in the cycloaddition of diene **101** and *n*butylalkynylboronate **95**. To confirm the identity of the two product regioisomers we decided to carry out a derivatisation. Specifically, the minor regioisiomer **171** was subjected to a Suzuki cross coupling reaction with iodobenzene to form the symmetrical adduct **177** (**Scheme 3.17**) which allowed confirmation of the regiochemistry by ^{13}C NMR spectroscopy.



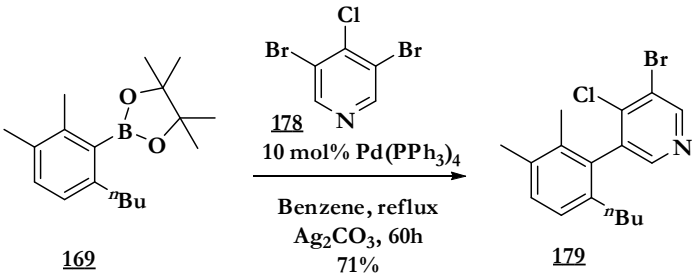
Scheme 3.17

3.4 Synthesis of polysubstituted aromatic boronic esters : An application to the synthesis of aminopyridine derivatives

In recent years, small molecules capable of catalysing enantioselective acyl transfer have attracted great interest in the synthetic community, especially because they are an alternative to enzymes in transformations amenable to nucleophilic catalysis. Several kinds of chiral nucleophilic catalysts have been developed that offer practically useful levels of steroselectivity in acylative kinetic resolution (KR)[5] and asymmetric desymmetrization[6] of alcohols, as well as other transformations.

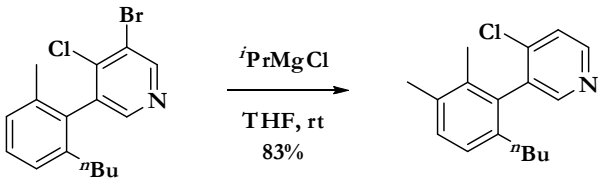
Several groups have been studying this family of chiral catalysts, and have reported derivatives of 4-(dimethylamino)pyridine (DMAP)[7] and other analogs including proline-derived diamines[8] or chiral bicyclic phosphines[9]. Spivey and co-workers[10] have reported that axially chiral, atropoisomeric biaryl 4-aminopyridines are an effective catalyst for KR of various aryl alkyl sec-alcohols. We envisaged that we could employ the Co-catalysed benzannulation chemistry to form a Spivey-type DMAP analog, which could potentially be a good nucleophilic catalyst for enantioselective acyl transfer.

The first step of the synthesis was the cross coupling between the aromatic boronic ester **169** and a pyridine **178**. The use of $Pd(PPh_3)_4$ in refluxing benzene in the presence of silver carbonate provided a reliable method for the synthesis of **179** (**Scheme 3.18**).



Scheme 3.18

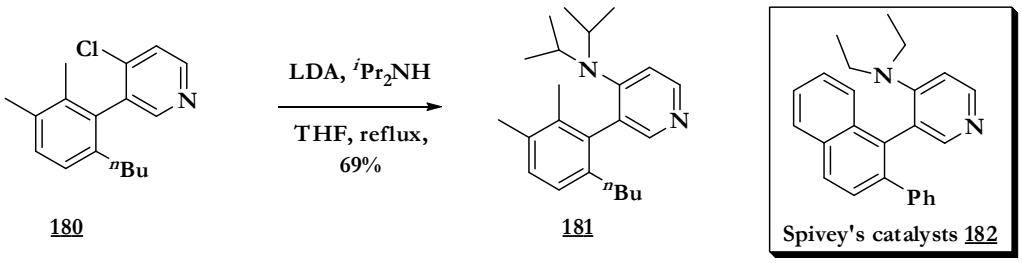
The next step of the synthesis was the reduction of the remaining bromide, which was performed at room temperature in THF using isopropylmagnesium chloride. The desired product **180** was obtained within 2 hours in good yield (**Scheme 3.19**).



179 180

Scheme 3.19

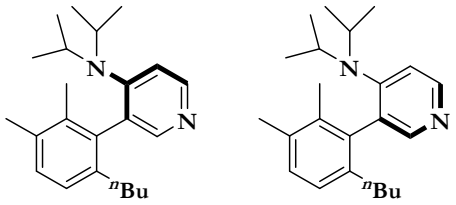
The final step involved incorporation of the 4-amino substituent by a nucleophilic aromatic substitution reaction (SN_{Ar}). The reaction was carried out overnight in refluxing THF in the presence of isopropylamine and LDA providing 69% of the final compound **181** (**Scheme 3.20**).



180 181

Scheme 3.20

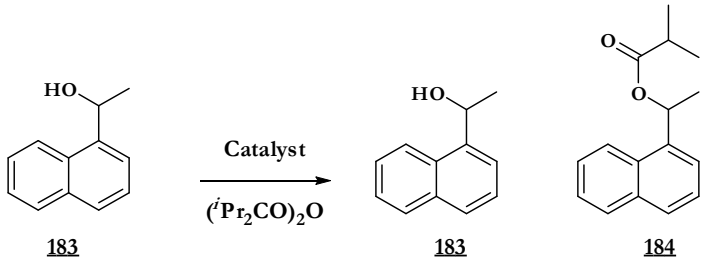
This new compound could be an alternative to Spivey's catalysts (**Scheme 3.20**) as the *diortho*-substituted phenyl group would play the role of the naphthyl group. To test the catalytic activity of this new compound, in collaboration with Prof. Spivey[11], the racemic mixture **181** was separated by chiral HPLC using a ChiralPak IA column. Atropoisomers **181a** and **181b** were separated at 10.5 min and 14.0 min[11] (**Figure 3.3**).



181a **181b**

Figure 3.3

Surprisingly, the separation conditions developed by Spivey for his catalyst **182** led to a really poor separation of our compounds. Also, racemisation happened at room temperature. We assumed a low energy of rotation around the atropoisomeric axis which was a quite unexpected result due to the hindrance of the methyl and the butyl group on both sides which should have induced a higher energy barrier for racemisation compared to Spivey catalyst **182**. Computational studies were carried out and did not seem to be in agreement with the facile racemisation. To understand the discrepancy, the catalytic activity of our racemic catalyst **181** and a racemic version of Spivey catalyst **182** in the acylation of alcohol **183** with isobutyric anhydride were compared (**Table 3.1**).



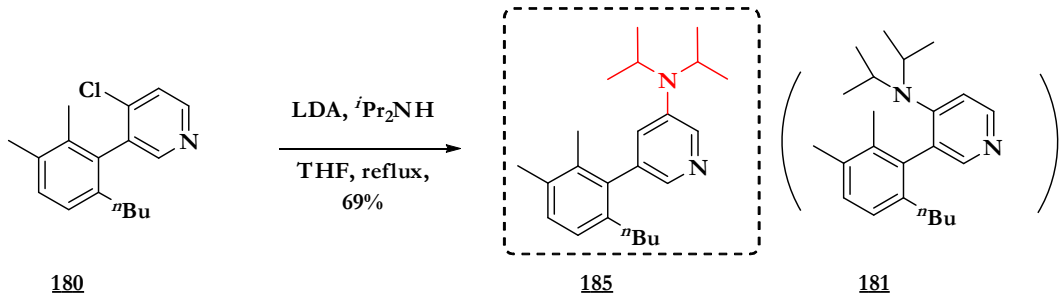
183 **183** **184**

Catalyst	Reaction time	Conversion
Our catalyst **181**	24 h	0
Spivey's catalyst **182**	3 h	Full

Table 3.1

Disappointingly, after 24 hours there was no acylation of the starting material **183** with our catalyst **181**. However, the strong nucleophilic activity of catalyst **182** resulted complete conversion to the acylated product **184** within 3 hours (**Table 3.1**). This result led us to reconsider the structure of our compound

and suggested that we had actually made the regioisomer **185**, and not **181** (**Scheme 3.21**).



180 **185** **181**

Scheme 3.21

NMR studies were carried out by Spivey and co-workers in order to characterise the product regiochemistry. A strong nOe was observed with the diisopropyl protons on the aminopyridine ring with aromatic protons H_4 and H_6. This observation confirmed that regioisomer **185** was formed instead of **181** (**Figure 3.4**, *see appendices*).

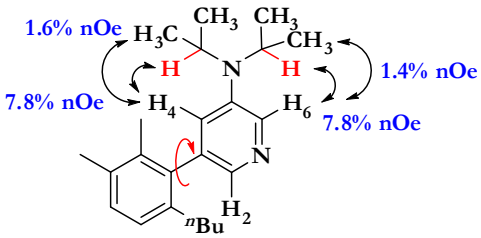
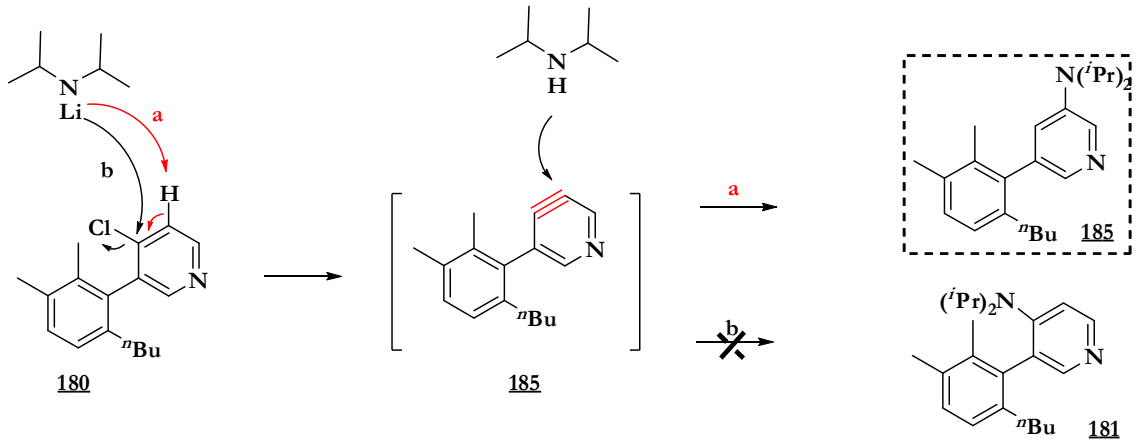


Figure 3.4

To our disappointment, the route we developed had led to the formation of compound **185**. It appears that steric hinderance slows down the SN_{Ar}, and the formation of the benzyne intermediate **186** is much faster. The nucleophile attacks the least hindered position leading to compound **185**. That explains the requirement of excess amine. This result follows Spivey's observation on these kinds of substrates[10]. Using diethylamine, he always observed a ratio 2:1 in favour of the least hindered compound. In our case, the use of a more hindered amine reduces the chance to form regioisomer **181**, forming **185** exclusively instead (**Scheme 3.21**).



Scheme 3.21

3.5 Conclusion

Benzannulation reactions represent one of the most efficient and direct methods for assembling highly substituted aromatic compounds. Despite the challenges associated with chemoselectivity and regioselectivity, we developed an efficient strategy for the synthesis of aromatic boronic ester derivatives with a high level of regiocontrol, good yields under really mild conditions. The strategy provides a powerful means for the generation of highly substituted aromatic derivatives.

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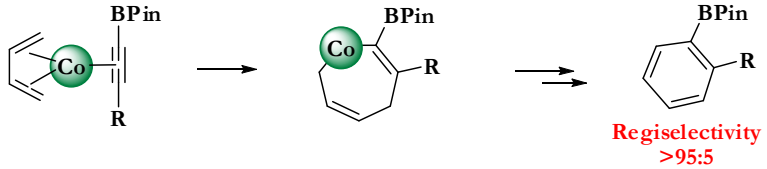
CHAPTER IV

Nickel-catalyzed cycloaddition

1.0 Introduction

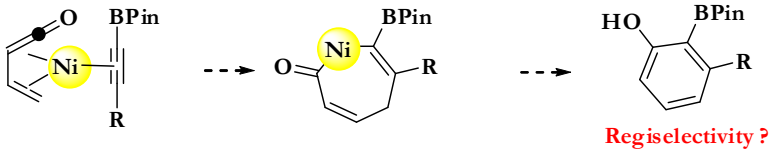
As described in the previous chapter, cobalt promotes the [4 + 2] cycloaddition of 1,3-unactivated dienes with alkynylboronates under ambient conditions. The method is general and convenient for the synthesis of aromatic boronic ester derivatives and provides excellent levels of regiocontrol (**Scheme 4.1**). In order to further develop this concept, we wanted to access more heavily substituted benzene based aromatic boronic esters. Specifically, we envisaged a metal mediated [4 + 2] cycloaddition of an alkynylboronate and a vinyl ketene equivalent to provide the corresponding oxygenated aromatic ring (**Scheme 4.2**). Promising results in the literature[1] led us to further study this strategy. Indeed, Liebeskind[1] has shown that nickel is able to catalyze the formation of substituted phenols from a cyclobutenone and an alkyne (**Table 4.1**).

[4 + 2] cobalt-mediated cycloaddition



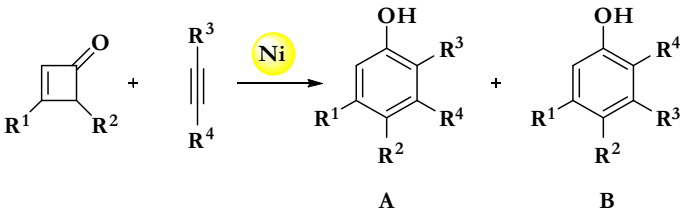
Scheme 4.1

Potential [4 + 2] nickel-mediated cycloaddition



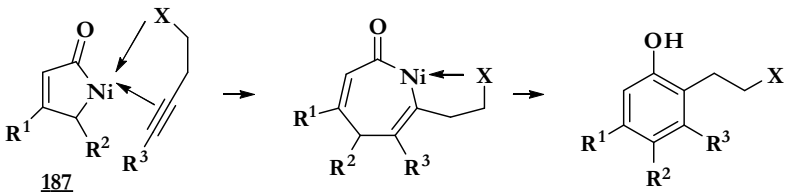
Scheme 4.2

The results reported in the literature[1] showed poor regioselectivities for this transformation (up to 3:1). There appeared to be little regiocontrol based on the size of the alkyne substituents (**Table 4.1**, entry 1 & 2). However alkynes bearing heteroatom-substituted chains did show a modest selectivity which was greater with a two-carbon tether than the corresponding three-carbon tether (**Table 4.1**, entry 4 & 5). In all cases, the major product bears the heterosubstituted chain *ortho* to the hydroxyl group. These observations are consistent with a mechanism in which the alkyne inserts preferentially into the metal-C4 bond of the vinylketene complex **187** followed by reductive elimination (**Scheme 4.3**).



Entry	R^1	R^2	R^3	R^4	Ratio A:B	Yield (%)
1	Ph	H	Me	^{i}Pr	50:50	81
2	Ph	H	Me	TMS	45:55	58
3	Ph	Me	Me	$(CH_2)_2OTBDMS$	75:25	63
4	Bu	H	Me	$(CH_2)_2OTBDMS$	75:25	59
5	Bu	H	Me	$(CH_2)_3OTBDMS$	50:50	67

Table 4.1



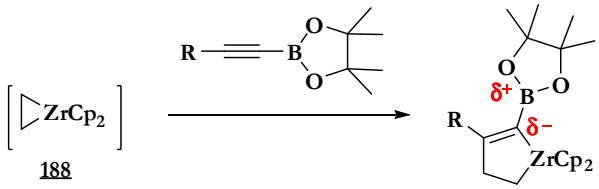
Scheme 4.3

However, it might be possible to control the regioselectivity by adding a boronate moiety on the alkyne to stabilize the intermediate as shown by Srebnik[2]. In his report, the alkyne inserts into a zirconacyclopropane **188**

creating a partial negative charge at the carbon α to the metal which can be stabilized with the vacant p-orbital of boron (**Scheme 4.4**).

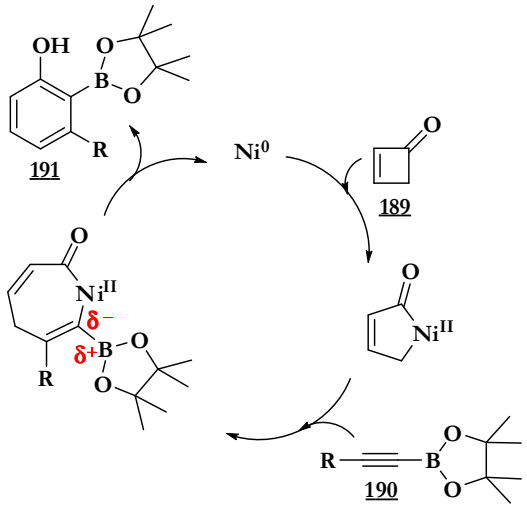
The cyclobutenone **189** is a vinyl ketene equivalent and could play the role of the "diene" partner to participate in a [4 + 2] cycloaddition with an alkynylboronate **190**. The nickel catalyzed [4 + 2] cycloaddition of ketenes with alkynylboronates is a promising concept for the synthesis of phenol boronic ester derivatives. Following Srebnik's work[2], the nickel catalyst might play the same role as zirconium and direct the cycloaddition towards the formation of a single regioisomer **191** (**Scheme 4.5**).

Srebnik's work



Scheme 4.4

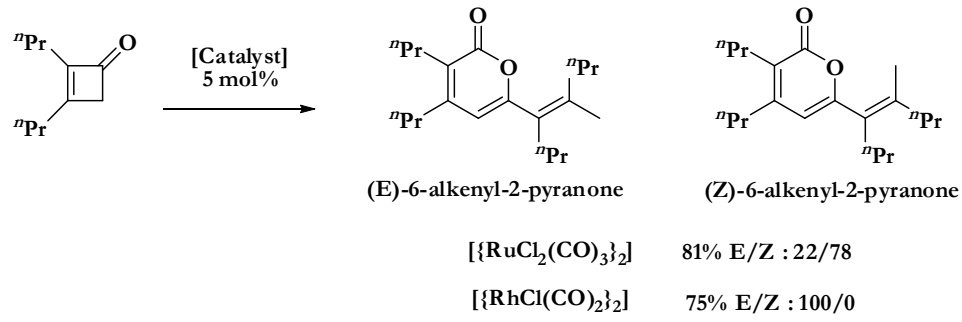
Proposed access to regioselective installment of boronate



Scheme 4.5

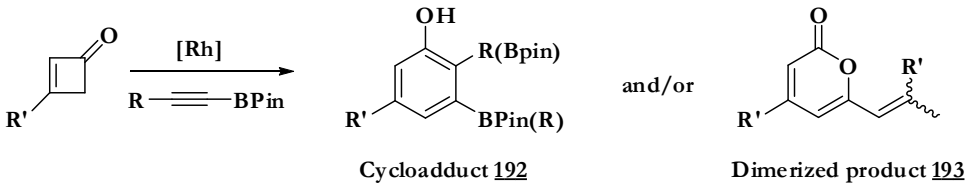
4.1 Preliminary studies : Rhodium catalysis

Kondo and Mitsudo[3] reported a rhodium and ruthenium catalyzed ring-opening dimerization of cyclobutenones to give 2-pyranones (**Scheme 4.6**).



Scheme 4.6

We wanted to study the potential of the rhodium-catalyzed reaction to incorporate an alkynylboronate into a cycloadduct **192**, as opposed to simply promoting dimerisation to the 2-pyranone **193** (**Scheme 4.7**).



Scheme 4.7

In the event, the addition of 3-butylcyclobutenone **135** and *n*butylalkynylboronate **95** to the rhodium catalyst provided a mixture of pyranone **194** (exclusively as the (*E*)-isomer) and pyranone **195** (**Scheme 4.8**).

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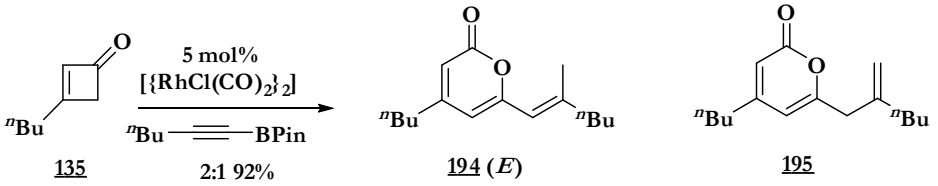
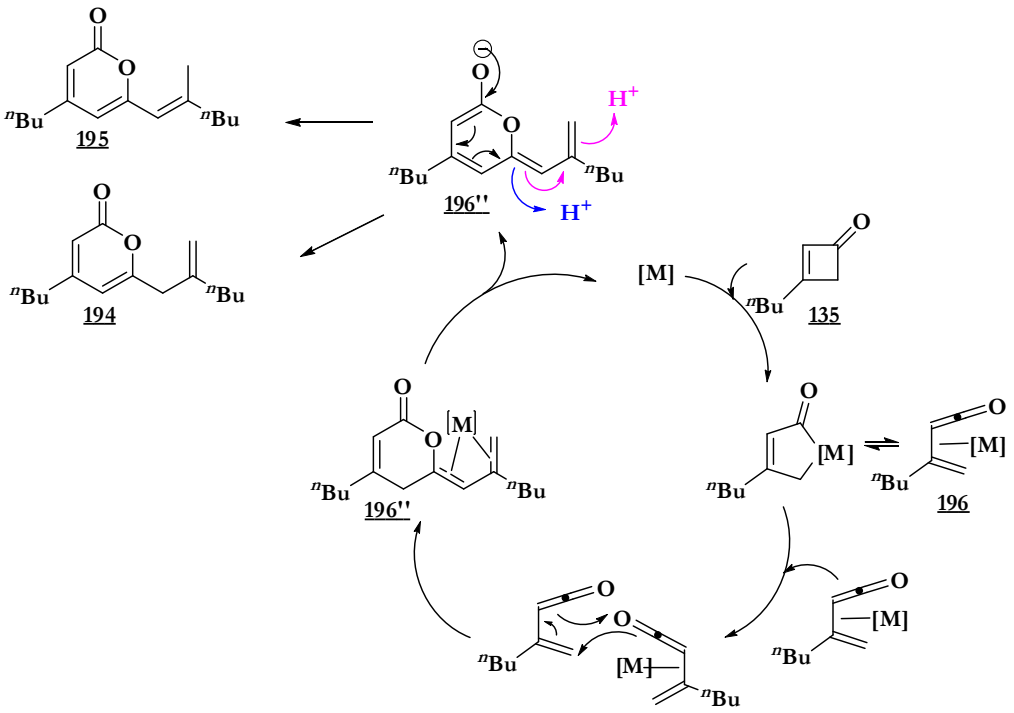


Scheme 4.8

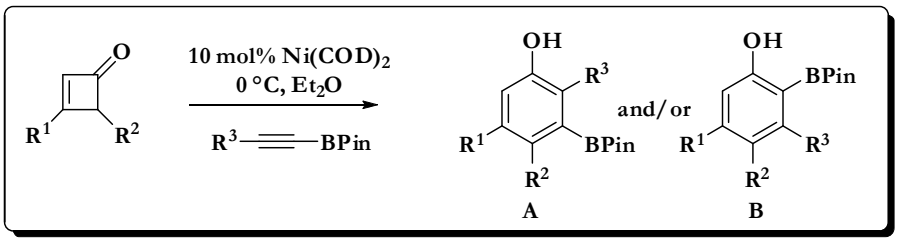
The proposed mechanism[3] for the ring-opening dimerization of cyclobutenones is illustrated in (**Scheme 4.9**). The initial step might consist of regioselective ring-opening of the cyclobutenone **135** by an active metal centre to give an η^4-vinylketene intermediate **196**, which rapidly reacts with another molecule of metal-bound vinylketene in a hetero-Diels-Alder reaction. Finally, tautomerisation of **196'** could form the extended enolate **196''** and subsequent protonation would give rise to the observed products **194** and **195**.



Scheme 4.9

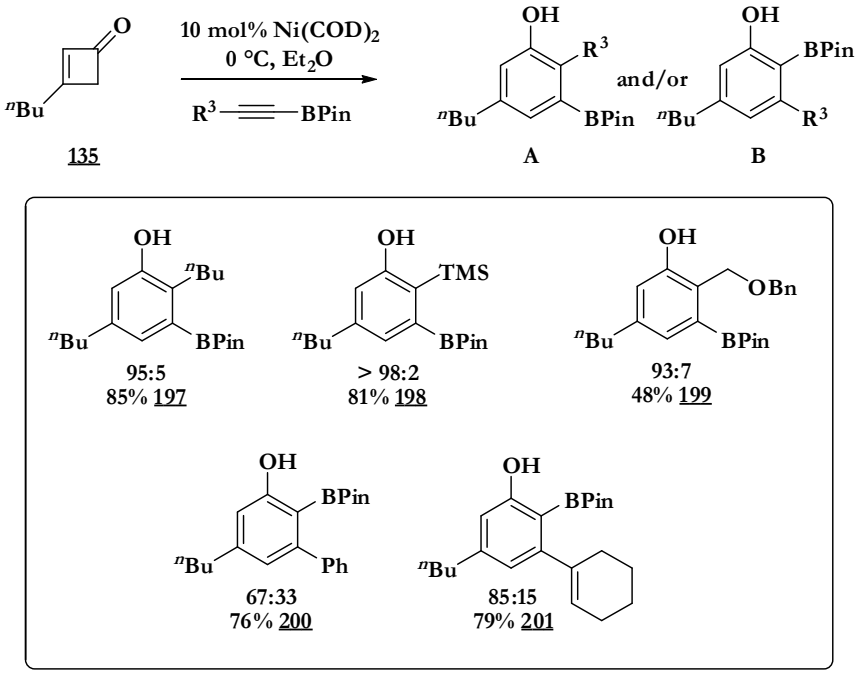
4.2 Benzannulation reactions

We then decided to turn our attention to the nickel chemistry following Liebeskind studies[1]. To investigate the scope of this strategy, a range of cyclobutenones have been selected and investigated in the cycloaddition process. In all cases, the reaction was performed in diethyl ether at 0 °C with 10 mol% of nickel catalyst (**Scheme 4.10**).



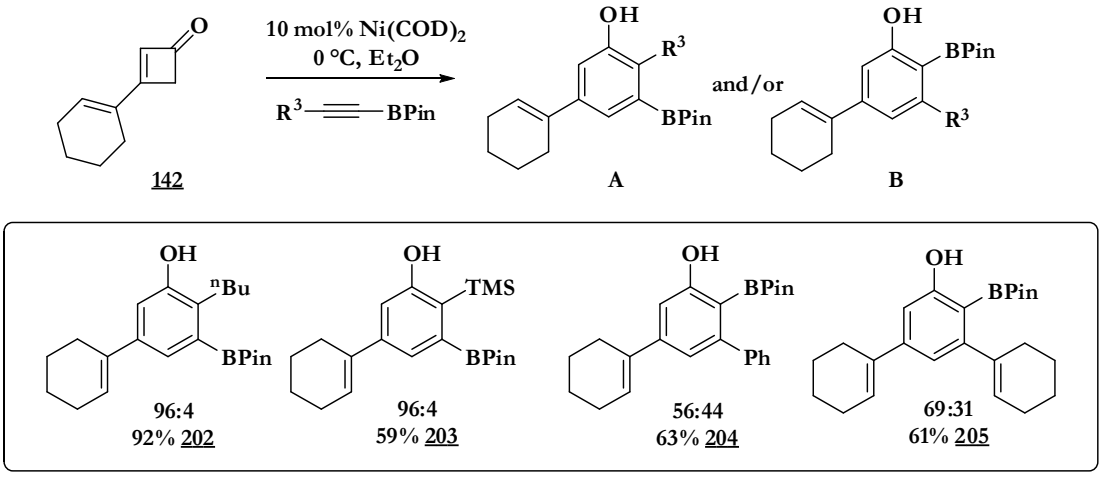
Scheme 4.10

The cycloaddition of 3-butylcyclobutenone **135** with an alkynylboronate provided the desired phenol boronic ester derivatives in good yields up to 85% as shown in **Scheme 4.11**. The scope of the chemistry is very good with respect to the alkynylboronate, and this method provides a convenient way of preparing tetrasubstituted aromatic compounds. The regioselectivity was found to be excellent when sp^3 (Bu, TMS) substituents were employed, providing regioisomer **A**. In contrast, poorer selectivities were observed when the substituent on the alkynylboronate was sp^2 (Ph, cyclohexenyl), providing **B** as the major regioisomer as shown in **Scheme 4.11**. The compound **199** provides a good illustration of this point, as it contains an aromatic moiety but it is linked by a sp^3 carbon to the ring resulting in high levels of regiocontrol. Overall therefore, it appears that the regioselectivity has a strong dependance on the size of the substituent attached to the alkynylboronate.



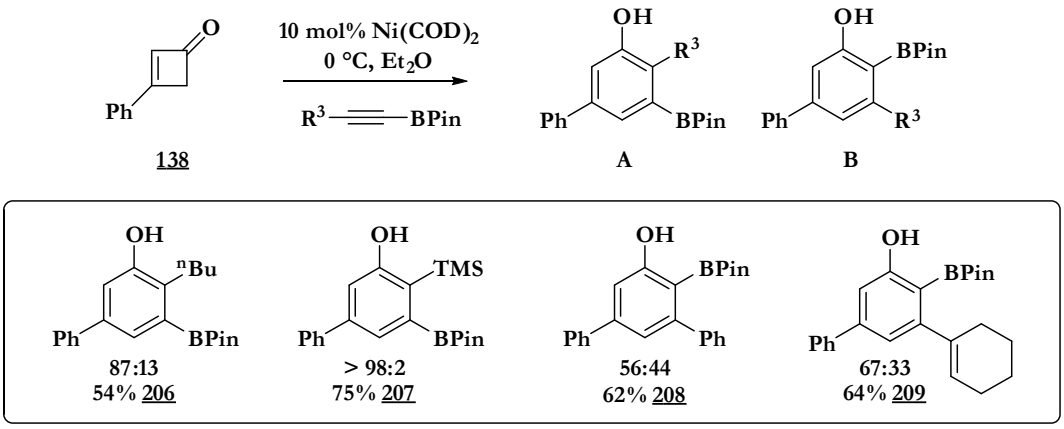
Scheme 4.11

We wanted to further investigate the cycloaddition with different cyclobutenones to broaden the scope of the reaction with this substrate, and to study if sp^2 substituted cyclobutenones would also influence the regioselectivity. We envisaged that 3-cyclohexenylcyclobutenone **142** could be an interesting substrate to investigate in this regard, and explored its participation in the nickel-catalyzed [4 + 2] cycloaddition (**Scheme 4.12**).



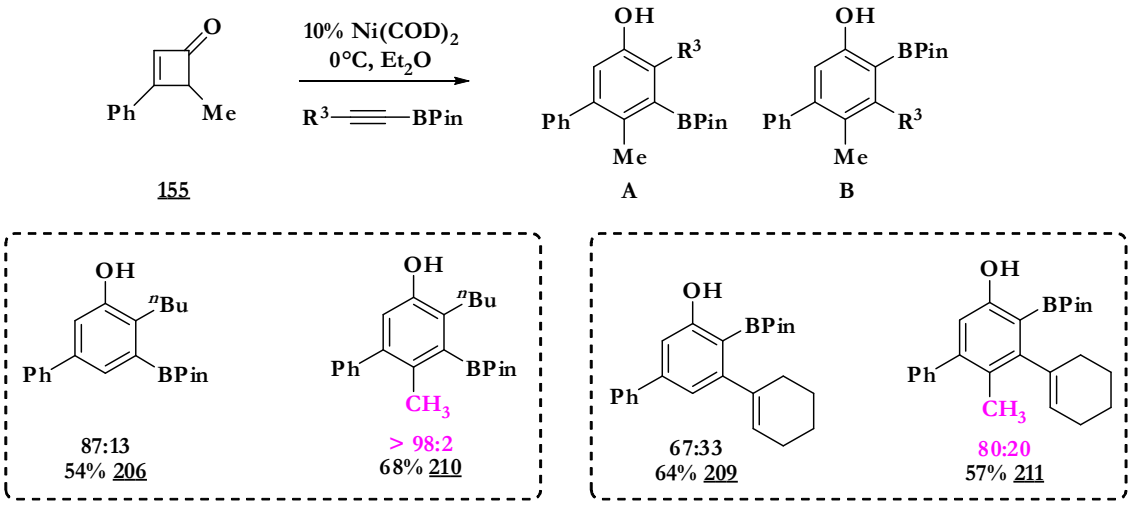
Scheme 4.12

Pleasingly, the cycloaddition between 3-cyclohexynylcyclobutenone **142** and an alkynylboronate provided the desired phenol boronic ester derivatives in good yields (up to 92%) as shown in **Scheme 4.12**. As observed with 3-butylcyclobutenone **135**, the regioselectivity was found to be excellent when sp^3 (Bu, TMS) substituted alkynes were employed, providing regioisomer **A** and poor when the substituent on the alkynylboronate was a sp^2 (Ph, cyclohexynyl), providing **B** as the major regioisomer. The regioselectivity seemed to be strongly dependent of the substituent attached to the alkynylboronate but the cyclobutenone 3-substituted did not seem to be crucial. To confirm these results, we next investigated the influence of 3-phenylcyclobutenone **138** in the cycloaddition reaction.



Scheme 4.13

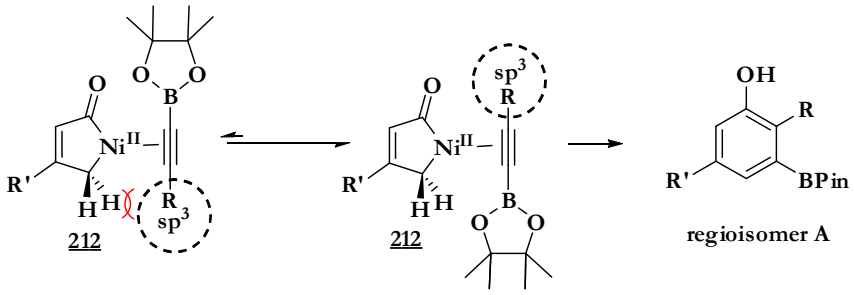
To our delight, the cycloaddition between 3-phenylcyclobutenone **138** and an alkynylboronate provided the desired phenol boronic ester derivatives in good yields up to 75 % as shown in **Scheme 4.13**. Once again, the regioselectivity was similar to that observed with other cyclobutenones (**Scheme 4.11** & **Scheme 4.12**). The results observed with 3-substituted cyclobutenones led us to study more heavily substituted analogues in an effort to establish whether or not these would improve the regioselectivity overall. The choice of cyclobutenone **155** with a methyl at C4 was chosen as it provided a good comparison with its analogue **138** (**Scheme 4.14)**.



Scheme 4.14

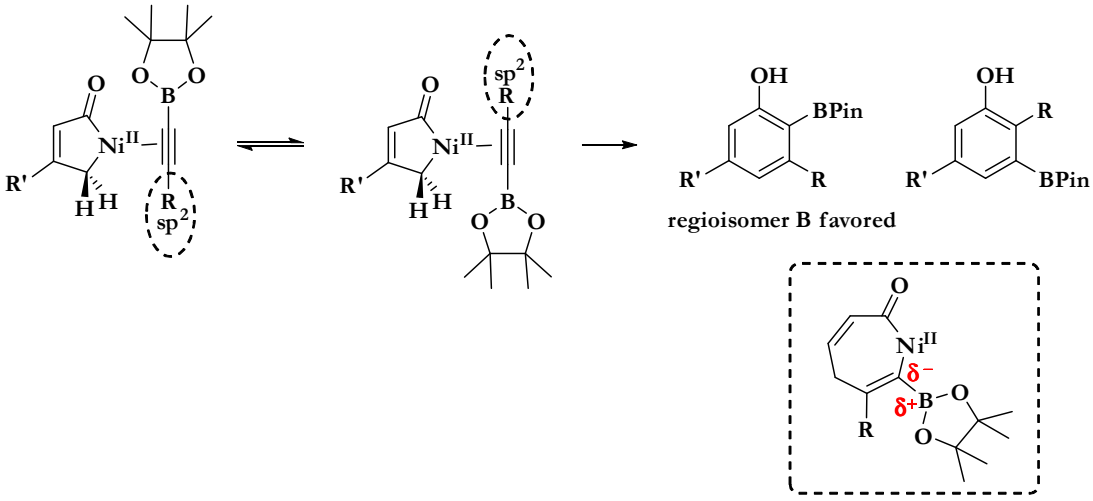
Substrate **155** provided pentasubstituted phenol boronic esters in useful yields. To our delight, a single regioisomer **210** could be obtained with the *n*butylalkynylboronate **95**. Moreover, a large improvement in regiocontrol was observed with cyclohexenylalkynylboronate **97** (**Scheme 4.14**). The regioselectivity is highly dependent of the size of the alkynylboronate and also, it appears, dependent on the substituent at C4 of the cyclobutenone. However, the substitutent at C3 seems to be to far away from the active site to control any regioselectivity. From these results we can conclude that the regiocontrol is governed by sterics.

From a mechanistic viewpoint, as we said earlier in **Scheme 4.5**, the insertion of nickel in the cycloaddition can direct the regioselectivity towards one regioisomer when sp^3 centers are involved. Surprinsigly, the regioselectivity was opposite to the one expected. We can rationalise that Ni^{II} is a square planar complex which means that the large R (sp^3) group prefers to stay away from the CH_2 of the metallacyclopentenone **212** and then due to sterics leads to a single regioisomer **A** (**Scheme 4.15**).



Scheme 4.15

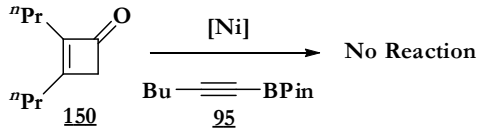
In the case of sp^2 substituents, these are planar and can compete with the boronate moiety for incorporation adjacent to the more hindered position (**Scheme 4.16**). Interestingly, stabilisation of the partial negative charge by the vacant boron p-orbital does not appear to be significant. This is perhaps reflected in the fact that the p-orbital is saturated by the lone pairs on oxygen.



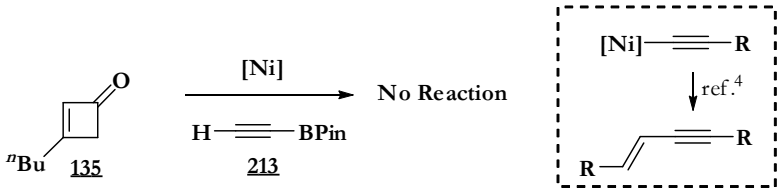
Scheme 4.16

In order to further establish the scope of the reaction with respect to cyclobutenone, we opted to explore 2,3-disubstituted cyclobutenones. Unfortunately, when the reaction was conducted with 2,3-di-propylcyclobutenone **150**, no reaction was observed and the cyclobutenone appeared to be inert to cycloaddition (**Scheme 4.17**). This was disappointing as it would have been a nice example to confirm that the regioselectivity is dictated by the effect of the substituents close to the site of the metal-

insertion. Finally, treatment of terminal alkynyboronate **213** with cyclobutenone **135** resulted in a complex mixture of products and no cycloadduct could be isolated (**Scheme 4.18**). This result can be explained by the fast polymerisation of terminal alkynes with nickel.[4]

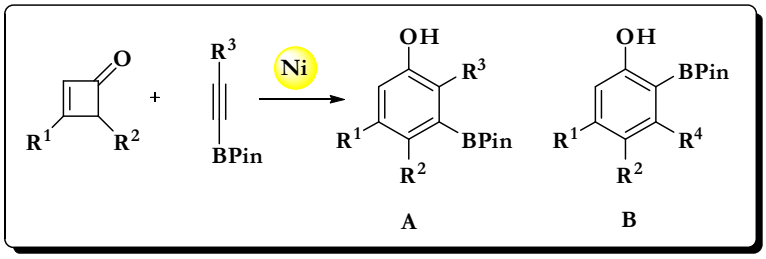


Scheme 4.17



Scheme 4.18

4.3 Regiochemical assignments



Scheme 4.19

The regiochemistry of the cycloadducts derived from cyclobutenones and alkynyboronates can be directly assigned by inspection of phenolic-OH resonance using ^{1}H NMR spectroscopy. Regioisomer **A** shows a broad signal at ~5 ppm whereas the signal is shifted to ~8 ppm in regioisomer **B** due to hydrogen bonding to the adjacent boronate (**Figure 4.1**). The regiochemistry of compound **197** was also confirmed by X-ray crystallography (**Figure 4.2**).

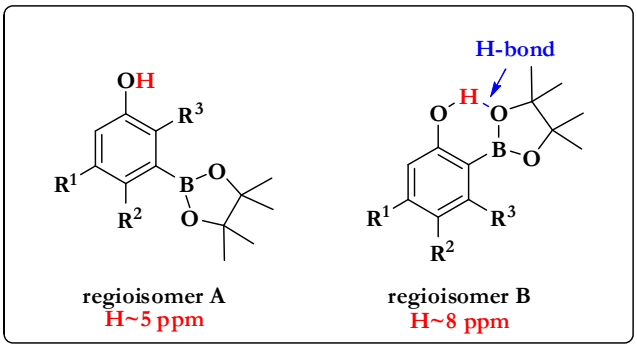


Figure 4.1

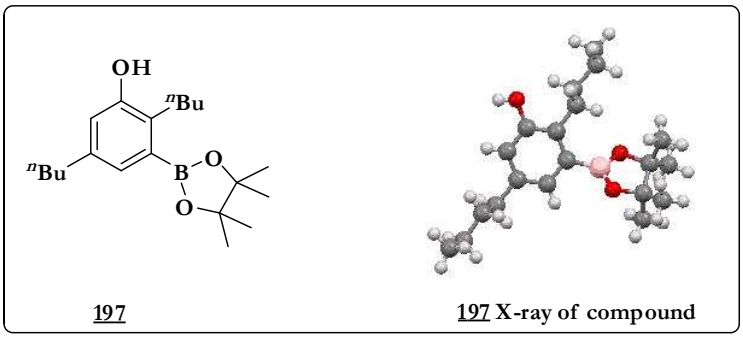


Figure 4.2

4.4 Cycloaddition/cross-coupling "One-Pot" strategy

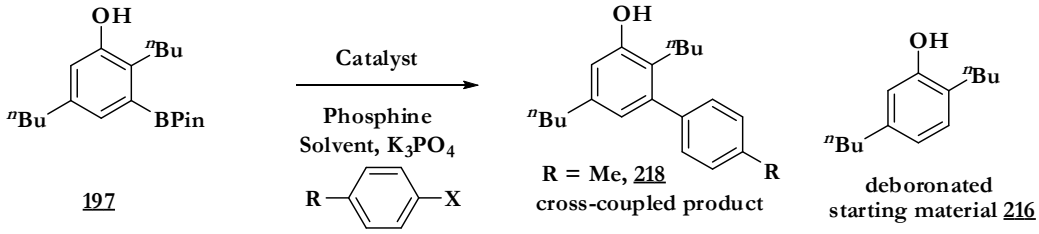
Investigation of the cross-coupling reaction

$Ni(COD)_2$ can catalyze efficiently the [4 + 2] cycloaddition of a cyclobutenone with an alkynylboronate. This process offered the tempting opportunity to explore a tandem catalytic process, whereby Ni-mediates the benzannulation and a subsequent reaction at the C-B bond. Firstly, we wanted to explore the boronate functionalization process. In this regard, a few promising examples in the literature[5] led us to investigate a Ni-catalyzed cross-coupling reaction. Different conditions were studied such as changing catalyst loading (5-50%), temperature, the aryl acceptor, and the phosphine ligand as described in **Table 4.2**. All the reactions failed at room temperature or in refluxing THF with iodobenzene derivatives, and we observed only recovery of the phenol boronic ester **197** in quantitative yield (**Table 4.2**, entry 1-4). We decided to turn our attention to a Pd catalyst[6] as it is known to catalyze cross-couplings efficiently, the desired product was accessed within 5 hours at room temperature. (**Table 4.2**, entry 5). Returning to the nickel catalyst system, in the reactions involving iodobenzene as aryl acceptor, we noticed that we were not recovering the aryl acceptor, recovering instead benzene or toluene. We assumed that the aryl partner was too reactive with the nickel catalyst and turned our attention to the less reactive chlorobenzene derivatives. Unfortunately, the cross-coupling failed under the same set of conditions (**Table 4.2**, entry 6 & 7). Also trying to change the Ni catalyst (**Table 4.2**, entry 8) did not improve the results.

Molander[7] recently reported a Ni-catalyzed cross-coupling involving trifluoroborate moieties with sulfonylated aryl acceptors. He showed the best results to be with mesylates. Trying the new conditions (PCy_3HBF_4, K_3PO_4, $^tBuOH/H_2O$) with mesylate **214** allowed us to access the desired compound **215**. However, compound **215** was contaminated with a small amount of deboronated product **216** (**Table 4.2**, entry 9). Unfortunately, we were not able to separate cleanly the two compounds. The next step was to run the reaction with mesylate **217** to see if it would be possible to separate the desired product from the side product. Once again the cross-coupling was successful

but we recovered a inseparable mixture of the desired compound **218** and the deboronated product **216** (**Table 4.2**, entry 10).

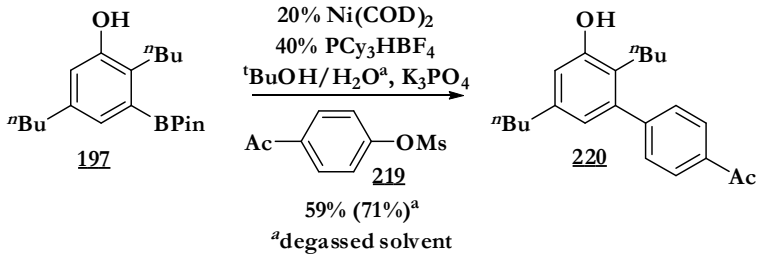
- *Optimisation conditions*



Entry	ArX	Catalyst	Phosphine	Solvent	Outcome
1	PhI	$Ni(COD)_2$	PCy_3HBF_4	THF	Recovery **197**
2	*p*-MeC_6H_4I	$Ni(COD)_2$	PCy_3HBF_4	THF	Recovery **197**
3	PhI	$Ni(COD)_2$	PPh_3	THF	Recovery **197**
4	*p*-MeC_6H_4I	$Ni(COD)_2$	PPh_3	THF	Recovery **197**
5	***p*-MeC_6H_4I**	**$Pd(OAc)_2$**	**-**	**DMF/H_2O**	**81% 218**
6	PhCl	$Ni(COD)_2$	PPh_3	THF	Recovery **197**
7	*p*-MeC_6H_4Cl	$Ni(COD)_2$	PPh_3	THF	Recovery **197**
8	*p*-MeC_6H_4Cl	$NiCl_2(PPh_3)_2$	PPh_3	Toluene	Recovery **197**
9	PhOMs **214**	$Ni(COD)_2$	PCy_3HBF_4	$^tBuOH/H_2O$	**218**+**216**
10	*p*-MeC_6H_4OMs **217**	$Ni(COD)_2$	PCy_3HBF_4	$^tBuOH/H_2O$	**218**+**216**

Table 4.2

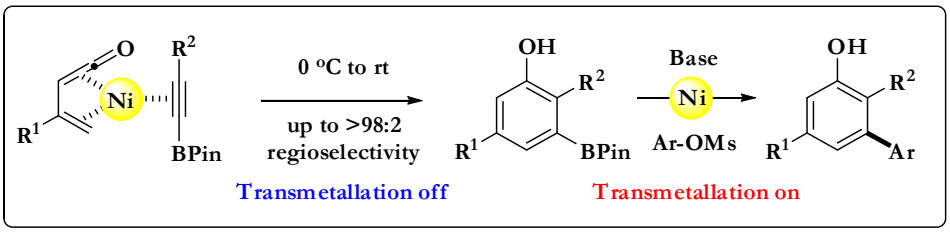
In light of the aforementioned problems, we decided to use a more polar aryl acceptor which could provide a means to separate the cross-coupled product from protodeboronated material by chromatography. Accordingly, we investigated the reaction with mesylate **219** and found really promising results, providing the desired compound **220** in 59%. As we were aware that $Ni(COD)_2$ is air sensitive, the same reaction run with degassed solvent improved significantly the yield to 71% (**Scheme 4.20**). We carried out the optimisation conditions using mesylate **219** and using degassed solvents.



Scheme 4.20

- *Investigation of the nickel-catalyzed "One-Pot" Process*

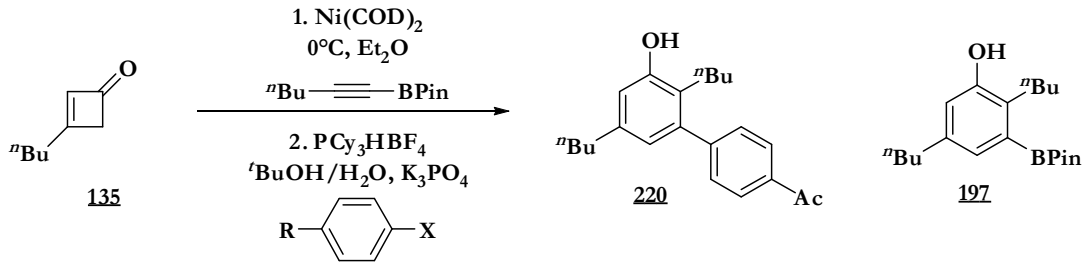
The next step was to investigate if the nickel catalyst would be able to carry out the benzannulation and the cross-coupling in a "one-pot" process. Specifically, we hoped that upon addition of base and the aryl acceptor to the benzannulation reaction mixture, the products would be activated towards Ni-catalyzed cross-coupling (**Scheme 4.21**).



Scheme 4.21

In the event, the cross-coupling conditions described by Molander[7] (PCy_3HBF_4, K_3PO_4, $^tBuOH/H_2O$) provided the desired compound **220**. However, the best conditions we found either involved a large quantity of the catalyst or gave a poor yield with lower loadings of Ni. Investigating the conditions in more detail, with 20 mol% of nickel we were getting an approximately equal mixture of the phenol boronic ester **197** and the cross-coupled adduct **220** (**Table 4.3**, entry 1). We decided to study the reaction with different sulfonylated aryl acceptors to find one that would provide a respectable yield. As outlined in **Table 4.3** , entry 2; the aryl tosylate **221** gave a slightly lower yield of the desired compound **220**. We next focused on mesylated aryl acceptors. Really poor conversions were observed with

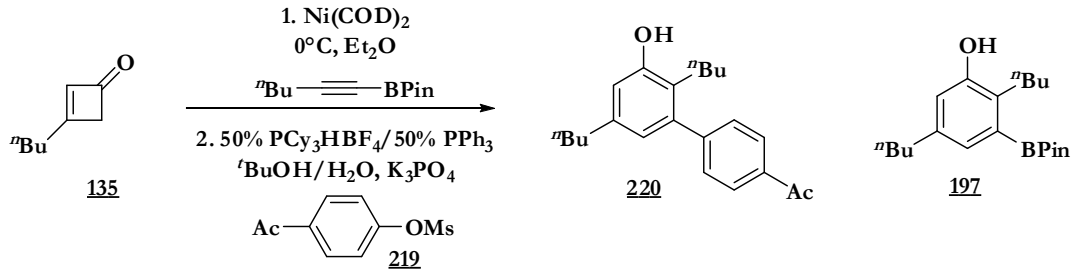
mesylates **222**-**225** (**Table 4.3**, entry 3-6). The best conversion was obtained with initial mesylate **219** (**Table 4.3**, entry 1).



Entry	$Ni(COD)_2$	ArX	Phosphine (%)	Outcome
1	20 mol%	*p*-AcC_6H_4OMs **219**	PCy_3HBF_4 (40)	45% **220**; 43% **197**
2	20 mol%	*p*-AcC_6H_4OTs **221**	PCy_3HBF_4 (40)	40% **220**; 21% **197**
3	20 mol%	*p*-$MeOC_6H_4OMs$ **222**	PCy_3HBF_4 (40)	Poor conversion
4	20 mol%	*p*-CNC_6H_4OMs **223**	PCy_3HBF_4 (40)	Poor conversion
5	20 mol%	*p*-$EtCO_2C_6H_4OMs$ **224**	PCy_3HBF_4 (40)	Poor conversion
6	20 mol%	*p*-$MeCO_2$-*o*-$MeOC_6H_4OMs$ **225**	PCy_3HBF_4 (40)	Poor conversion
7	20 mol%	*p*-AcC_6H_4OMs**219**	PCy_3HBF_4 (50)	45% **220**; 43% **197**
8	20 mol%	*p*-AcC_6H_4OMs **219**	PCy_3HBF_4 (100)	45% **220**; 43% **197**

Table 4.3

Detailed studies of Percec et al[8] highlighted PCy_3/PPh_3 as a suitable ligand combination and so we decided to employ these conditions in the one-pot reaction. Carrying out the reaction with 10 mol% Ni-catalyst resulted in formation of **220** in poor yield (**Table 4.4**, entry 1). We noted, however, that the reaction mixture contained a significant amount of boronate cycloadduct **197** suggesting that the Ni catalyst had decomposed during the benzannulation reaction. Increasing the loading of the Ni catalyst resulted in improved conversion to the biaryl product **220** (**Table 4.4**). This result demonstrated that a single Ni catalyst can perform sequential catalytic process in a single vessel.



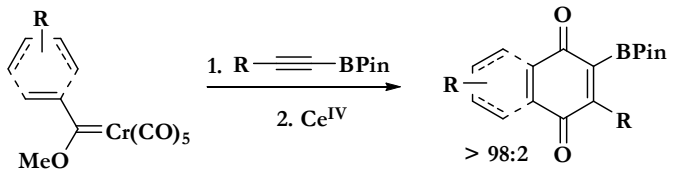
135 219 220 197

$Ni(COD)_2$	ArX	Phosphine (mol%)	Yield (%) 220:197
10 mol%	**219**	PPh_3/PCy_3HBF_4(50/50)	8:71
20 mol%	**219**	PPh_3/PCy_3HBF_4(50/50))	51:34
30 mol%	**219**	PPh_3/PCy_3HBF_4(50/50)	59:17
40 mol%	**219**	PPh_3/PCy_3HBF_4(50/50)	71:8
20 mol%	**219**	PPh_3/PCy_3HBF_4(50/50)	47:31
30 mol%	**219**	PPh_3/PCy_3HBF_4(50/50)	63:29

Table 4.4

4.5 Access to quinone boronic ester derivatives

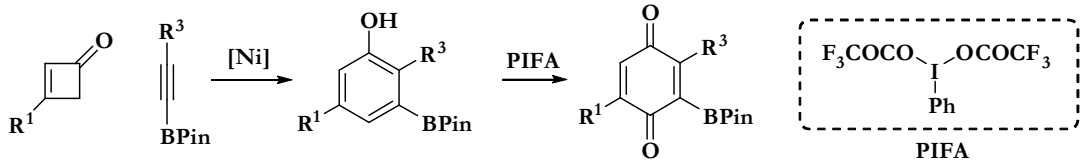
Quinone boronic ester derivatives can serve as precursors to bioactive quinones and have recently emerged as useful substrates for regio- and stereocontrolled Diels-Alder reactions. Previous studies in the group[9], showed that quinone boronic esters can be accessed *via* the Dötz benzannulation in good yields and with excellent level of regiocontrol (**Scheme 4.22**).



Scheme 4.22

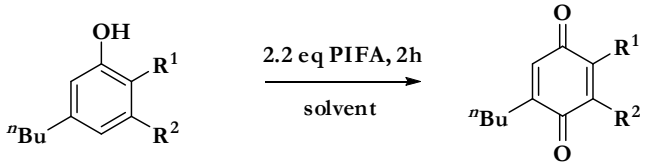
However, the main drawback of this technique is the requirement of stoichiometric organochromium regents. We therefore decided to develop catalytic approach. The Cr-mediated benzannulation reaction can be envisaged to be a Cr-templated ketene electrocyclization. We had developed an alternative strategy as described above involving a metal-templated vinylketene [4 + 2] cycloaddition. Readily available cyclobutenones were used as the

vinylketene precursor to prepare phenol boronic ester systems. These new oxygenated aromatic boronic ester could be smoothly oxidized with PIFA[10] to the corresponding quinone boronic esters (**Scheme 4.23**).



Scheme 4.23

To our delight, compound **197** was oxidized to the corresponding quinone within 2 hours in quantitative yield (**Table 4.5**, entry 1). The chemistry was further employed on regioisomers **200a** and **200b**; the former compound underwent oxidation in high yield (**Table 4.5**, entry 2) whereas the latter phenol gave a lower yielding reaction due to the surprising instability of quinone **228** and had to be conducted at lower temperature (**Table 4.5**, entry 3 & 4). The methodology is quite powerful as quinone boronic esters could be accessed only using stoichiometric quantities of Fisher carbene complex. We can now prepare such compounds under really mild conditions.



Entry	R^1, R^2	Temperature (°C)	Solvent	Yield (%)	Product
1	Bu, BPin **197**	0	ACN/H_2O/DCM	100	**226**
2	Ph, BPin **200a**	0	ACN/H_2O	70	**227**
3	BPin, Ph **200b**	0	ACN/H_2O	0	-
4	BPin, Ph **200b**	-10	ACN/H_2O	50	**228**

Table 4.5

4.6 Conclusion

The nickel mediated [4 + 2] cycloaddition of alkynylboronates with cyclobutenones is a powerful methodology for remarkably regioselective benzannulation reactions providing the corresponding phenol boronic ester derivatives. This chemistry offers a versatile and catalytic route to quinone boronic esters, as well as the opportunity to carry out benzannulation and cross-coupling reactions in one-pot with a single nickel pre-catalyst.

References

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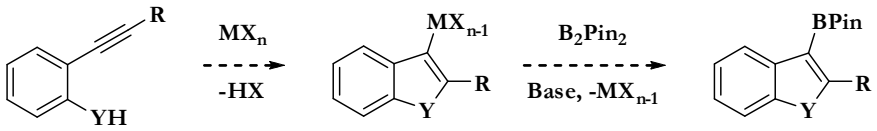
CHAPTER V

Palladium-catalyzed cyclization

5.0 Introduction

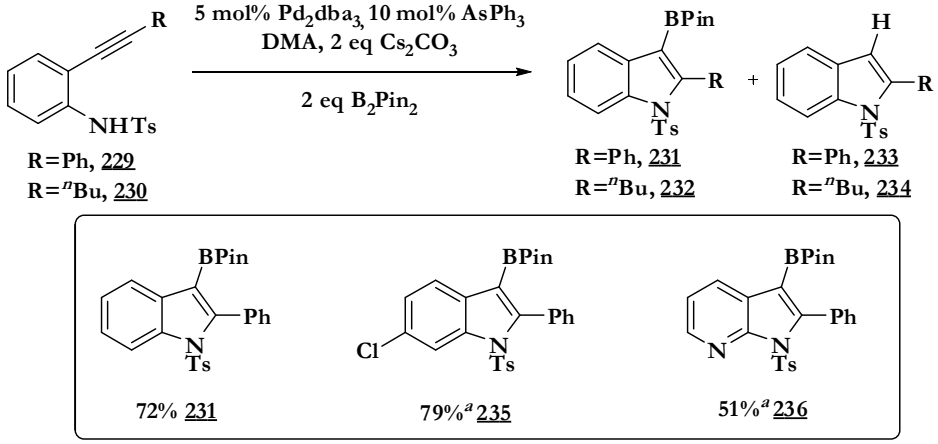
The benzannulation strategy whereby the boronate is installed during aromatic ring formation has proven to be a generally useful method to access aromatic boronic acid derivatives[1]. In this context, alkynylboronates have proven to be useful precursors to a range of heteroaromatic and benzene based boronic ester derivatives *via* metal[2] promoted and pericyclic processes[3]. To extend the strategy we envisaged an alternative sequence that employed a metal catalyzed benzannulation process that was terminated by a boration reaction leading to the corresponding indole boronic ester (**Scheme 5.1**). The metal catalyzed cyclisation of *o*-alkynylaniline derivatives has become a well established method for the synthesis of indoles[4]. As well as providing 2-substituted indoles, Pd catalysis allows the strategy to be expanded to permit the incorporation of substituents at the 3-position by additional metal catalyzed coupling reactions[5].



Scheme 5.1

This strategy has been realised recently within the group, providing direct access indole 3-boronic esters selectively[6]. The reaction proceeded between readily available 2-alkynyl anilines and bis(pinacolato) diborane (B_2Pin_2) under palladium catalysis. This methodology is powerful as a range of indole boronic esters including bifunctional indoles **235**, and azaindoles **236**, could be prepared easily (**Scheme 5.2**). However, subsequent attempts to repeat the reaction with 2-phenylalkynyl aniline **229** showed that the process was rather capricious. Specifically, the deboronated indole **233** was regularly observed as

the major product. Therefore, we decided to embark upon further studies in order to improve the robustness and reproducibility of the reaction.



R=Ph, 229
R=^{n}Bu, 230

R=Ph, 231
R=^{n}Bu, 232

R=Ph, 233
R=^{n}Bu, 234

72% 231

79%[a] 235

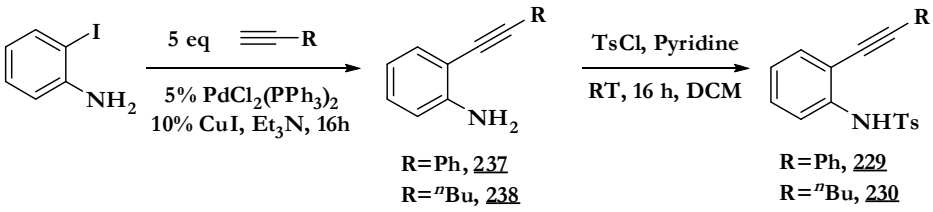
51%[a] 236

[a]Reaction coducted with 10 mol% Pd_2dba_3, 40 mol% $AsPh_3$

Scheme 5.2

5.1 Sonogashira reaction

To start the investigation of the borylative cyclisation, we had to prepare the amino alkynes. This was readily achieved *via* Sonoagashira coupling of an appropriate alkyne and *o*-haloaniline. A large excess (5 equivalents) of the alkyne was required as Glaser coupling was found to compete with the desired cross-coupling reaction. The transformation took place at ambient temperature with phenylacetylene (**Table 5.1**, entry 1). Surprisingly however, the reaction with 1-hexyne required heating (60 °C) (**Table 5.1**, entry 2 and 3). Once the conditions were optimised, the reaction proceeded well producing the desired amino alkyne **237** & **238** in good yields. The next step was the tosylation leading to the precursors **229** and **230** for the investigation of the borylative cyclisation.



R=Ph, 237
R=^{n}Bu, 238

R=Ph, 229
R=^{n}Bu, 230

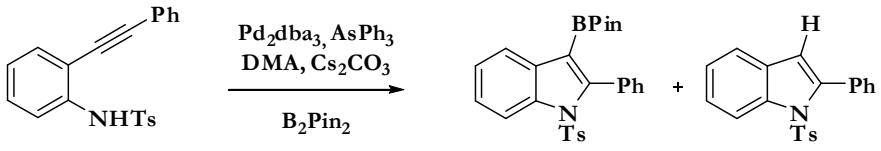
Entry	R	Temperature	Yield (Sonogashira)	Yield (Tosylation)
1	Ph	RT	67 % **237**	84 % **229**
2	^{n}Bu	RT	-	-
3	^{n}Bu	60 °C	60 % **238**	59% **230**

Table 5.1

5.2 Cyclisation strategy

Initial conditions

Following conditions developed within the group[6], the desired indole boronic esters could be accessed within a short reaction time. Unfortunately however, under the conditions reported (**Table 5.2**, entry 1), we were unable to repeat the documented selectivity for the desired indole boronate **231**. Indeed, the reaction run under the same conditions was complete within 30 minutes but provided indole-H **233** as the major product (**Table 5.2**, entry 2). This result led us to investigate this reaction in more detail.



229 231 233

Entry	[Pd] (%)	L (%)	Atm.	Ratio 231:233
1 (Literature[7])	5	10	N_2	3.5:1
2 (Our attempt)	5	10	N_2	1:3.7

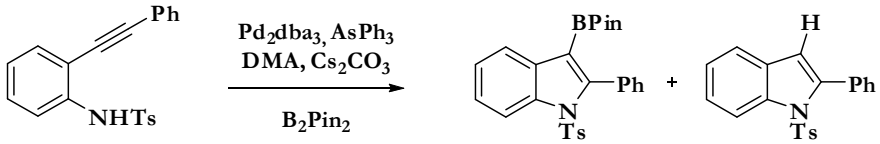
Experiment conducted using 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA, 60 °C, 30 min, full conversion

Table 5.2

We decided to investigate the effect of changing the reaction time and temperature on product distribution. Moreover, we also wanted to explore the sensitivity of the reaction to the presence of air and water. As described in the

next table (**Table 5.3**), the reaction time seemed to be important (**Table 5.3**, entry 1-3). Also, the presence of water (**Table 5.3**, entry 12) and running the reaction under N_2 seemed to dramatically increase the formation of indole-H **233** (**Table 5.3**, entry 3 & 5). However, addition of molecular sieves to the reaction mixture, under oxidative conditions (air) reduced the formation of indole-H (**Table 5.3**, entry 6). These results were quite promising but were not in agreement with the previous observations.

Optimisation conditions



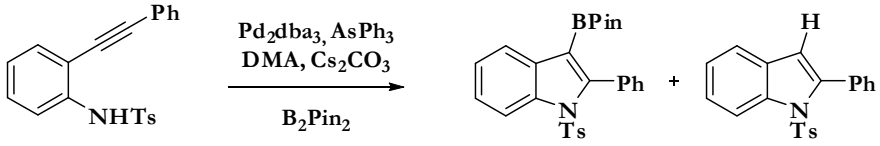
229 **231** **233**

Entry	T (°C)	Time	additive	Atm.	Ratio 231:233
1	60	16 h	-	N_2	0:1
2	60	1.5 h	-	N_2	1:6
3	60	0.5 h	-	N_2	1:3.7
4	60	0.5 h	-	O_2	1:8
5	60	0.5 h	-	Air	1:2.5
6	**60**	**0.5 h**	**MS**	**Air**	**1:1.7**
8	80	0.5 h	MS	Air	1:1.8
9	80	0.5 h	-	Air	1:12
10	120	0.5 h	MS	Air	0:1
11	180	0.5 h	MS	Air	0:1
12	60	0.5 h	1 drop H_2O	Air	0:1

Experiment conducted using 10 mol% Pd_2dba_3, 20 mol% $AsPh_3$, 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA

Table 5.3

We continued to investigate the reaction parameters and **Table 5.4** shows how the loading of the ligand and the base can affect the reaction. Increasing or decreasing the loading of the ligand or base disfavored the formation of indole-BPin **231**. The best compromise we found was with 10 mol% catalyst, 20 mol% ligand and 2 equivalents of base as developed in the group[6]. We showed as well that the concentration did not significantly affect the ratio.



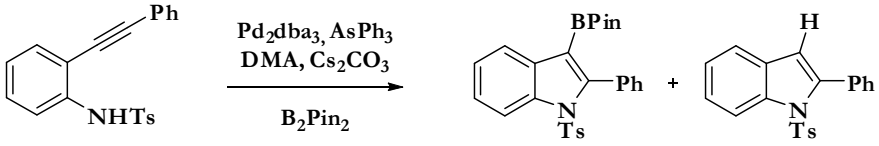
229 **231** **233**

Entry	Pd_2dba_3 (%)	$AsPh_3$ (%)	Cs_2CO_3 (eq)	Ratio 231:233
1	10	20	1	1:2.2
2	10	20	3	1:3.1
3	10	5	2	1:3.1
4	10	10	2	1:2
5	**10**	**20**	**2**	**1:1.7**
6	10	40	2	1:3.6

Experiment conducted using, 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA, 60 °C, Air

Table 5.4

As we were not able to repeat the results previously reported, we decided to investigate different sources of palladium to try to understand which species were catalyzing the formation of indole-BPin **231**, the formation of indole-H **233** and/or the protodeboronation. The reaction conducted with 1 equivalent of Pd^0 without ligand (**Table 5.5**, entry 1) provided mainly the starting material **229** and trace of indole-H **233** with no evidence for the corresponding boronic esters **231**. From this observation, we assumed that Pd^{II} might be the active catalyst in the cyclisation reaction. As described in **Table 5.5**, Pd^{II} was more efficient than Pd^0 for the formation of indole-BPin **231**. Stoichiometric amounts of Pd^{II} drove the reaction to completion but provided indole-H **233** as the major compound (**Table 5.5**, entry 2). The presence of ligand did not seem to affect the ratio (**Table 5.5**, entry 3). Catalytic amounts of Pd^{II} (**Table 5.5**, entry 4 & 5) slightly improved the ratio but did not produce optimal results.



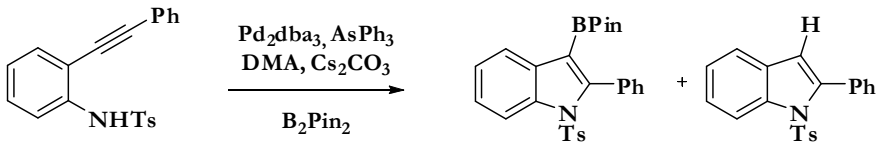
229 231 233

Entry	[Pd]	loading (%)	L (%)	Ratio 231:233
1	Pd_2dba_3	100	-	Low conversion 0:1
2	$PdCl_2(PPh_3)_2$	100	-	1:1.8
3	$PdCl_2(PPh_3)_2$	100	200	1:2
4	$PdCl_2(PPh_3)_2$	20	-	1:1
5	$PdCl_2(PPh_3)_2$	10	**-**	**1:1.5**

Experiment conducted using, 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA, 60 °C, Air

Table 5.5

Initially, the reagents were introduced all together at the same time and heated to 60 °C. We next trialled an alternative procedure whereby the solids (**229**, Pd_2dba_3, $AsPh_3$, Cs_2CO_3, B_2Pin_2) were heated to 60 °C and then the solvent was introduced. The latter procedure seemed to be slightly more efficient but did not lead to a significantly improved ratio. Finally, we attempted to deprotonate the amino alkyne first and then add the catalyst, ligand and B_2Pin_2. In this regard, NaH and Cs_2CO_3 were pre-mixed with **229** in DMA at 60 °C for 5 minutes before adding the other reagents. The results obtained were quite promising as the major compound was indole-BPin **231** (**Table 5.6**).



229 **231** **233**

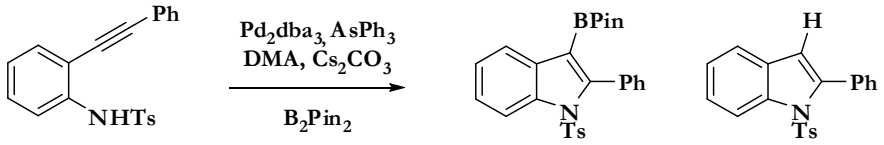
Entry	[Pd] (%)	L (%)	NaH (eq)	Conversion (231:233)
1	5	10	1.2	64% (1.64:1)
2	10	20	1.2	49% (5.9:1)
3	5	10	0.6	85% (2.77:1)
4	**10**	**20**	**0.6**	**100% (2.32:1)**
5	7.5	15	0.6	82% (1.75 : 1)
6	10	20	0.8	78% (1.92 : 1)
7	10	20	-	90% (2.31 : 1)
8	**10**	**20**	**-**	**93% (2.94 : 1)**

Experiment conducted using 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA, 4Å MS, 20 min, 60 °C, pre-mix 5 min

Table 5.6

As the results significantly improved toward the formation of indole-BPin **231** by pre-mixing a base (NaH), this suggested that deprotonation was essential before addition of the reagents. We next decided to test if Cs_2CO_3 was able to promote the reaction in the absence of NaH. Pleasingly, as described in **Table 5.6**, entry 6 & 7 pre-mixing Cs_2CO_3 and the aminoalkyne led to the same results showing that the use NaH was not required.

Pre-mixing the base and the starting material in distilled DMA for a longer period of time (10-15 minutes) and rapid stirring improved the ratio and completed the reaction within 15 minutes (**Table 5.7**).



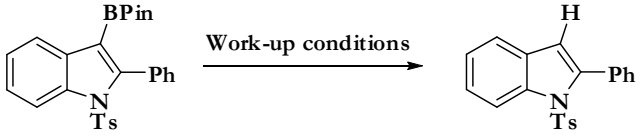
229 231 233

Entry	[Pd] (%)	L (%)	DMA/Cs_2CO_3	Conversion % (231:233)
1	10	20	Old/Old	100% (1.9:1)
2	10	20	Distilled/Old	100% (2.95:1)
3	5	10	Distilled/Old	100% (1.9:1)
4	**10**	**20**	**Distilled/New**	**100% (3.4:1)**

Conditions: 2 eq Cs_2CO_3, 2 eq B_2Pin_2, DMA, 4 Å MS, 15 min, 60 °C, pre-mix 10-15 min

Table 5.7

Surprisingly, we observed that deboronation was occuring during the work-up. We decided to try different work-up conditions on the purified indole-BPin **231** to understand what was promoting this process. H_2O, brine and Cs_2CO_3 did not produce indole-H (**Table 5.8**, entry 1-3). However, Cs_2CO_3 in combination with Pd_2dba_3, gave a small amount of indole-H **233** (**Table 5.8**, entry 4). This observation was amplified when $AsPh_3$ was added along with Pd_2dba_3 (**Table 5.8**, entry 5). We found that working-up the reaction as quickly as possible was the best way to reduce the deboronation (*See experimental section, p 194*).



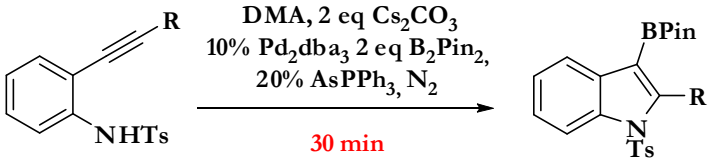
231 233

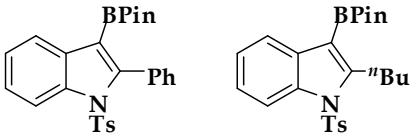
Entry	Work-up	Ratio 231:233
1	H_2O	1:0
2	Brine	1:0
3	Cs_2CO_3	1:0
4	Pd_2dba_3, Cs_2CO_3	12:1
5	Pd_2dba_3, Cs_2CO_3, $AsPh_3$	6:1

Table 5.8

The optimisation conditions were carried out on aminoalkyne **229** providing a 72% yield of the desired indole **231** in accordance with the litterature (**Scheme 5.3a**). This methodology could be applied to another substrate and provided indole **232** in 63 % yield (**Scheme 5.3b**).

Previous results[6]

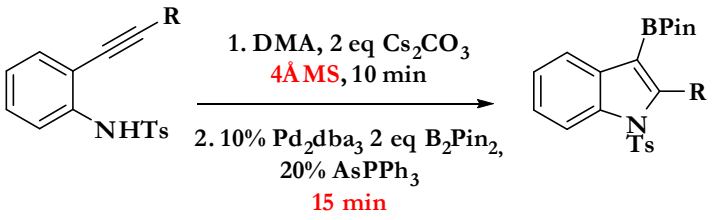


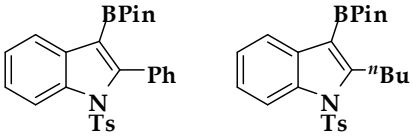


72% **231** 74% **232**

Scheme 5.3a

Reproducible conditions



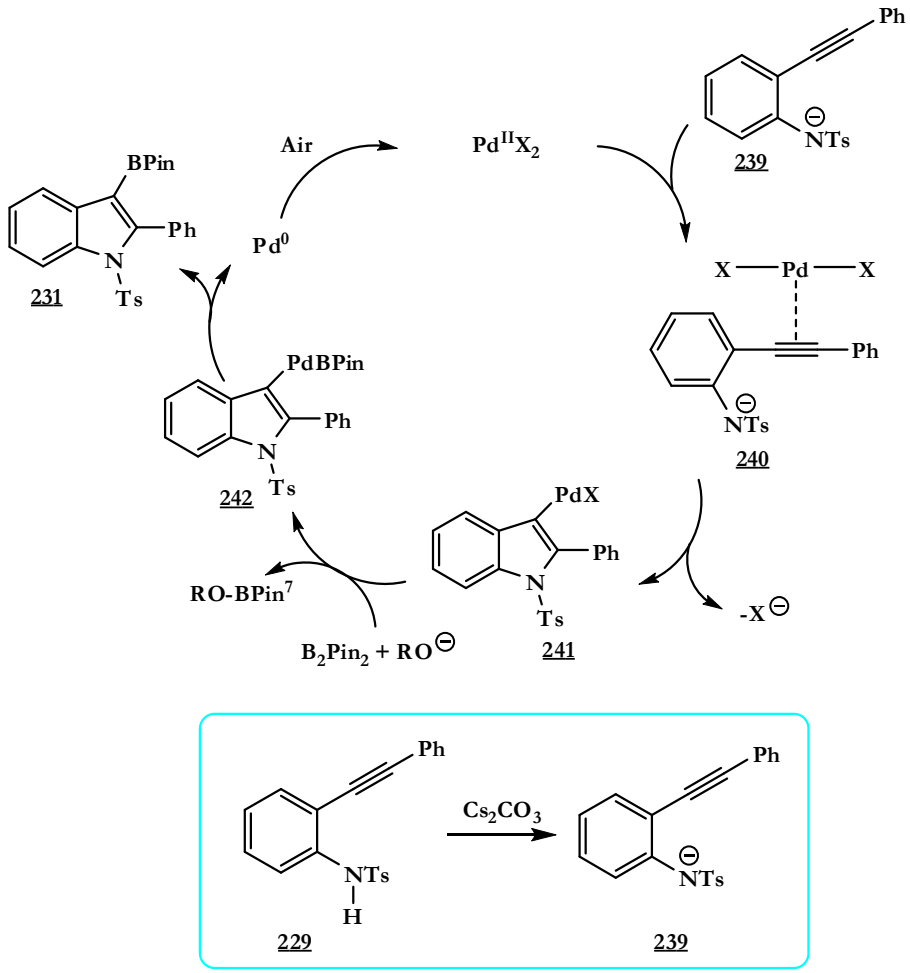


72% **231** 63% **232**

Scheme 5.3b

Proposed mechanism

Following our optimisation studies, we can propose a mechanism that is in keeping with the key findings made (**Scheme 5.4**). Deprotonation of amine **229** would lead to the formation of sulfonamide **239** which could coordinate to the Pd^{II} catalyst providing intermediate **240** which would cyclise to form intermediate **241**. Ligand exchange with $BPin^7$ would lead to **242**. Finally, reductive elimination would provide indole-BPin **231** and a Pd^0 complex, the Pd(II) catalyst is then regenerated after air oxidation.



Scheme 5.4

5.3 Conclusion

The optimisation studies demonstrated that the yield of deboronated indole was extremely sensitive to variation of all parameters. Clearly, Pd^0 catalyzed the deboronation of **242** and/or **231** and Pd^{II} catalyzed the formation of indole-BPin **231** but also the deboronation. Pd^0 and Pd^{II} were both present in the reaction mixture, careful optimisation of catalyst loading and reaction time was required. The best results were obtained upon heating a combination of 10 mol% $Pd_2(dba)_3$, 20 mol% $AsPh_3$, 2 eq Cs_2CO_3, 4ÅMS and 2 eq B_2Pin_2 in anhydrous DMA at 60 °C for 15 minutes. The reaction was also complete within 15 minutes using 5 mol% $Pd_2(dba)_3$ and 20 mol% $AsPh_3$ but a larger amount of indole-H **233** was obtained. The most important parameter was that the base and the starting material had to be pre-mixed in DMA at 60 °C before adding the catalyst and the other reagents. The reaction time was also found to be crucial: the indole-BPin **231** once formed, was rapidly deboronated. Therefore, the reaction had to be stopped as soon as the conversion was complete to prevent protodeboronation of indole-BPin product **231**.

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CHAPTER VI

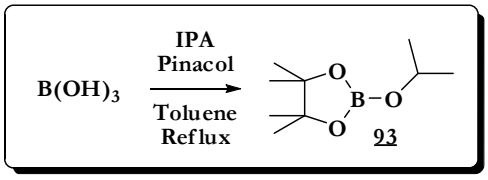
Experimental

6.0 General informations

^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz), AMX-400 (400 MHz) or DRX-500 (500 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ 7.27). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, m = multiplet, *app* = apparent), coupling constants (Hz), assignments. ^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz), AMX-400 (100.6 MHz) or DRX-500 (249.9 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). In all ^{13}C NMR data the alpha-carbon at boron does not appear because of the quadripolar character and short relaxation time of boron. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in EI (EI+) mode. 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). 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)[1]. Starting alkynylboronates[3] and dienes[9-18] were prepared according to established procedures. 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.

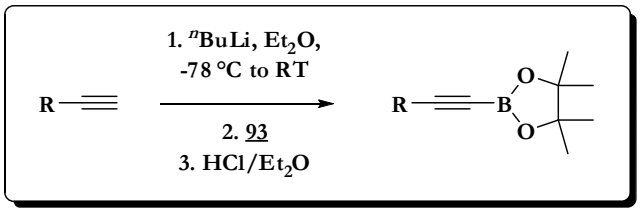
6.1 Synthesis of pinacol based alkynylboronates

- *Synthesis of 2-isopropoxy-4,4,5,5-tetramethy-1,3,2-dioxaborolane* **93**



Boric acid (26.2 g, 420 mmol), pinacol (50.0 g, 420 mmol), propan-2-ol (153 mL, 2 mol), and toluene (200 mL) were heated to reflux in a round-bottom flask connected to a Dean-Stark condenser. The azeotropic removal of water ceased after 2 days. The volatiles were removed *in vacuo* and crude materials purified by vacuum distillation (b.p. 73 °C, 15 mmHg) to give 2-isopropoxy-4,4,5,5-tetramethy-1,3,2-dioxaborolane **93** (50.0 g, 64%) as a moisture sensitive colourless liquid. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[2]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.19 (6H, d, J = 6.0 Hz, ^{i}PrC**H**$_3$), 1.24 (12H, s, PinC**H**$_3$), 4.32 (1H, m, ^{i}PrC**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.2, 24.4, 67.1, 82.2.

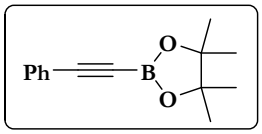
General procedure for the synthesis of alkynylboronates[3]



To a solution of the alkyne (1 eq) in diethyl ether (1 M) at -78 °C was added a solution of *n*-butyllithium in hexanes (~2.5 M). The reaction was stirred at -78 °C for 1 hour and then allowed to warm room temperature before 2-isopropoxy-4,4,5,5-tetramethy-1,3,2-dioxaborolane **93** (1 eq) was added. The reaction was stirred for 3 hours before an anhydrous solution of hydrogen chloride in diethyl ether (1.3 eq, 1 M) was added and stirred for a further 30

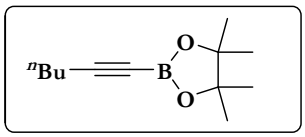
minutes. The salts were removed by filtration under nitrogen and washed with more diethyl ether. The volatiles were removed *in vacuo* and crude products purified by crystallisation in petrol or by distillation under vacuum.

- *Synthesis of 4,4,5,5-tetramethyl-2-(2-phenylethynyl)1,3,2-dioxaborolane* **94**



A solution of phenylacetylene (5.0 g, 49 mmol), in diethyl ether (49 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 21.3 mL, 49 mmol), then **93** (9.1 g, 49 mmol) was added to the mixture before treatment with anhydrous HCl in diethyl ether (1.0 M, 64.0 mL, 64 mmol). The product **94** was isolated by crystallisation in petrol as a colourless solid (7.1 g, 64%). M.pt.: 58-59 °C {*lit.*[4] 58-60 °C}. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[4]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (12H, s, PinC**H**$_3$), 7.22-7.56 (5H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.7, 84.4, 101.8, 121.9, 128.3, 129.4, 132.6.

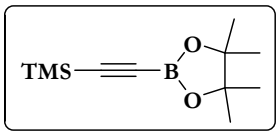
- *Synthesis of 2-(hex-1-ynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **95**



A solution of 1-hexyne (6.0 g, 73 mmol), in diethyl ether (73 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 31.8 mL, 73 mmol), then **93** (13.6 g, 73 mmol) was added to the mixture before treatment with anhydrous HCl in diethyl ether (1.0 M, 95.0 mL, 95 mmol). The product **95** was isolated by vacuum distillation (76 °C, 0.3 mmHg) as a colourless oil (11.4 g, 75%). The product showed satisfactory spectroscopic and analytical data in comparison to the

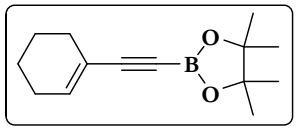
literature[5]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.25 (12H, s, PinC**H**$_3$), 1.31-1.58 (4H, m, C**H**$_2$), 2.25 (2H, t, *J* = 7.0 Hz, C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.5, 19.2, 21.9, 24.6, 30.1, 64.6, 84.0.

- *Synthesis of trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl)silane* **96**



A solution of trimethylsilylacetylene (4.0 g, 41 mmol), in diethyl ether (41 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 17.7 mL, 41 mmol), then **93** (7.6 g, 41 mmol) was added to the mixture before treatment with anhydrous HCl in diethyl ether (1.0 M, 53.0 mL, 53 mmol). The product **96** was isolated by crystallisation from petrol as a colourless solid (4.8 g, 53%). M.pt.: 93-95 °C. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[6]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.00 (9H, s, SiC**H**$_3$), 1.09 (12H, s, PinC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ -0.5, 24.6, 84.4, 111.3.

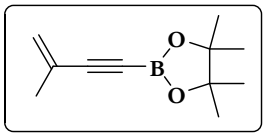
- *Synthesis of 2-(cyclohexenylethynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **97**



A solution of 1-ethynylcyclohex-1-ene (5.0 g, 47 mmol), in diethyl ether (47 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 20.5 mL, 47 mmol), then **93** (7.8 g, 47 mmol) was added to the mixture before treatment with anhydrous HCl in diethyl ether (1.0 M, 61.0 mL, 61 mmol). The product **93** was isolated by crystallisation in petrol as a colourless solid (9.4 g, 86%). M.pt.: 34-36 °C.

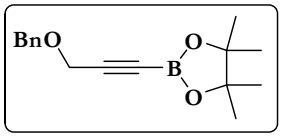
^{1}H NMR (250 MHz, $CDCl_3$): δ 1.28 (12H, s, PinC**H$_3$**), 1.54-1.62 (4H, m, C**H$_2$**), 2.08-2.14 (4H, m, C**H$_2$**), 6.35 (1H, m, C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.3, 22.1, 24.7, 25.8, 28.6, 83.9, 120.1, 126.4, 137.0. FTIR (film): 2979 (m), 2933 (m), 2183 (s), 1450 (w), 1389 (m), 1334 (s), 1315 (m), 1140 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{14}H_{22}BO_2$ 233.1713 found 233.1724.

- *Synthesis of 4,4,5,5-tetramethyl-2-(3-metylbut-3-en-1-ynyl)-1,3,2-dioxaborolane* **98**



A solution of 2-methylbut-1-en-3-yne (5.0 g, 76 mmol), in diethyl ether (76 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 32.9 mL, 76 mmol), then **93** (14.1 g, 76 mmol) was added to the mixture before treatment with anhydrous HCl in diethyl ether (1.0 M, 98.0 mL, 98 mmol). The product **98** was isolated by vacuum distillation (76 °C, 2 mmHg) as a clear oil (11.0 g, 76 %). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[5]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.08 (12H, s, PinC**H$_3$**), 1.69 (3H, s, C**H$_3$**), 5.04-5.14 (1H, m, C**H**H), 5.40-5.49 (1H, m, CH**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 22.7, 24.7, 83.9, 120.6, 124.5, 126.6.

- *Synthesis of 2-(3-(benzyloxy)-prop-1-ynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **99**

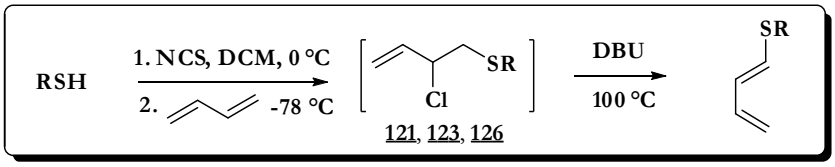


A solution of ((prop-2-ynyloxy)methyl)benzene (5.0 g, 34 mmol), in diethyl ether (34 mL), at -78 °C was treated with ^{n}BuLi (2.3 M, 14.9 mL, 34 mmol), then **93** (6.4 g, 34 mmol) was added to the mixture before treatment with

anhydrous HCl in diethyl ether (1.0 M, 45.0 mL, 45 mmol). The product **99** was isolated by vacuum distillation (120 °C, 30 mmHg) as a clear oil (4.8 g, 52 %). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[5]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.28 (12H, s, PinC**H**$_3$), 4.21 (2H, s, C**H**$_2$), 4.61 (2H, s, C**H**$_2$), 7.26-7.39 (5H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.7, 57.5, 71.6, 84.5 98.6, 127.9, 128.1, 128.4, 137.3.

6.2 Synthesis of Dienes

General procedure for the synthesis of S-substituted dienes[9]

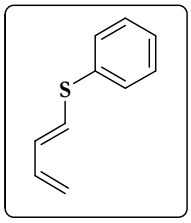


To a rapidly stirred suspension of *N*-chlorosuccinimide (1.02 eq) in dry dichloromethane (1 M) at room temperature in a three necked round bottom flask equipped with a pressure-equalizing dropping funnel and an efficient water-cooled condenser was added a small portion of thiol. Gentle heating in an oil bath for 1-2 minutes was required to initiate the reaction. Once initiated, the reaction vessel was immersed in an ice bath and the remaining thiol (1 eq in total) added dropwise within 15 minutes. When the addition was complete, the ice bath was immediately removed and the homogenous orange solution was stirred at room temperature for an additional 30 minutes. The solution was filtered and transferred by cannula into another flask. The solution was cooled to -78 °C before addition of butadiene (4 eq). The mixture was allowed to reach room temperature and concentrated *in vacuo*. The resulting residue was diluted with carbon tetrachloride and stirred for 1 hour. Filtration and concentration of the filtrate *in vacuo* afforded the chloroalkene intermediate, precursor of the diene.

The crude chloroalkene (1 eq) was added *via* syringe to DBU (2 eq) at 100 °C. The mixture was stirred for 10 minutes at 100 °C, cooled to room temperature

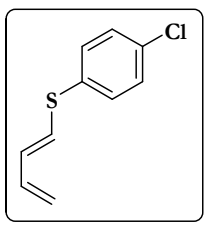
and diluted with 2% aqueous hydrochloric acid. Diethyl ether was added and the resulting organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. No further purification was required.

- *Synthesis of buta-1,3-dienyl(phenyl)sulfane* **122**



Following the general procedure, thiophenol (5.0 g, 45 mmol) was treated with NCS (6.2 g, 46 mmol) and a solution of butadiene in toluene (20 wt.%, 60.8 mL, 182 mmol) to give **121** as a pale yellow oil (8.7 g, 97%). No further purification was required for the next step.
Chloroalkene **121** (2.0 g, 10 mmol) was treated with DBU (3.1 g, 20 mmol) to give **122** (1.3 g, 79%) as an oil. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[9]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.06-5.38 (m, 2H, C**H**$_2$), 6.27-6.49 (m, 3H, C**H**), 7.22-7.32 (5H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 116.3, 118.8, 127.0, 127.3, 129.1, 130.1, 132.3, 135.5.

- *Synthesis of buta-1,3-dienyl(4-chlorophenyl)sulfane* **124**

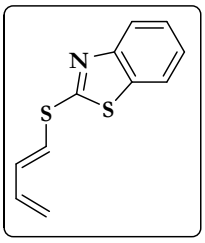


Following the general procedure, 4-chlorothiophenol (5.0 g, 35 mmol) was treated with NCS (4.7 g, 36 mmol) and a solution of butadiene in toluene (20

wt.%, 46.3 mL, 139 mmol) to give **123** as an orange oil (6.9 g, 86%). No further purification was required for the next step.

Chloroalkene **123** (2.0 g, 9 mmol) was treated with DBU (2.6 g, 17 mmol) to give **124** (1.0 g, 59%) as an oil. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[9]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.9-5.5 (m, 2H, C**H**$_2$), 6.0-6.5 (m, 3H, C**H**), 7.10-7.40 (4H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 116.9, 119.4, 126.3, 129.2, 29.3, 130.4, 131.2, 131.4.

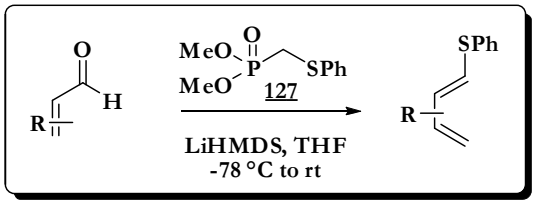
- *Synthesis of 2-(buta-1,3-dienylthio)benzothiazole* **126**



Following the general procedure, 2-mercaptobenzothiazole (5.0 g, 30 mmol) was treated with NCS (4.1 g, 31 mmol) and a solution of butadiene in toluene (20 wt.%, 40.1 mL, 120 mmol) to give **125** as a dark red oil (4.6 g, 65%). No further purification was required for the next step.

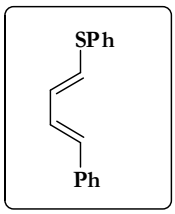
Chloroalkene **125** (1.0 g, 4 mmol) was treated with DBU (1.2 g, 8 mmol) to give **126** (0.7 g, 77%) as an oil. The product was characterised by ^{1}H,^{13}C NMR spectroscopy only. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.18-5.40 (2H, m, C**H**$_2$), 6.31-6.80 (3H, m, C**H**), 7.19-7.40 (2H, m, Ar**H**), 7.70-7.72 (1H, m, Ar**H**), 7.86-7.83 (1H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 120.9, 121.0, 121.9, 124.5, 126.3, 134.9, 137.2, 144,7, 161.2, 167.0, 180.5.

General procedure for the synthesis of functionalised S-substituted dienes



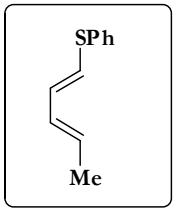
To a solution of phosphonate **127** (1.3 eq) in THF was added a solution of LiHMDS in THF (1.3 eq) at -78 °C. Once the addition was complete, the reaction mixture was allowed to reach room temperature and stirred for a further hour. The mixture was cooled to -78 °C, the aldehyde (1 eq) was added and the reaction mixture stirred for 1 hour at -78 °C before warming up to room temperature. Solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography with petrol.

- *Synthesis of 4-phenylbuta-1,3-dienyl)sulfane* **128**



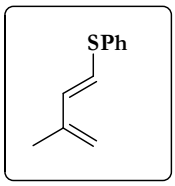
Following the general procedure, cinnamaldehyde (1.0 g, 8 mmol) in THF (10 mL) was added at -78 °C to the preformed ylide (phosphonate **127**, 2.3 g, 9 mmol; LiHMDS, 1.0 M, 10.0 mL, 10 mmol) in THF (80 mL) to give the desired diene **128** (1.6 g, 89%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[10]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.54-6-56 (3H, m, C**H**), 6.83-6.90 (1H, m, S-C**H**), 7.23-7.47 (10H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 126.4, 126.9, 127.1, 127.5, 127.6, 128.7, 129.2, 129.9, 131.5, 132.2, 134.9, 137.1.

- *Synthesis of penta-1,3-dienyl(phenyl)sulfane* **129**



Following the general procedure, crotonaldehyde (1.0 g, 14 mmol) in THF (10 mL) was added at -78 °C to the preformed ylide (phosphonate **127**, 4.3 g, 19 mmol; LiHMDS, 1.0 M, 19.0 mL, 19 mmol) in THF (100 mL) to give the desired diene **129** (1.8 g, 71%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[11]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.8 (3H, dd, *J* = 7.0, 2.0 Hz, C**H**$_3$), 5.67-5.76 (1H, m, C**H**), 6.09-6.21 (1H, m, C**H**), 6.22-6.25 (1H, m, C**H**), 6.33-6.46 (1H, m, S-C**H**), 7.22-7.23 (5H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.1, 122.4, 126.5, 129.2, 129.7, 130.2, 134.0, 135.9, 141.0.

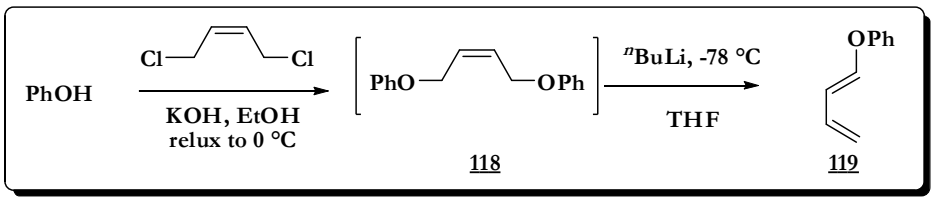
- *Synthesis of 3-methylbuta-1,3-dienyl(phenyl)sulfane* **130**



Following the general procedure, methacrolein (1.0 g, 14 mmol) in THF (10 mL) was added at -78 °C to the preformed ylide (phosphonate **127**, 4.3 g, 19 mmol; LiHMDS, 1.0 M, 19.0 mL, 19 mmol) in THF (100 mL) to give the desired diene **130** (1.7 g, 69%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[12]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.91 (3H, s, C**H**$_3$), 4.96 (1H, s, C**H**$_2$), 4.99 (1H, s, C**H**$_2$), 6.38 (1H, d, *J* = 15.5 Hz, C**H**), 6.50 (1H, d, *J* = 15.5 Hz, S-C**H**), 7.27-7.30 (1H, m, Ar**H**

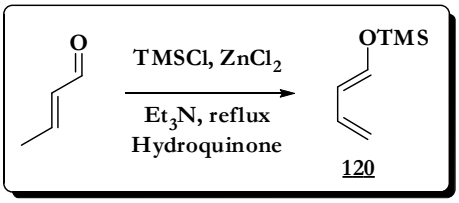
), 7.32-7.42 (4H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.5, 116.1, 123.3, 126.9, 129.1, 129.8, 134.7, 135.3, 140.9.

- *Synthesis of buta-1,3-dienyloxybenzene* **119**



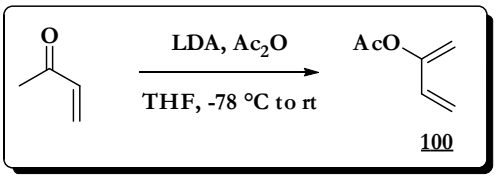
A mixture of phenol (4.5 g, 48 mmol) and potassium hydroxide (2.7 g, 48 mmol) was heated under reflux in ethanol for 15 minutes. Then, (*Z*)-1,4-dichlorobut-2-ene (3.0 g, 24 mmol) was added slowly with stirring at 0 °C. After stirring at 0 °C for 6 hours and at room temperature for 16 hours, the precipitate was removed by filtration through celite and the solid washed with ethanol (10 mL x 2). The filtrate was then dissolved in dichloromethane (120 mL). The resulting organic layer was washed with water (3 x 40 mL) and dried over $MgSO_4$. Solvent evaporation gave **118** as a sticky oil (4.3 g, 74%). A solution of *n*-butyllithium in hexanes (2.3 M, 5.5 mL, 13 mmol) was added dropwise to a solution of crude **118** (1.5 g, 6 mmol) in THF (40 mL) at -78 °C. The mixture was stirred at -78 °C for 30 minutes. The mixture was then warmed to room temperature and stirred for another 2 hours. Diethyl ether (40 mL) was added, the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude mixture was purified by flash chromatography eluting with petrol/EtOAc (9/1), yielding **119** (0.5 g, 49%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[13]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.00 (1H , dd, J = 10.5, 1.5 Hz, CH$\mathbf{H}_{cis}$), 5.16 (1H, dd, J = 17.0, 1.5, Hz, CH$\mathbf{H}_{trans}$), 6.02 (1H, t, J = 11.5 Hz, C**H**), 6.26-6.42 (1H, m, C**H**), 6.80 (1H, d , J = 11.5 Hz, C**H**), 7.02-7.14 (3H, m, Ar**H**), 7.28-7.38 (2H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 114.4, 114.6, 117.0, 123.3, 129.6, 132.1, 146.2, 156.9.

- *Synthesis of buta-1,3-dienyloxytrimethlsilane* **120**



To a solution of crotonaldehyde (4.0 g, 57 mmol) and triethylamine (6.0 g, 59 mmol) in anhydrous benzene (8 mL) was added zinc chloride (52 mg, 0.38 mmol), hydroquinone (94 mg, 0.86 mmol) and chlorotrimethylsilane (6.5 g, 59 mmol). The mixture was heated at 70 °C overnight, quenched with aqueous sodium bicarbonate and filtered through celite. Volatiles were evaporated carefully under vacuum. The crude mixture was purified by distillation (b.p. 56-60 °C, 50 mmHg) yielding a colourless oil **120** (4.3 g, 53%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[14]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.22 (9H, s, SiC**H**$_3$), 4.84 (1H, dd, *J* = 10.0, 2.0 Hz, CH**H**$_{cis}$), 5.00 (1H, dd, *J* = 18.0 Hz, 2.0 Hz, CH**H**$_{trans}$), 5.72 (1H, t, *J* = 10.0 Hz, C**H**), 6.25 (1H, dt, *J* = 18.0, 10.0 Hz, C**H**), 6.55 (1H, d, *J* = 10.0 Hz, C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 0.38, 112.2, 114.5, 133.3, 144.7.

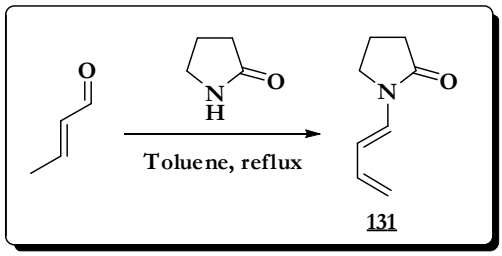
- *Synthesis of buta-1,3-dien-2-yl acetate* **100**



A solution of *n*-butyllithium in hexanes (2.3 M, 15.3 mL, 35 mmol) was added dropwise to a solution of diisopropylamine (3.9 g, 39 mmol) in THF (32 mL) at -78 °C. The mixture was allowed to reach -25 °C for 15 minutes. The mixture was cooled again to -78 °C before a solution of methyl vinyl ketone

(2.3 g, 32 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 15 minutes at -78 °C and acetic anhydride was added, resulting in a viscous yellow suspension. The mixture was allowed to warm to room temperature and stirred for further 15 minutes. Pentane (30 mL) was then added, along with saturated aqueous sodium bisulfate (40 mL). The aqueous layer was extracted with pentane (3 x 30 mL). The resulting organic layer was washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated carefully under vacuum. The crude mixture was purified by flash chromatography eluting with pentane/DCM (50/50) yielding **100** as a colourless oil (2.8 g, 76%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[15]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.24 (3H, s, CH_3), 4.94 (1H, s broad, CH**H**), 5.04 (1H, s broad, CH**H**), 5.18 (1H, d, J = 11.0 Hz, CH$\mathbf{H}_{cis}$), 5.29 (1H, d, J = 17.5 Hz, CH$\mathbf{H}_{trans}$), 6.28 (1H, dd, J = 17.5, 11.0 Hz C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.7, 106.1, 115.3, 130.9, 151.8, 168.7.

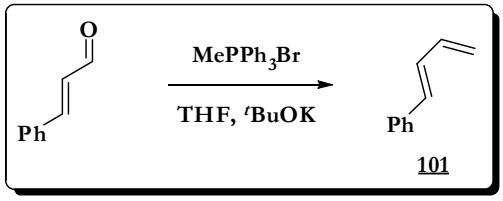
- *Synthesis of buta-1,3-dienylpyrrolidin-2-one* **131**



To a solution of 2-pyrrolidinone (6.0 g, 71 mmol) and crotonaldehyde (5.0 g, 71 mmol) in toluene (110 mL) was added TsOH (36 mg, 0.2 mmol). The mixture heated to reflux until water removal by a Dean-Stark apparatus had ceased. The mixture was cooled to room temperature, washed with a solution of sodium bicarbonate and then with water. The aqueous layer was extracted with diethyl ether, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was dissolved in the minimum of dichloromethane and pentane was added to perform a crystallisation. The solution was left in the freezer

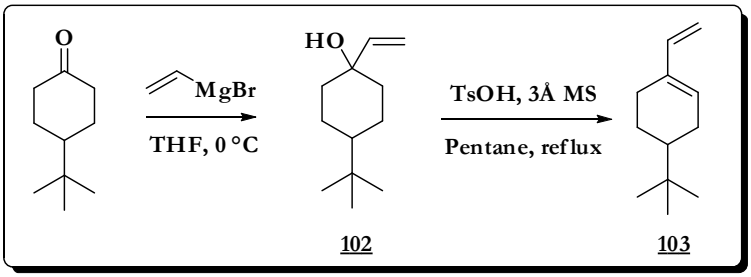
overnight to give **131** after filtration as a colourless solid (3.9 g, 40%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[16]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01-2.11 (2H, m, C**H**$_2$), 2.40 (2H, t, *J* = 8.5 Hz, C**H**$_2$), 3.49 (2H, t, *J* = 7.5 Hz, C**H**$_2$), 4.92 (1H, dd, *J* = 10.5, 1.0 Hz, CH**H**$_{cis}$), 5.07 (1H, dd, *J* = 17.0, 1.0 Hz, CH**H**$_{trans}$), 5.56 (1H, dd, *J* = 14.5, 10.5 Hz, C**H**), 6.28 (1H, dt, *J* = 17.0, 10.5 Hz C**H**), 7.04 (1H, d, *J* = 14.5 Hz, N-C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.4, 29.9, 43.7, 111.2, 112.7, 125.5, 133.8, 171.7.

- *Synthesis of buta-1,3-dienylbenzene* **101**



To a suspension of methyltriphenylphosphonium bromide (7.4 g, 21 mmol) in THF (50 mL) was added a solution of potassium *tert*-butoxide in THF (2.5 g, 5.5 mL, 22 mmol). The reaction mixture was stirred at room temperature for 10 minutes to give an orange colour. The reaction was cooled to -78 °C and cinnamaldehyde (2.1 g, 16 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 15 hours. Hexane (110 mL) was added and the cloudy mixture was filtered through celite and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with petrol to give **101** as a colourless oil (1.2 g, 58%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[17]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.22 (1H, dd, *J* = 10.0, 1.0 Hz, CH**H**$_{cis}$), 5.38 (1H, dd, *J* = 17.0, 1.0 Hz, CH**H**$_{trans}$), 6.51-6.63 (2H, m, C**H**), 6.83 (1H, dd, *J* = 16.0, 10.5 Hz, C**H**), 7.25-7.29 (1H, m, Ar**H**), 7.34-738 (2H, m, Ar**H**), 7.44-7.46 (2H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 118.0, 126.9, 128.0, 129.0, 130.0, 133.3, 137.5, 137.6.

- *Synthesis of 4-tert-butyl-1-vinylcyclohex-1-ene* **103**

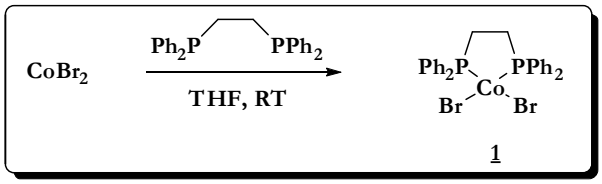


A solution of 4-*tert*-butylcyclohexanone (3.0 g, 20 mmol) in THF (20 mL) was cooled to 0 °C before a solution of vinylmagnesium bromide in THF (1.0 M, 22.0 mL, 22 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2 hours. The mixture was quenched with $HCl_{(aq)}$ 1 M solution and extracted with diethyl ether (75 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with petrol/EtOAc (90/10). Only one isomer **102** could be isolated cleanly as an oil. Its stereochemistry was not determined (1.2 g, 34%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87-0.88 (9H, s, C**H**$_3$), 1.09-1.26 (1H, m, C**H**), 1.50-1.93 (8H, m, C**H**$_2$), 5.18 (1H, dd, *J* = 11.0, 1.5 Hz, CH**H**$_{cis}$), 5.35 (1H, dd, *J* = 18.0, 1.5 Hz, CH**H**$_{trans}$), 5.35 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.5, 27.6, 32.3, 39.3, 47.5, 33.4, 113.8, 142.8.

To a solution of **102** (356 mg, 2.0 mmol) in pentane (4 mL) was added TsOH (104 mg, 0.6 mmol) and 3Å molecular sieves (31 mg). The mixture was heated to reflux overnight and then filtered through Celite, washed with pentane and concentrated *in vacuo*. The crude mixture was filtered through silica to give the clean diene **103** (230 mg, 71%) as a colourless oil. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[18]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (9H, s, C**H**$_3$), 1.10-1.36 (1H, m, C**H**), 1.86-2.39 (6H, m, C**H**$_2$), 4.91 (1H, d, *J* = 11.0 Hz CH**H**$_{cis}$), 5.07 (1H, d, *J* = 18.0 Hz CH**H**$_{trans}$), 5.77-5.79 (1H, m, C**H**), 6.38 (1H, dd, *J* = 18.0, 11.0 Hz, C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.7, 25.2, 27.2, 27.4, 32.2, 44.3, 109.8, 130.0, 136.0, 139.7.

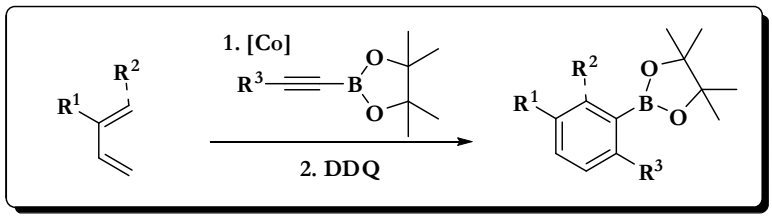
6.3 Cobalt catalyzed cycloadditions

Synthesis of [1,2-bis-diphenylphosphino-ethane]cobalt(II) 1



To a solution of ethylenebis(diphenylphosphine) (5.0 g, 13 mmol) in THF (150 mL) was added $CoBr_2$ (2.8 g, 13 mmol). The brown mixture was vigorously stirred overnight to generate a green precipitate that was collected by filtration, washed with pentane and dried *in vacuo* providing the green cobalt complex **1** (7.7 g, 100%). Due to the paramagnetic nature of Co(II) complexes, the compound could not be analysed by NMR spectroscopy.

General Procedure for the Cycloaddition-Oxidation Strategy (General procedure A)

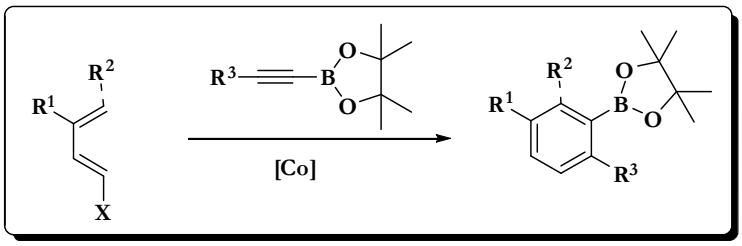


A flame dried Schlenk tube was charged with [$CoBr_2$(dppe)] **1** (62 mg, 10 mol%), zinc iodide (64 mg, 20 mol%) and powdered zinc (13 mg, 20 mol%) in anhydrous dichloromethane (1 mL) under an argon atmosphere. The mixture was stirred for 15 minutes before addition of the diene (1 mmol) and alkynylboronate (1 mmol), the reaction mixture was stirred at ambient temperature for 4 hours. The mixture was filtered through a pad of silica gel and the solvent removed *in vacuo*. The crude mixture was dissolved in benzene (10 mL) and DDQ (1.1 mmol) was added. The mixture was stirred for 1 hour.

A basic solution (10 % NaOH / 10 % $Na_2S_2O_3$, 20 mL) was introduced and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The resulting organic layer was washed with brine and dried over $MgSO_4$. After evaporarion *in vacuo*, the crude product was purified by flash chromatography over silica gel.

Important information to assure optimal reproducibility: *The reactions must be carried out under an argon atmosphere. Zinc iodide was dried at 160 °C for 2 hours under high vacuum prior to use. The catalyst, zinc and zinc iodide were warmed with a heat gun under high vacuum for 5 seconds before adding the solvent.*

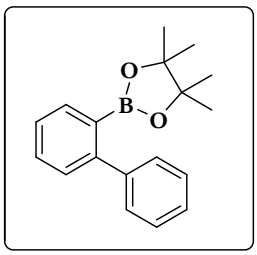
General Procedure for the Cycloaddition-Elimination Strategy (General procedure B)



A flame dried Schlenk tube was charged with [$CoBr_2$(dppe)] **1** (62 mg, 10 mol%), zinc iodide (64 mg, 20 mol%) and powdered zinc (13 mg, 20 mol%) in anhydrous dichloromethane (1 mL) under an argon atmosphere. The mixture was stirred for 15 minutes before addition of the diene (1 mmol) and alkynylboronate (1 mmol), the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was filtered through a pad of silica gel and the solvent removed *in vacuo*. The crude product was purified by flash chromatography over silica gel.

Important information to assure optimal reproducibility: *The reactions must be carried out under an argon atmosphere. Zinc iodide was dried at 160 °C for 2 hours under high vacuum prior to use. The catalyst, zinc and zinc iodide were warmed with a heat gun under high vacuum for 5 seconds before adding the solvent.*

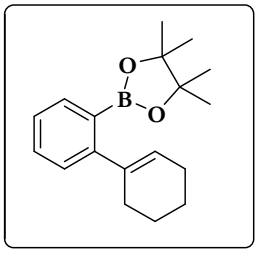
- *Synthesis of 2-(biphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **159**



Following general procedure A, addition of butadiene (54 mg, 1 mmol) and phenylalkynylboronate **94** (228 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **159** as a clear oil (190 mg, 68%).

Following the general procedure B, addition of the diene **122** (162 mg, 1 mmol) and phenylalkynylboronate **94** (228 mg, 1 mmol) to the catalyst in dichloromethane furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **159** as a clear oil (246 mg, 88%). The product showed satisfactory spectroscopic data in comparison to the literature[19]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27 (12H, s, PinC**H**$_3$), 7.36-7.51 (8H, m, Ar**H**), 7.79 (1H, d, *J* = 7.5 Hz, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.6, 83.7, 126.3, 126.9, 127.8, 129.0, 129.2, 130.1, 134.5, 143.3, 147.6.

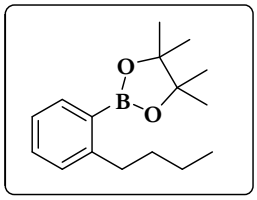
- *Synthesis of 2-(2-cyclohexenylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **160**



Following general procedure A, addition of butadiene (54 mg, 1 mmol) and cyclohexynylalkynylboronate **97** (232 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **160** as a clear oil (182 mg, 64%).

Following the general procedure B, addition of the diene **122** (162 mg, 1 mmol) and cyclohexynylalkynylboronate **97** (232 mg, 1 mmol) to the catalyst in dichloromethane furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **160** as a clear oil (222 mg, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (12H, s, PinC**H**$_3$), 1.65-1.83 (4H, m, C**H**$_2$), 2.15-2.19 (2H, m, C**H**$_2$), 2.35-2.38 (2H, m, C**H**$_2$), 5.55-5.58 (1H, m, C**H**), 7.19-7-27 (2H, m, Ar**H**), 7.33-7.40 (1H, m, Ar**H**), 7.63-7.66 (1H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 22.1, 23.2, 24.8, 25.7, 30.6, 83.5, 125.2, 125.7, 127.1, 129.8, 134.3, 140.9, 150.7; FTIR (film): 2978 (s), 2926 (s), 1596 (w), 1392 (s), 1145 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{18}H_{26}BO_2$: 285.2021 found 285.2026.

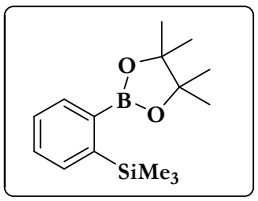
- *Synthesis of 2-(2-n-butylphenyl)4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **161**



Following general procedure A, addition of butadiene (54 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **161** as a clear oil (174 mg, 67%).

Following the general procedure B, addition of the diene **122** (162 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **161** as a clear oil (211 mg, 81%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.5 Hz, C**H**$_3$), 1.39 (12H, s, PinC**H**$_3$), 1.39-1.47 (2H, m, C**H**$_2$), 1.56-1.60 (2H, m, C**H**$_2$), 2.90-2.94 (2H, m, C**H**$_2$), 7.20-7-23 (2H, m, Ar**H**), 7.36-7.40 (1H, m, Ar**H**), 7.80-7.83 (1H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0, 22.8, 24.9, 35.6, 35.7, 83.3, 124.8, 129.2, 130.8, 136.0, 150.2; FTIR (film): 3051 (w), 2977 (s), 2871 (m), 1600 (s), 1442 (s), 1146 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{16}H_{26}BO_2$: 261.2037 found 261.2026.

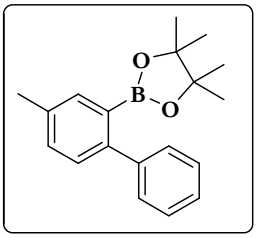
- *Synthesis of trimethyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)silane* **162**



Following general procedure A, addition of butadiene (54 mg, 1 mmol) and trimethylsilylalkynylboronate **96** (224 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **162** as a clear oil (141 mg, 51%).

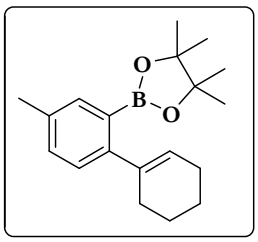
Following the general procedure A, addition of the diene **122** (162 mg, 1 mmol) and trimethylsilylalkynylboronate **96** (224 mg, 1 mmol) to the catalyst in dichloromethane furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **162** as a colorless solid (149 mg, 54%). M.pt.: 85-88 °C {*lit.*[20] 84-86 °C}. The product showed satisfactory spectroscopic and analytical data in comparison to the literature.[20] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.36, (9H, s, C**H**$_3$), 1.37 (12H, s, PinC**H**$_3$), 7.33-7.45 (2H, m, Ar**H**), 7.62-7.65 (1H, m, Ar**H**), 7.91-7.94 (1H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 1.1, 25.0, 83.8, 127.8, 129.7, 134.3, 136.1, 146.0.

- *Synthesis of 4,4,5,5-tetramethyl-2-(4-methylbiphenyl-2-yl)-1,3,2-dioxaborolane* **163**



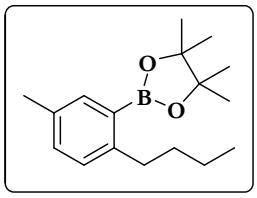
Following general procedure A, addition of isoprene (69 mg, 1 mmol) and phenylalkynylboronate **94** (228 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **163** as a clear oil (247 mg, 84%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (12H, s, PinC**H**$_3$), 2.47 (3H, s, C**H**$_3$), 7.35-7-49 (7H, m, Ar**H**), 7.63 (1H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 24.7, 83.7, 126.7, 127.8, 129.1, 129.2, 130.9, 135.2, 135.8, 143.3, 144.9; FTIR (film): 3054 (w), 2978 (s), 2927 (m), 1603 (m), 1444 (m), 1145 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{19}H_{24}BO_2$: 295.1868 found 295.1869.

- *Synthesis of 2-(2-cyclohexenyl-5-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **164**



Following general procedure A, addition of isoprene (69 mg, 1 mmol) and cyclohexynylalkynylboronate **97** (232 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **164** as a clear oil (230 mg, 77%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (12H, s, PinC**H**$_3$), 1.65-1.82 (4H, m, C**H**$_2$), 2.15-2.18 (2H, m, C**H**$_2$), 2.35 (3H, s, C**H**$_3$), 2.33-2.38 (2H, m, C**H**$_2$), 5.52-5.56 (1H, m, C**H**), 7.03-7-20 (2H, m, Ar**H**), 7.46 (1H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 22.1, 23.2, 24.8, 25.7, 30.7, 83.4, 124.9, 127.2, 130.6, 134.9, 135.0, 140.7, 147.9; FTIR (film): 2978 (m), 2927 (s), 1598 (w), 1391 (m), 1145 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{19}H_{28}BO_2$: 299.2186 found 299.2182.

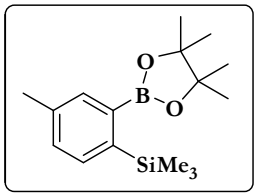
- *Synthesis of 2-(2-n-butyl-5-phenyl)4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **165**



Following general procedure A, addition of isoprene (69 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **165** as a clear oil (219 mg, 80%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.00 (3H, t, J = 7.5 Hz, C**H**$_3$), 1.39 (12H, s, PinC**H**$_3$), 1.49-1.39 (2H, m, C**H**$_2$), 1.54-1.62 (2H, m, C**H**$_2$), 2.37 (3H, s, C**H**$_3$), 2.89-2.93 (2H, m, C**H**$_2$), 7.05-7-22 (2H, m, Ar**H**), 7.65 (1H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0, 20.8, 22.8, 24.8, 35.1, 35.8, 83.3, 128.3, 129.2, 131.5, 136.5, 147.1; FTIR (film): 2977 (s), 2871 (s),

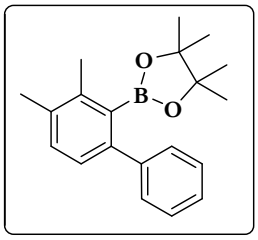
1610 (s), 1459 (s), 1146 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{17}H_{28}BO_2$: 275.2193 found 275.2182.

- *Synthesis of trimethyl(4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)silane* **166**



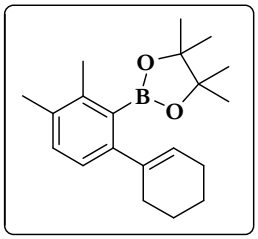
Following general procedure A, addition of isoprene (69 mg, 1 mmol) and trimethylsilylalkynylboronate **96** (224 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **166** as a clear oil (203 mg, 70%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.36 (9H, s, SiC**H**$_3$), 1.38 (12H, s, PinC**H**$_3$), 2.37 (3H, s, C**H**$_3$), 7.26-7.29 (1H, m, Ar**H**), 7.56-7.59 (1H, m, Ar**H**), 7.80 (1H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 0.0, 20.5, 24.3, 83.1, 129.9, 133.9, 136.3, 136.8, 142.7; FTIR (film): 2978 (m), 1596 (w), 1392 (m), 1142 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{16}H_{28}BO_2Si$: 291.1959 found 291.1952.

- *Synthesis of 2-(3,4-dimethylbiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **167**



Following general procedure A, addition of 3-methyl-1,3-pentadiene (82 mg, 1 mmol) and phenylalkynylboronate **94** (228 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **167** as a clear oil (230 mg, 74%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.20 (12H, s, PinC**H**$_3$), 2.34 (3H, s, C**H**$_3$), 2.43 (3H, s, C**H**$_3$), 6.90-6.93 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.06-7.09 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.34-7.50 (5H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.3, 20.0, 25.0, 83.7, 126.2, 126.7, 127.9, 129.2, 130.4, 134.7, 139.2, 143.9, 144.3; FTIR (film): 3024 (w), 2978 (s), 2930 (m), 1596 (w), 1441 (m), 1138 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{20}H_{26}BO_2$: 309.2026 found 309.2026.

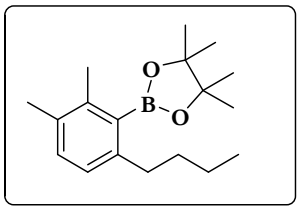
- *Synthesis of 2-(6-cyclohexenyl-2,3-dimethyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **168**



Following general procedure A, addition of 3-methyl-1,3-pentadiene (82 mg, 1 mmol) and cyclohexenylalkynylboronate **97** (232 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **168** as a clear oil (237 mg, 76%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37 (12H, s, PinC**H**$_3$), 1.63-1.79 (4H, m, C**H**$_2$), 2.13-2.20 (2H, m, C**H**$_2$), 2.24 (3H, s, C**H**$_3$), 2.28-2.39 (2H, m, C**H**$_2$), 2.34 (3H, s, C**H**$_3$), 5.60-5.61 (1H, m, C**H**), 6.91 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.07 (1H, d, *J* = 7.5 Hz, Ar**H**); ^{13}C NMR (62.9

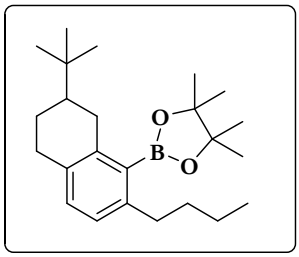
MHz, $CDCl_3$) δ 19.1, 19.9, 22.0, 23.1, 25.3, 25.5, 30.4, 83.5, 124.0, 125.0, 130.0, 134.0, 139.1, 141.4, 146.7; FTIR (film): 2977 (m), 2928 (m), 1598 (w), 1447 (w), 1138 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{20}H_{30}BO_2$: 313.2333 found 313.2339.

- *Synthesis of 2-(6-n-butyl-2,3-dimethyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **169**



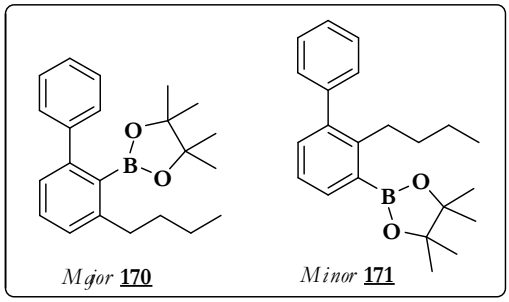
Following general procedure A, addition of 3-methyl-1,3-pentadiene (82 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **169** as a clear oil (153 mg, 73%; >95:5). ^1H NMR (250 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.29-1.43 (2H, m, C**H**$_2$), 1.43 (12H, s, PinC**H**$_3$), 1.52-1.62 (2H, m, C**H**$_2$), 2.22 (3H, s, C**H**$_3$), 2.32 (3H, s, C**H**$_3$), 2.59–2.66 (2H, m, C**H**$_2$), 6.91 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.03 (1H, d, *J* = 7.5 Hz, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.0, 18.3, 18.8, 21.7, 24.1, 34.0, 35.0, 82.7, 124.8, 129.6, 132.0, 138.3, 143.1; FTIR (film): 2978 (s), 2862 (m), 1597 (w), 1447 (w), 1138 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{18}H_{30}BO_2$: 289.2333 found 289.2339.

- *Synthesis of 2-(7-tert-Butyl-2-n-butyltetrahydronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **172**



Following general procedure A, addition of 4-*tert*-butyl-1-vinylcyclohex-1-ene **103** (165 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **172** as a clear oil (264 mg, 71%; >95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94-0.97 (12H, m, ^{t}BuC**H$_3$,** C**H$_3$**), 1.42 (12H, s, PinC**H$_3$**), 1.25-1.47 (2H, m, C**H$_2$**), 1.48-1.62 (2H, m, C**H$_2$**), 1.92-1.98 (1H, m, C**H**), 2.20 (2H, s, C**H$_2$**), 2.54-2.95 (6H, m, C**H$_2$**), 6.89 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.99 (1H, d, *J* = 8.0 Hz, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.1, 22.8, 24.4, 25.1, 27.4, 30.7, 31.5, 32.6, 35.1, 36.1, 45.1, 83.6, 125.6, 129.6, 133.3, 140.5, 143.8; FTIR (film): 2957 (s), 2862 (m), 1574 (w), 1420 (m), 1142 (s) cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd for $C_{24}H_{39}BO_2$: 370.3042 found 370.3043.

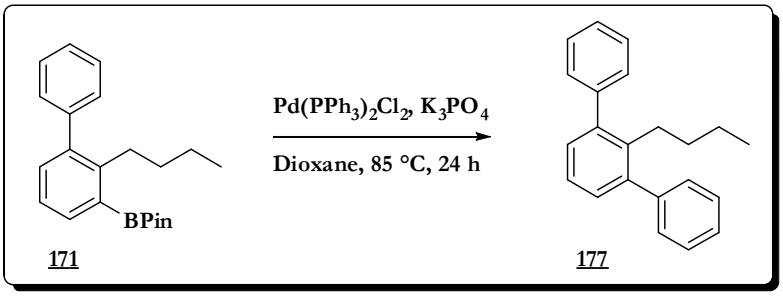
- *Synthesis of 2-(3-n-butylbiphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **170** & *2-(2-n-Butylbiphenyl-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* **171**



Following general procedure A, addition of 1-phenylbutadiene **101** (130 mg, 1 mmol) and *n*-butylalkynylboronate **95** (208 mg, 1 mmol) to the catalyst in dichloromethane furnished a crude mixture that was directly dissolved in benzene and treated with DDQ. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided a mixture of compounds **170** and **171** as a clear oil (259 mg, 77%; 85:15). *Major regioisomer* **170**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.0 Hz, C**H**$_3$), 1.12-1.29 (2H, m, C**H**$_2$), 1.32-1.46 (14H, m, PinC**H**$_3$, C**H**$_2$), 2.73-2.79 (2H, m, C**H**$_2$), 7.12-7-17 (1H, m, Ar**H**), 7.31-7-41 (7H, m, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.1, 22.9, 24.9, 34.8, 36.4, 83.7, 126.0, 126.8, 127.0, 127.9, 128.7, 129.2, 143.9, 146.4, 146.6; *Minor regioisomer* **171**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.76 (3H, t, J = 7.0 Hz, C**H**$_3$), 1.12-1.29 (2H, m, C**H**$_2$), 1.32-1.46 (14H, m, PinC**H**$_3$, C**H**$_2$), 2.79-2.86 (2H, m, C**H**$_2$), 7.19-7-44 (7H, m, Ar**H**), 7.80 (1H, dd, J = 2.5 Hz, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 23.0, 24.8, 31.8, 35.9, 83.4, 124.6, 126.5, 127.8, 129.4, 132.6, 135.3, 142.0, 142.7, 147.2; *major/minor regioisomers*: FTIR (film): 3055 (w), 2978 (m), 2862 (m), 1583 (w), 1424 (m), 1141(s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{22}H_{30}BO_2$: 337.2345 found 337.2339.

Regiochemistry Assignment of 171

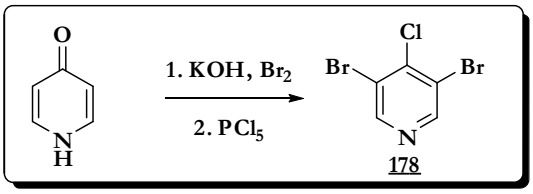
- *Synthesis of 2-butyl-3-phenylbiphenyl* **177**



To a solution of the minor regioisomer **171** (20 mg, 59 μmol, 1 eq) in dioxane (0.5 mL) was added K_3PO_4 (38 mg, 178 μmol, 3 eq) and $Pd(PPh_3)_2Cl_2$ (4 mg, 6 μmol, 10 mol%). The mixture was heated at 85 °C for 24 h. After cooling to room temperature, the mixture was quenched by water. The aqueous layer was extracted with dichloromethane and the resulting organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with pentane to give the product **177** as a clear oil (5.4 mg, 32%). Spectroscopic analysis indicated that the product **177** was a symmetrical 1,2,3-trisubstituted aromatic, thereby confirming that the boronic ester had been incorporated in the 3-position. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.48 (3H, t, J = 7.0 Hz, C**H**$_3$), 0.79-0.94 (2H, m, C**H**$_2$), 1.02-1.15 (2H, m, C**H**$_2$), 2.51-2.58 (2H, m, C**H**$_2$), 7.18-7-24 (3H, m, Ar**H**), 7.30-7.47 (10H, m, Ar**H**) ; ^{13}C NMR (249.9 MHz, $CDCl_3$) δ 13.3, 22.4, 29.4, 32.6, 125.0, 126.7, 127.9, 129.3, 129.4, 138.3, 142.6, 142.7; FTIR (film): 3057 (w), 3025 (w), 2956 (m), 2926 (m), 2857 (m), 2871 (m), 1601 (w), 1495 (m),1458 (m), 1379 (w), 760 (s), 702 (s) HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{22}$: 286.1724 found 286.1722.

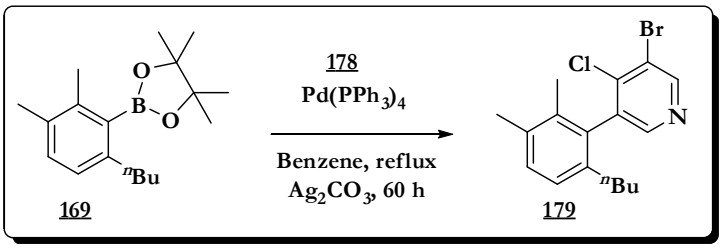
6.4 Aminopyridine derivatives

- *Synthesis of 3,5-dibromo-4-chloropyridine* **178**



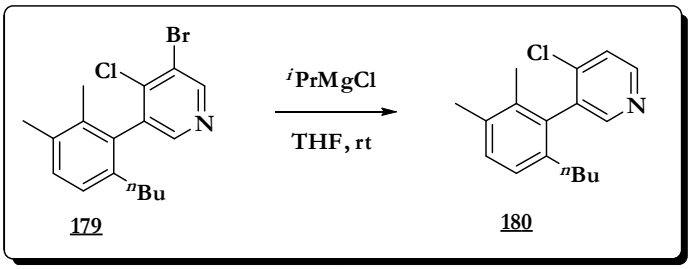
To a solution of 4-pyridinone (5.0 g, 53 mmol) and KOH (6.0 g, 106 mmol) in water (100 mL) cooled to 0 °C was added Br_2 (17.0 g, 105 mmol) dropwise. The reaction mixture was stirred for 30 minutes. The resulting white precipitate was filtered off, washed with a copious amount of water and dried *in vacuo*. The crude solid was used in the next step without further purification. Thus, a mixture of the resulting dibromide and PCl_5 (10.9 g, 55 mmol) was heated at 160 °C for 3 hours. Then, the reaction mixture was cooled to 0 °C and quenched by slow addition of water. The precipitate was isolated by filtration, crushed, washed with water and dried *in vacuo*. The crude mixture was purified by flash chromatography eluting with DCM. Crystallization with EtOH gave **178** as colourless needles (9.9 g, 69%). M.pt.: 93-95 °C {*lit.*[2] 95.0-96-5 °C}. The product showed satisfactory spectroscopic and analytical data in comparison to the literature[21]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.67 (2H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 121.8, 144.0, 150.9. HRMS (EI): m/z $[M]^+$ calcd for $C_5H_2{}^{79}Br_2{}^{35}ClN$: 268.8230 found 268.8242.

- *Synthesis of 3-bromo-5-(6-n-butyl-2,3-dimethylphenyl)-4-chloropyridine* **179**



To a solution of **169** (196 mg, 0.68 mmol) and 3,5-dibromo-4-chloropyridine **178** (148 mg, 0.54 mmol) in benzene (7 mL) was added silver (I) carbonate (375 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (79 mg, 0.07 mmol, 10 mol%) and the resulting mixture was heated at reflux for 60 h. The reaction mixture was filtered and the organic layer washed with water and brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture was purified by flash chromatography eluting with pentane/CH_2Cl_2 (25/75) to give **179** as a pale yellow oil (135 mg, 71%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.79 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.15-1.25 (2H, m, C**H**$_2$), 1.33-1.43 (2H, m, C**H**$_2$), 1.91 (3H, s, C**H**$_3$), 2.11-2.19 (1H, m, C**H**H), 2.25-2.31 (1H, m, CH**H**), 2.33 (3H, s, C**H**$_3$), 7.11 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.23 (1H, d, *J* = 8.0 Hz, Ar**H**), 8.31 (1H, s, Ar**H**), 8.79 (1H, s, Ar**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2, 17.2, 20.7, 22.8, 33.3, 33.6, 122.1, 126.8, 130.8, 134.7, 134.8, 135.2, 138.2, 138.9, 144.2, 150.3, 151.7; FTIR (film): 2955 (s), 2929 (s), 2863 (m), 1558 (w), 1425 (m), 1389 (s), 749 (s) cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd for $C_{17}H_{19}{}^{79}Br^{35}ClN$: 351.0401 found 351.0389.

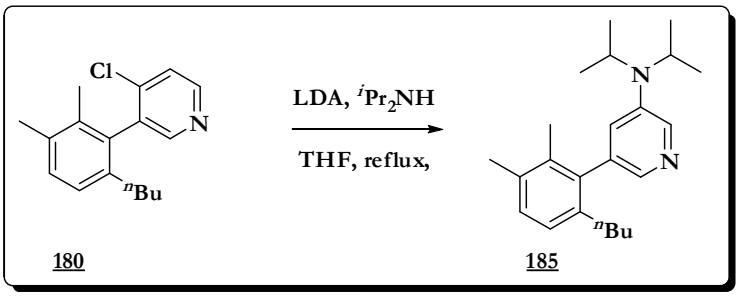
- *Synthesis of 3-(6-n-butyl-2,3-dimethylphenyl)-4-chloropyridine* **180**



179 **180**

To a solution of **179** (41 mg, 0.12 mmol) in THF (1 mL) was added dropwise at room temperature a solution of ^{i}PrMgCl (2 M, 90 μL, 0.17 mmol) in THF. After stirring at room temperature for 2 h, the reaction mixture was quenched with water, extracted with dichloromethane and the extracts washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with petrol/EtOAc (5/1) to give **180** as a pale orange oil (26 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.14-1.23 (2H, m, C**H**$_2$), 1.32-1.42 (2H, m, C**H**$_2$), 1.91 (3H, s, C**H**$_3$), 2.13-2.21 (1H, m, CH**H**), 2.26-2.33 (1H, m, C**H**H), 2.33 (3H, s, C**H**$_3$), 7.10 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.21 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.48 (1H, d, *J* = 5.5 Hz, Ar**H**), 8.41 (1H, s, Ar**H**), 8.54 (1H, d, *J* = 5.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8, 16.8, 20.3, 22.4, 32.9, 33.3, 124.3, 126.3, 130.1, 134.2, 134.4, 135.0, 136.2, 138.9, 144.0, 149.2, 151.8; FTIR (film): 2958 (s), 2928 (s), 2861 (m), 1581 (w), 1456 (m), 1260 (m), 1194 (w), 750 (s) cm^{-1}; HRMS (EI): m/z $[MH]^+$ calcd for $C_{17}H_{20}{}^{35}ClN$: 273.1271 found 273.1284.

- *Synthesis of 3-(6-n-butyl-2,3-dimethylphenyl)-N,N-diisopropylpyridin-4-amine* **185**



180 **185**

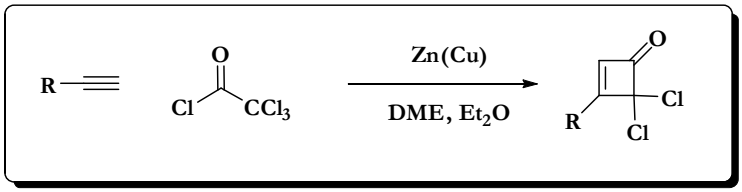
To a solution of **180** (15 mg, 0.05 mmol) in THF (0.5 mL) was added diisopropylamine (48 mg, 0.50 mmol). A freshly prepared solution of lithium diisopropylamide in THF (2.1 M, 55 μL, 0.11 mmol) was then added at room temperature *via* syringe. The mixture was heated to reflux for 16 h. The reaction mixture was cooled to room temperature, and then the solvent removed *in vacuo*. The residue was extracted from water with dichloromethane, the organic layer dried over $MgSO_4$ and solvent removed *in vacuo*. The crude mixture was purified by flash chromatography eluting with petrol/EtOAc (2/1) to give **185** as a yellow oil (11 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.15-1.30 (14H, m, N[CH(C**H**$_3$)$_2$]$_2$, C**H**$_2$), 1.36-1.44 (2H, m, C**H**$_2$), 1.98 (3H, s, C**H**$_3$), 2.32-2.35 (5H, m, C**H**$_3$, C**H**$_2$), 3.76-3.87 (2H, m, C**H**$_2$), 6.98-6.99 (1H, m, Ar**H**), 7.07 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.15 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.83 (1H, d, *J* = 1.5 Hz, Ar**H**), 8.26 (1H, d, *J* = 3.0 Hz, Ar**H**); ^{13}C NMR (249.9 MHz, $CDCl_3$) δ 13.8, 17.4, 20.4, 21.1, 21.4, 22.6, 33.4, 33.7, 47.7, 126.2, 126.4, 129.2, 134.1, 135.0, 136.3, 138.3, 138.9, 139.3, 139.6, 143.7; FTIR (film): 2965 (s), 2930 (s), 2871 (m), 1582 (w), 1456 (s), 1368 (m), 1195 (s), 817 (w) cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd for $C_{23}H_{34}N_2$: 338.2711 found 338.2722.

6.5 Synthesis of cyclobutenones

Synthesis of zinc-copper couple Zn(Cu)

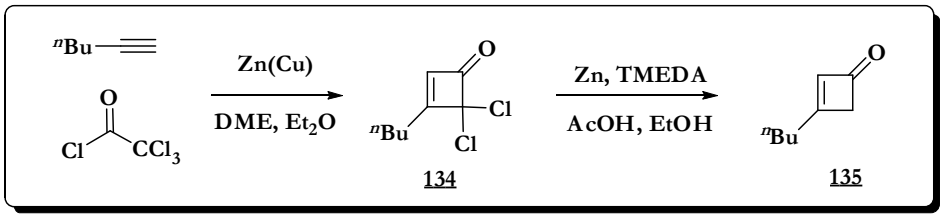
Zinc powder (32.7 g, 500 mmol) was introduced into a 500 mL conical flask and water (50 mL) was added. Solid $Cu(SO_4).5H_2O$ (3.8 g, 15 mmol) was introduced in 2 portions (2 x 1.9 g) with 30 seconds interval. The mixture was stirred for 1 minute, filtered, washed with water (2 x 25 mL), washed with acetone (2 x 25 mL) and washed with diethyl ether (2 x 25 mL). The resulting dark grey solid was left overnight at 100 °C under vacuum to give Zn(Cu) (31.1 g, 98%) that was directly in subsequent transformations.

General procedure for the synthesis of 4,4-dichlorocyclobutenones[22]



A 500 mL, three-necked, round-bottomed flask was equipped with a magnetic stirring bar, two glass stoppers, and a 250-mL pressure-equalizing addition funnel fitted with a nitrogen inlet adapter. The flask was charged with zinc–copper couple (3 eq), diethyl ether, and alkyne (1 eq). The dropping funnel was charged with a solution of trichloroacetyl chloride (2 eq) in dimethoxyethane, and this solution was then added dropwise to the reaction mixture over 15 minutes. After 18 h, the resulting brown mixture was filtered through a sintered-glass Büchner funnel, and the black solid was thoroughly washed with hexane (50 mL). The filtrate was washed successively with ice-cold 0.5 *N* hydrochloric acid (50 mL), ice-cooled 5% sodium hydroxide solution (50 mL), and saturated sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, and then concentrated at reduced pressure using a rotary evaporator to give the crude 3-substituted-4,4-dichlorocyclobutenone. The residue was directly used in the next step without further purification.

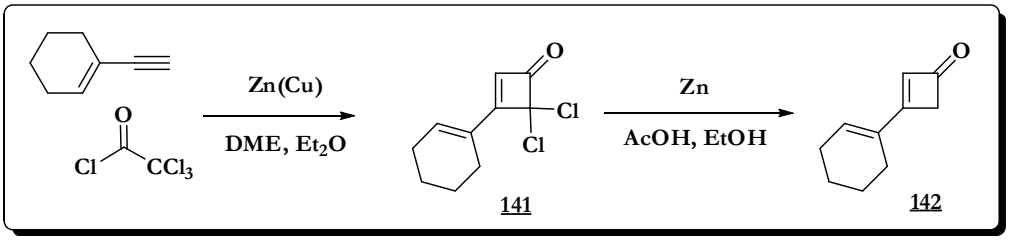
- *Synthesis of 3-butylcyclobut-2-enone* **135**



Following the general procedure, the flask was charged with Zn(Cu) (11.9 g, 183 mmol), diethyl ether (120 mL) and 1-hexyne (5.0 g, 61 mmol). Addition of trichloroacetyl chloride (13.6 mL, 122 mmol) in dimethoxyethane (38 mL) furnished the crude 3-butyl-4,4-dichlorocyclobut-2-enone **134** (11.8 g, 100%). The residue was directly used in the next step without further purification.

The flask was charged with zinc dust (23.2 g, 355 mmol) tetramethylethylenediamine (53.2 mL, 355 mmol) and absolute ethanol (120 mL). The mixture was cooled with an ice bath while glacial acetic acid (20.3 mL, 355 mmol) was added dropwise over 5 min. The reaction mixture was maintained at 0 °C while a solution of 3-butyl-4,4-dichlorocyclobutenone **134** (11.8 g, 61 mmol) in absolute ethanol (12 mL) was added over 10 min *via* a dropping funnel. After 15 min the ice bath was removed, and the reaction mixture was stirred for 2.5 h and then filtered through a sintered-glass Büchner funnel and washed with a 1 : 1 mixture of diethyl ether and pentane (750 mL). The filtrate was washed successively with 1 *N* hydrochloric acid (250 mL), water (250 mL), saturated sodium bicarbonate solution (500 mL), and saturated sodium chloride solution (500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to give 3-butylcyclobut-2-enone **135** as a yellow oil (6.5 g, 86%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[22]. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.5 Hz, C**H**$_3$), 1.40-1.46 (2H, m, C**H**$_2$), 1.61-1.65 (2H, m, C**H**$_2$), 2.57-2.61 (2H, m, C**H**$_2$), 3.17 (2H, s, C**H**$_2$), 5.91 (1H, s, C**H**); ^{13}C NMR (249.9 MHz, $CDCl_3$) δ 13.7, 22.4, 28.2, 31.8, 50.7, 134.2, 181.4, 188.1.

- *Synthesis of 3-cyclohexenylcyclobut-2-enone* **142**

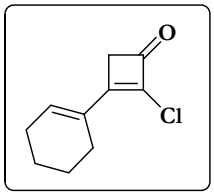


Following the general procedure, the flask was charged with Zn(Cu) (9.3 g, 142 mmol), diethyl ether (95 mL) and 1-ethynylcyclohex-1-ene (5.0 g, 47 mmol). Addition of trichloroacetyl chloride (10.5 mL, 94 mmol) in dimethoxyethane (30 mL) furnished the crude 3-cyclohexenyl-4,4-dichlorocyclobut-2-enone **141** (10.2 g, 100%). The residue was directly used in the next step without further purification.

The flask was charged with zinc dust (30.8 g, 471 mmol) and absolute ethanol (95 mL). The mixture was cooled with an ice bath while glacial acetic acid (13.5 mL, 236 mmol) was added dropwise over 5 min. The reaction mixture was maintained at 0 °C while a solution of 3-cyclohexenyl-4,4-dichlorocyclobutenone **141** (10.2 g, 47 mmol) in absolute ethanol (9 mL) was added over 10 min *via* a dropping funnel. The reaction mixture was stirred for 2.5 h and then filtered through a sintered-glass Büchner funnel and washed with a 1 : 1 mixture of diethyl ether and pentane (750 mL). The filtrate was washed successively with 1 *N* hydrochloric acid (250 mL), water (250 mL), saturated sodium bicarbonate solution (500 mL), and saturated sodium chloride solution (500 mL) , dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The crude mixture was purified by flash chromatography eluting with petrol/EtOAc (95/5) to give 3-cyclohexenylcyclobut-2-enone **142** as a yellow oil (6.3 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.73 (2H, m, C**H**$_2$), 1.75-1.81 (2H, m, C**H**$_2$), 2.32-2.35 (4H, m, C**H**$_2$), 3.29 (2H, s, C**H**$_2$), 5.91 (1H, s, C**H**), 6.34 (1H, s, C**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.8, 22.2, 24.9, 26.8, 48.5, 128.4, 133.3, 141.2, 172.7, 189.1; FTIR (film): 2931 (m), 1756 (s), 1623 (s), 1552 (s),

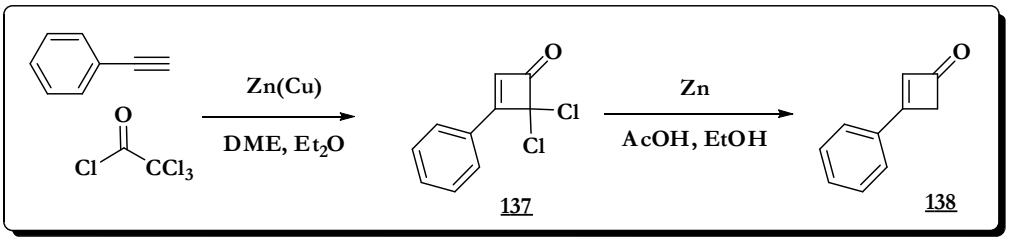
1421 (w), 1257 (w), 1421 (w), 1193 (w), 1035 (w); HRMS (EI): m/z $[MH]^+$ calcd for $C_{10}H_{13}O$: 149.0966 found 149.0959.

- *2-Chloro-3-cyclohexenylcyclobut-2-enone* **144**



144: M.pt.: 58-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.72 (2H, m, C**H**$_2$), 1.75-1.81 (2H, m, C**H**$_2$), 2.32-2.37 (2H, m, C**H**$_2$), 2.59-2.63 (2H, m, C**H**$_2$), 3.21 (2H, s, C**H**$_2$), 6.36-6.38 (1H, m, C**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3, 21.9, 25.6, 26.6, 46.2, 117.9, 132.5, 142.6, 166.4, 184.4; FTIR (film): 1763 (s), 1611 (m), 1564 (m); HRMS (EI): m/z $[M]^+$ calcd for $C_{10}H_{11}O^{35}Cl$: 182.0498 found 182.0506.

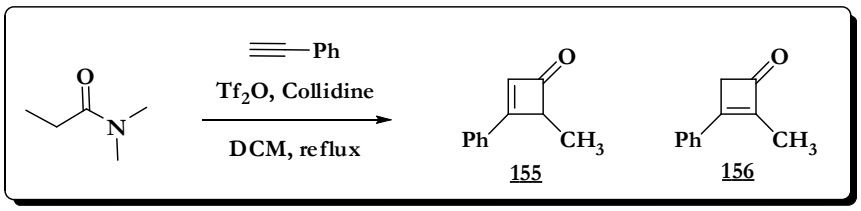
- *Synthesis of 3-phenylcyclobut-2-enone* **138**



Following the general procedure, the flask was charged with Zn(Cu) (9.6 g, 147 mmol), diethyl ether (100 mL) and phenylacetylene (5.0 g, 49 mmol). Addition of trichloroacetyl chloride (10.9 mL, 98 mmol) in dimethoxyethane (30 mL) furnished the crude 3-phenyl-4,4-dichlorocyclobut-2-enone **137** (10.4 g, 100%). The residue was directly used in the next step without further purification.

The flask was charged with zinc dust (32.0 g, 490 mmol) and absolute ethanol (100 mL). The mixture was cooled with an ice bath while glacial acetic acid (14.0 mL, 245 mmol) was added dropwise over 5 min. The reaction mixture was maintained at 0 °C while a solution of 3-phenyl-4,4-dichlorocyclobutenone **137** (10.4 g, 49 mmol) in absolute ethanol (10 mL) was added over 10 min *via* the dropping funnel. The reaction mixture was stirred for 2.5 h and then filtered through a sintered-glass Büchner funnel and washed with a 1 : 1 mixture of diethyl ether and pentane (750 mL). The filtrate was washed successively with 1 *N* hydrochloric acid (250 mL), water (250 mL), saturated sodium bicarbonate solution (500 mL), and saturated sodium chloride solution (500 mL) , dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The crude mixture was purified by flash chromatography eluting with petrol/EtOAc (95/5) to give 3-phenylcyclobut-2-enone **138** as a colourless solid (8.4 g, 84%). M.pt.: 50-52 °C. {*lit.*[20] 51-53 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56 (2H, s, C**H**$_2$), 6.40 (1H, s, C**H**), 7.53-7-54 (3H, m, Ar**H**), 7.64-7.66 (2H, m, Ar**H**) ; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 48.6, 128.8, 129.0, 131.4, 132.0, 141.2, 171.0, 187.4; FTIR (film): 2957 (m), 1763 (s), 1530 (s), 1440 (w), 1404 (w), 1235 (w), 1190 (w), 1034 (w); HRMS (EI): m/z $[MH]^+$ calcd for $C_{10}H_9O$: 145.0653 found 145.0659

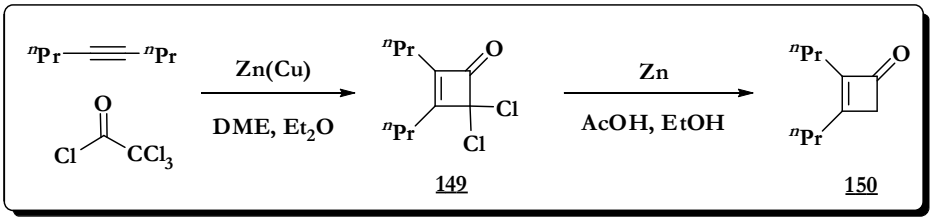
- *Synthesis of 4-methyl-3-phenylcyclobut-2-enone* **155**



Trifluoromethanesulfonic anhydride (5.0 g, 18 mmol) was added to a solution of *N*,*N*-dimethylphenylacetamide (1 mL, 9 mmol) in dichloromethane (10 mL) at 0 °C. The mixture was stirred for 30 minutes at 0 °C and then stirred at room temperature for a further 30 minutes. The mixture was cooled to 0 °C

before adding collidine (3 mL). Phenylacetylene (1 mL, 9 mmol) was added and the reaction mixture was heated to reflux overnight. The mixture was extracted with dichloromethane (100 mL). A 5 M sodium hydroxide solution (50 mL) was added and the mixture was stirred for 30 minutes, then washed with brine (50 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The resulting mixture was purified by flash chromatography eluting with petrol/EtOAc (90/10) leading to 4-methyl-3-phenylcyclobut-2-enone **155** and 4-methyl-3-phenylcyclobut-3-enone **156** (1:1, 0.7 g, 45%). **155**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (3H, d, *J* = 7.0 Hz, C**H**$_3$), 3.94 (1H, q, *J* = 14.0, 7.0 Hz, C**H**), 6.36 (1H, s, C**H**), 7.50-7-55 (3H, m, Ar**H**), 7.61-7-66 (2H, m, Ar**H**); *mixture* **155** & **156**: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 9.4, 13.7, 48.2, 55.8, 128.2, 128.9, 129.0, 129.1, 129.2, 131.0, 131.9, 134.9, 137.9, 159.8, 172.9, 183.1, 192.0, 196.5; FTIR (film): 2959 (m), 1765 (s), 1532 (s), 1445 (w), 1236 (w), 1192 (w), 1034 (w); HRMS (EI): m/z $[M]^+$ calcd for $C_{11}H_{11}O$: 159.0810 found 159.0813

- *Synthesis of 2,3-dipropylcyclobut-2-enone* **150**



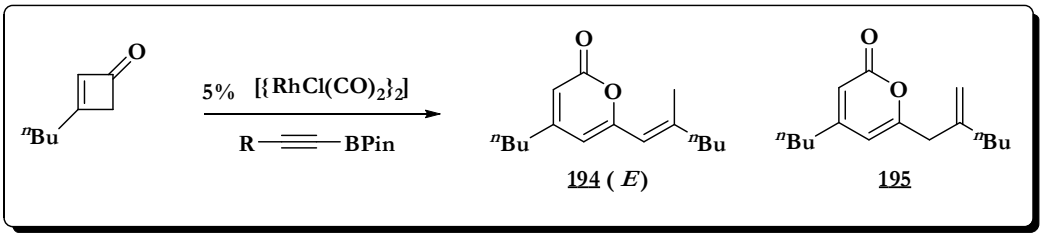
Following the general procedure, the flask was charged with Zn(Cu) (8.0 g, 123 mmol), diethyl ether (80 mL) and 4-octyne (6 mL, 41 mmol). Addition of trichloroacetyl chloride (9.1 mL, 82 mmol) in dimethoxyethane (38 mL) furnished the crude 2,3-dipropyl-4,4-dichlorocyclobut-2-enone **149** (9.0 g, 100%). The residue was directly used in the next step without further purification.

The flask was charged with zinc dust (15.6 g, 239 mmol) tetramethylethylenediamine (35.7 mL, 239 mmol) and absolute ethanol (80 mL). The mixture was cooled with an ice bath while glacial acetic acid (13.6

mL, 239 mmol) was added dropwise over 5 min. The reaction mixture was maintained at 0 °C while a solution of 2,3-dipropyl-4,4-dichlorocyclobut-2-enone **149** (9.0 g, 41 mmol) in absolute ethanol (10 mL) was added over 10 min *via* the dropping funnel. After 15 min the ice bath was removed, and the reaction mixture was stirred at 10-15 °C for 2.5 h,filtered through a sintered-glass Büchner funnel and washed with a 1 : 1 mixture of diethyl ether and pentane (750 mL). The filtrate was washed successively with 1 *N* hydrochloric acid (250 mL), water (250 mL), saturated sodium bicarbonate solution (500 mL), and saturated sodium chloride solution (500 mL) , dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The resulting mixture was purified by flash chromatography eluting with petrol/EtOAc (90/10) to lead dipropylcyclobut-2-enone **150** (3.1 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.5 Hz, C**H$_3$**), 1.02 (3H, t, *J* = 7.5 Hz, C**H$_3$**), 1.50-1.59 (2H, m, C**H$_2$**), 1.61-1.70 (2H, m, C**H$_2$**), 2.05-2.08 (2H, m, C**H$_2$**), 2.52-2.56 (2H, m, C**H$_2$**), 3.10 (2H, m, C**H$_2$**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4, 14.5, 20.0, 21.1, 25.8, 32.1, 49.6, 148.7, 173.1, 190.6; FTIR (film): 2929 (m), 1745 (s), 1620 (s), 1553 (s), 1420 (w), 1258 (w), 1419 (w), 1189 (w), 1029 (w); HRMS (EI): m/z $[MH]^+$ calcd for $C_{10}H_{17}O$: 153.1279 found 153.1275.

6.6 Synthesis of pyranones

- *Synthesis of (E)-4-butyl-6-(2-methylhex-1-enyl)-2H-pyran-2-one* <u>*194*</u> *& 4-butyl-6-(2-methylenehexyl)-2H-pyran-2-one* <u>*195*</u>

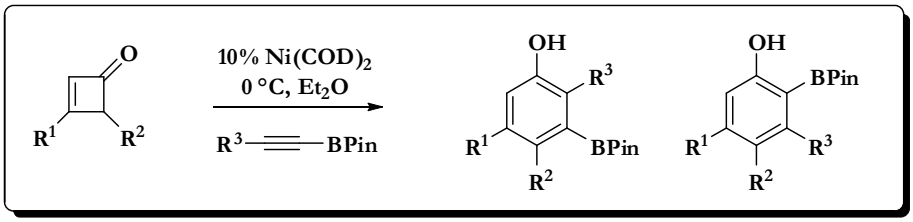


A mixture of *n*butylcyclobutenone **<u>135</u>** (15 mg, 0.12 mmol), *n*butylalkynylboronate **<u>95</u>** (25 mg, 0.12 mmol), $[\{RhCl(CO)_2\}_2]$ (2.5 mg, 6

μmol, 5 mol%) and toluene (1 mL) was placed in a Shlenck tube. The reaction mixture was stirred overnight under argon at 110 °C. The reaction mixture was filtered through a pad of silica providing a mixture of compounds **194** and **195** as an oil (2:1, 14 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90-0.98 (6H, m, C**H**$_3$, C**H**$_3$), 1.27-1.60 (8H, m, C**H**$_2$, C**H**$_2$), 1.61 (2H, s, C**H**$_3$), 2.14 (0.67H, s, C**H**$_2$), 2.16-2.20 (2H, m, C**H**$_2$, C**H**$_2$), 2.38-2.41 (2H, m, C**H**$_2$, C**H**$_2$), 4.90 (0.33H, s, C**H**$_2$), 4.96 (0.33H, s, C**H**$_2$), 5.81 (0.67H, s, C**H**), 5.90 (1H, s, C**H**), 5.91 (0.33H, s, C**H**), 5.94 (0.67H, s, C**H**), 5.98 (0.33H, s, C**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.7, 13.8, 13.9, 14.0, 19.3, 20.2, 22.3, 22.4, 29.7, 29.9, 30.2, 30.4, 32.9, 34.9, 35.0, 35.3, 40.7, 41.5, 105.8, 106.7, 109.2, 110.0, 113.7, 116.9, 143.8, 149.9, 160.1, 160.5, 162.9, 163.0; FTIR (film): 2958 (s), 2931 (s), 2872 (m), 1770 (w), 1729 (s), 1645 (m), 1535 (m), 1466 (w), 1379 (w), 1103 (w); HRMS (EI): m/z [MH$^+$] calcd for $C_{16}H_{25}O_2$ 249.1855 found 249.1848.

6.7 Nickel catalyzed cycloadditions

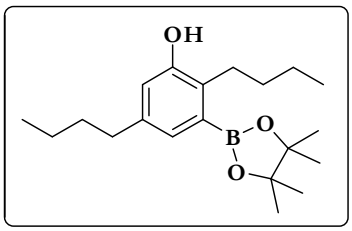
General procedure for the cycloaddition reactions



A flame dried Schlenk tube was charged with cyclobutenone (1 eq) and alkynylboronate (2 eq) in anhydrous diethyl ether (1 mL) under an argon atmosphere. The mixture was cooled to 0 °C before addition of $Ni(COD)_2$ (5 mol%). The mixture was stirred at 0 °C for 1.5 h and another portion of $Ni(COD)_2$ (5 mol%) was added. The mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was filtered through a pad of silica gel and the volatiles removed *in vacuo*. The crude mixture was purified by flash chromatography over silica gel.

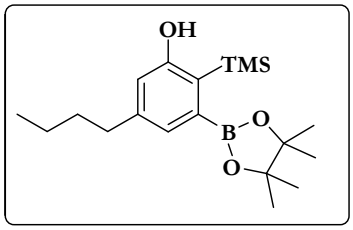
Important information to assure optimal reproducibility: *$Ni(COD)_2$ is extremely air sensitive and needs to be handled under an argon atmosphere (not necessarily in a glovebox). Once opened to air, a convenient way to store the catalyst is to flush the bottle/vial periodically with argon balloons (the active catalyst appears as yellow/orange cristals).*

- *Synthesis of 2,5-dibutyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **197**



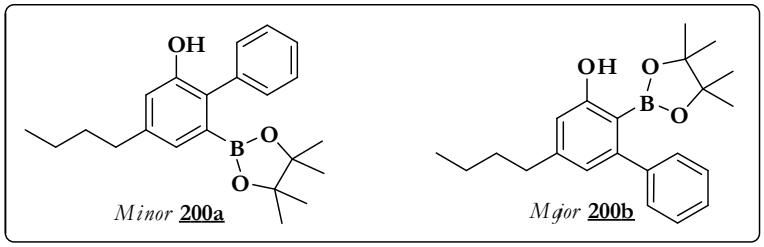
Following the general procedure, addition of $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) to a mixture of 3-*n*-butylcyclobutenone **135** (50 mg, 0.40 mmol) and *n*-butylalkynylboronate **95** (168 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound as an oil. Crystallisation from petrol provided the product **197** as a crystalline solid (114 mg, 85%, 95:5). M.pt.: 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91-0.98 (6H, m, C**H**$_3$), 1.34-1.64 (20H, m, PinC**H**$_3$, C**H**$_2$), 2.52-2.56 (2H, m, C**H**$_2$), 2.87-2.91 (2H, m, C**H**$_2$), 4.68 (1H, br, O**H**), 6.73 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.19 (1H, d, *J* = 1.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 14.1, 22.5, 23.1, 24.8, 27.9, 33.6, 33.7, 35.1, 83.4, 118.0, 128.5, 132.0, 141.1, 153.1; FTIR (film): 3412 (br), 2957 (s), 2930 (s), 2859 (m), 1608 (w), 1580 (w), 1424 (m), 1369 (s), 1144 (s); HRMS (EI): m/z [MH^+] calcd for $C_{20}H_{34}BO_3$ 333. 2601 found 333. 2595.

- *Synthesis of 5-butyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)phenol* **198**



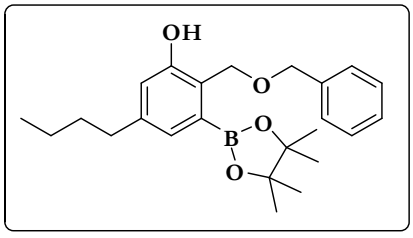
Following the general procedure, addition of $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) to a mixture of 3-*n*-butylcyclobutenone **135** (50 mg, 0.40 mmol) and trimethylsilylalkynylboronate **96** (181 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **198** as a solid (114 mg, 81%, > 98:2). M.pt.: 182-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.42 (9H, s, SiC**H**$_3$), 0.95 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.34-1.43 (14H, m, PinC**H**$_3$, C**H**$_2$), 1.55-1.64 (2H, m, C**H**$_2$), 2.53-2.57 (2H, m, C**H**$_2$), 4.96 (1H, br, O**H**), 6.60 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.14 (1H, d, *J* = 1.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 2.2, 14.3, 22.9, 25.6, 33.5, 33.6, 84.2, 117.5, 125.8, 128.4, 145.3, 165.5; FTIR (film): 3362 (b), 2953 (s), 2932 (s), 2870 (m), 1591 (w), 1567 (w), 1468 (w), 1381 (s), 1368 (s), 1136 (s) , 840 (s); HRMS (EI): m/z [MH^+] calcd for $C_{19}H_{34}BO_3Si$ 349.2370 found 349.2367.

- *Synthesis of 4-butyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-2-ol* **200a** *& 5-butyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **200b**



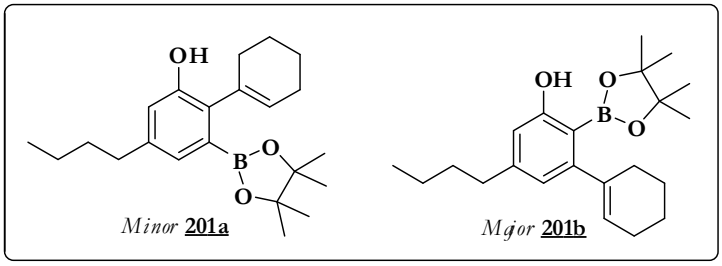
Following the general procedure, addition of $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) to a mixture of 3-*n*-butylcyclobutenone **135** (50 mg, 0.40 mmol) and phenylalkynylboronate **94** (184 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **200a** and **200b** as oils (108 mg, 76% , 33:67). *Major regioisomer* **200b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.21 (12H, s, PinC**H**$_3$), 1.33-1.46 (2H, m, C**H**$_2$), 1.57-1.69 (2H, m, C**H**$_2$), 2.58-2.64 (2H, m, C**H**$_2$), 6.72 (1H, d, *J* = 1.5 Hz, Ar**H**), 6.75 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.33 (5H, br, Ar**H**), 8.33 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 22.4, 24.5, 33.0, 35.7, 83.8, 114.3, 122.3, 126.6, 127.2, 129.3, 143.5, 148.1, 150.4, 164.1; FTIR (film): 3411 (br), 3059 (m), 3029 (m), 2958 (s), 2931 (s), 2860 (m), 1619 (s), 1558 (s), 1419 (S), 1380 (s), 1142 (s); HRMS (EI): m/z [MH^+] calcd for $C_{22}H_{30}BO_3$ 353.2288 found 353.2291; *Minor regioisomer* **200a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.13 (12H, s, PinC**H**$_3$), 1.36-1.45 (2H, m, C**H**$_2$), 1.61-1.69 (2H, m, C**H**$_2$), 2.61-2.65 (2H, m, C**H**$_2$), 4.97 (1H, s, O**H**), 6.90 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.14 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.29 (1H, s, Ar**H**), 7.34-7.47 (4H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 22.5, 24.5, 33.5, 35.3, 83.5, 117.3, 126.6, 127.7, 128.6, 130.1, 130.4, 137.0, 143.7, 152.1; FTIR (film): 3545 (br), 2977 (m), 2930 (m), 2859 (m), 1610 (w), 1558 (w), 1423 (m), 1372 (s), 1143 (s); HRMS (EI): m/z [MH^+] calcd for $C_{22}H_{30}BO_3$ 353.2288 found 353.2291.

- *Synthesis of 2-(Benzyloxymethyl)-5-butyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **199**



Following the general procedure, addition of $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) to a mixture of 3-*n*-butylcyclobutenone **135** (50 mg, 0.40 mmol) and methylene-benzyloxyalkynylboronate **99** (220 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **199** as an oil (77 mg, 48%, 93:7). ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.31 (12H, s, PinC**H**$_3$), 1.34-1.41 (2H, m, C**H**$_2$), 1.58-1.66 (2H, m, C**H**$_2$), 2.57-2.61 (2H, m, C**H**$_2$), 4.62 (2H, s, C**H**$_2$), 5.17 (2H, s, C**H**$_2$), 6.87 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.19 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.32-7.41 (5H, m, Ar**H**), 8.05 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.4, 22.9, 25.2, 33.9, 35.7, 70.2, 72.4, 84.1, 119.9, 125.3, 128.1, 128.4, 128.5, 128.9, 137.7, 144.2, 157.1; FTIR (film): 3959 (br), 2929 (s), 2859 (m), 1576 (w), 1424 (m), 1371 (s), 1143 (s); HRMS (EI): m/z [MH^+] calcd for $C_{24}H_{34}BO_4$ 397.2550 found 397.2569.

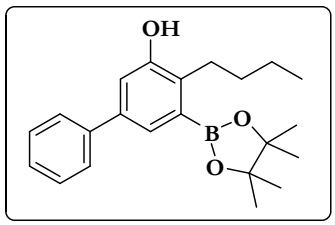
- *Synthesis of 5-butyl-2-cyclohexenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **201a** *& 5-butyl-3-cyclohexenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **201b**



Following the general procedure, addition of $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) to a mixture of 3-*n*-butylcyclobutenone **135** (50 mg, 0.40 mmol) and cyclohexenylalkynylboronate **97** (187 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **201a** and **201b** as an oils (114 mg, 79%, 15:85). *Major regioisomer* **200b** : ^1H NMR (400 MHz,

$CDCl_3$): δ 0.94 (3H, t, *J* = 7.5 Hz, C**H₃**), 1.35-1.43 (14H, m, PinC**H₃**, C**H₂**), 1.56-1.64 (2H, m, C**H₂**), 1.65-1.72 (2H, m, C**H₂**), 1.75-1.81 (2H, m, C**H₂**), 2.11-2.16 (2H, m, C**H₂**), 2.24-2.83 (2H, m, C**H₂**), 2.54-2.58 (2H, m, C**H₂**), 5.43-5.46 (1H, m, C**H**), 6.54 (1H, d, *J* = 1.5 Hz, Ar**H**), 6.63 (1H, d, *J* = 1.5 Hz, Ar**H**), 8.29 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.3, 22.5, 22.8, 23.6, 25.2, 26.0, 31.7, 33.5, 36.1, 84.0, 114.1, 120.8, 124.5, 141.5, 148.6, 154.2, 164.4; FTIR (film): 3414 (br), 2929 (s), 2858 (m), 1616 (s), 1557 (s), 1422 (m), 1380 (s), 1142 (s); HRMS (EI): m/z [MH^+] calcd for $C_{22}H_{34}BO_3$ 357.2601 found 357.2589; *Minor regioisomer* **200a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.5 Hz, C**H₃**), 1.27-1.45 (14H, m, PinC**H₃**, C**H₂**), 1.55-1.80 (6H, m, C**H₂**), 2.19-2.23 (4H, m, C**H₂**), 2.53-2.60 (2H, m, C**H₂**), 5.54 (1H, bs, O**H**), 5.70-5.71 (1H, m, C**H**), 6.86 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.14 (1H, d, *J* = 1.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 22.0, 22.5, 23.1, 24.8, 25.6, 31.0, 33.5, 35.3, 83.4, 117.1, 127.3, 128.2, 133.2, 135.9, 142.6, 151.5; FTIR (film): 3421 (br), 2930 (s), 2858 (m), 1558 (s), 1424 (m), 1372 (s), 1145 (s); HRMS (EI): m/z [MH^+] calcd for $C_{22}H_{34}BO_3$ 357.2601 found 357.2589.

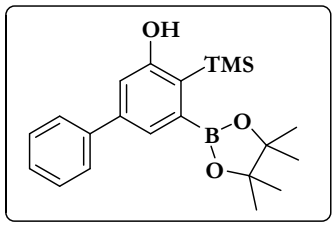
- *Synthesis of 4-butyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **206**



Following the general procedure, addition of $Ni(COD)_2$ (10 mg, 0.04 mmol, 10 mol%) to a mixture of 3-phenylcyclobutenone **138** (50 mg, 0.69 mmol) and *n*-butylalkynylboronate **95** (145 mg, 0.80 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **206** as an oil (66 mg, 54%, 87:13). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (3H, t, *J* = 7.5 Hz, C**H₃**), 1.39 (12H, s, PinC**H₃**), 1.44-1.53 (2H, m, C**H₂**), 1.54-1.63 (2H, m, C**H₂**), 2.96-

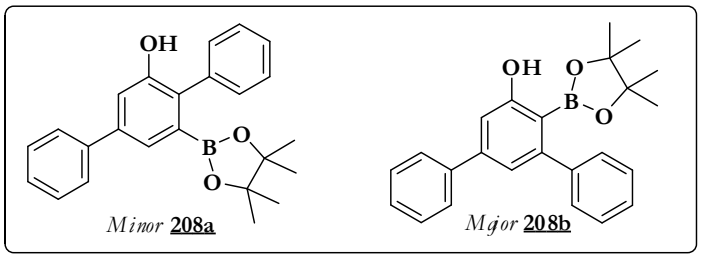
3.00 (2H, m, C**H**$_2$), 4.78 (1H, s, O**H**); 7.13 (1H, d, J = 2.0 Hz, Ar**H**), 7.32-7.36 (1H, m, Ar**H**), 7.41-7.46 (2H, m, Ar**H**), 7.60-7.63 (3H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.4, 23.5, 25.7, 28.4, 34.0, 84.0, 116.9, 127.3, 127.4, 127.7, 129.0, 134.5, 139.8, 141.2, 153.9; FTIR (film): 3395 (br), 2957 (s), 2931 (s), 2871 (m), 1605 (w), 1570 (w), 1403 (m), 1369 (s), 1142 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{22}H_{30}BO_3$ 353.2288 found 353.2298.

- *Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trimethylsilyl)biphenyl-3-ol* **<u>207</u>**



Following the general procedure, addition of Ni(COD)$_2$ (10 mg, 0.04 mmol, 10 mol%) to a mixture of 3-phenylcyclobutenone **<u>138</u>** (50 mg, 0.35 mmol) and trimethylsilylalkynylboronate **<u>96</u>** (156 mg, 0.69 mmol) in Et$_2$O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **<u>207</u>** as a solid (96 mg, 75%, > 98:2). M.pt.: 186-188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.45 (9H, s, SiC**H$_3$**), 1.39 (12H, s, PinC**H$_3$**), 5.15 (1H, bs, O**H**), 6.97 (1H, d, J = 1.5 Hz, Ar**H**), 7.34-7.38 (1H, m, Ar**H**), 7.42-7.46 (2H, m, Ar**H**), 7.52-7.53 (1H, m, Ar**H**), 7.58-7.60 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 0.0, 23.4, 82.2, 113.8, 124.7, 125.4, 125.7, 126.0, 126.9, 138.8, 141.0, 159.2; FTIR (film): 3385 (br), 2978 (m), 1653 (w), 1589 (w), 1471 (m), 1374 (s), 1142 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{21}H_{30}BO_3Si$ 369.2057 found 369.2050.

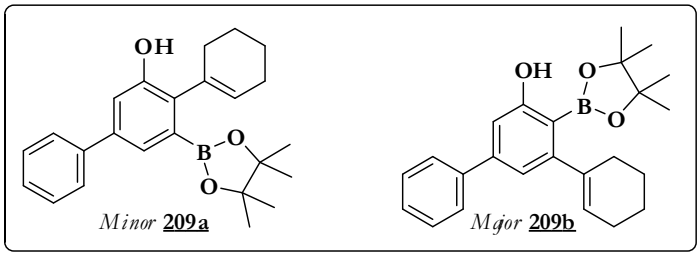
- *Synthesis of 4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **208a** *&* *5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **208b**



Minor **208a** *Major* **208b**

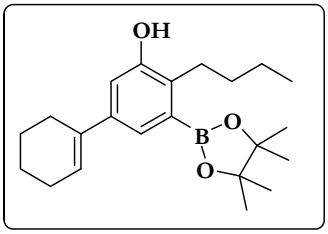
Following the general procedure, addition of $Ni(COD)_2$ (10 mg, 0.04 mmol, 10 mol%) to a mixture of 3-phenylcyclobutenone **138** (50 mg, 0.35 mmol) and phenylalkynylboronate **94** (158.2 mg, 0.69 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **208a** and **208b** as oils (80 mg, 62%,44:56). *Major regioisomer* **208b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (12H, s, PinC**H**$_3$), 7.15 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.17 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.35-7.40 (6H, m, Ar**H**), 7.43-7.47 (2H, m, Ar**H**), 7.66-7.69 (2H, m, Ar**H**), 8.45 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5, 84.0, 112.9, 120.7, 126.8, 127.2, 127.3, 127.8, 128.7, 129.3, 140.4, 143.3, 145.3, 151.0, 164.4; FTIR (film): 3397 (br), 3030 (w), 2979 (m), 1616 (s), 1544 (s), 1415 (m), 1372 (s), 1142 (s); HRMS (EI): m/z [MH^+] calcd for $C_{24}H_{26}BO_3$ 373.1975 found 373.1975; *Minor regioisomer* **208a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (12H, s, PinC**H**$_3$), 5.12 (1H, s, O**H**), 7.31 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.33-7.51 (8H, m, Ar**H**), 7.57 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.68-7.70 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.9, 84.0, 116.4, 125.7, 127.6, 127.8, 128.3, 129.0, 129.1, 130.7, 132.2, 137.1, 141.1, 142.2, 153.0; FTIR (film): 3411 (br), 2978 (m), 2859 (w), 1601 (w), 1412 (m), 1372 (s), 1141 (s); HRMS (EI): m/z [MH^+] calcd for $C_{24}H_{26}BO_3$ 373.1975 found 373.1975.

- *Synthesis of 4-cyclohexenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) biphenyl-3-ol* **209a** *& 5-cyclohexenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **209b**



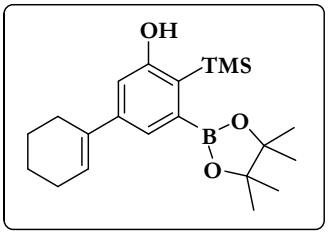
Following the general procedure, addition of $Ni(COD)_2$ (10 mg, 0.04 mmol, 10 mol%) to a mixture of 3-phenylcyclobutenone **138** (50 mg, 0.35 mmol) and cyclohexenylalkynylboronate **97** (161 mg, 0.69 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **209a** and **209b** as oils (84 mg, 64%, 33:67). *Major regioisomer* **209b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (12H, s, PinC**H**$_3$), 1.68-1.74 (2H, m, C**H**$_2$), 1.78-1.84 (2H, m, C**H**$_2$), 2.14-2.19 (2H, m, C**H**$_2$), 2.30-2.32 (2H, m, C**H**$_2$), 5.51-5.52 (1H, m, C**H**), 6.97 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.05 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.35-7.39 (1H, m, Ar**H**), 7.43-7.47 (2H, m, Ar**H**), 7.64-7.66 (2H, m, Ar**H**), 8.41 (1H, s, O**H**);^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.1, 23.2, 24.8, 25.6, 31.3, 83.4, 112.3, 118.9, 124.5, 127.2, 127.7, 128.6, 140.6, 141.0, 145.3, 154.3, 164.3; FTIR (film): 3406 (br), 2978 (m), 2929 (s), 1616 (s), 1544 (s), 1416 (m), 1372 (s), 1142 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{24}H_{30}BO_3$ 377.2288 found 377.2291; *Minor regioisomer* **209a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (12H, s, PinC**H**$_3$), 1.74-1.79 (2H, m, C**H**$_2$), 1.82-1.87 (2H, m, C**H**$_2$), 2.22-2.26 (4H, m, C**H**$_2$), 5.65 (1H, bs, O**H**), 5.77-5.79 (1H, m, C**H**), 7.27 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.32-7.36 (1H, m, Ar**H**), 7.41-7.45 (2H, m, Ar**H**), 7.57 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.62-7.65 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.9, 23.0, 24.8, 25.6, 30.9, 83.6, 115.8, 126.0, 127.0, 127.1, 128.5, 128.6, 134.8, 135.6, 140.7, 140.8, 152.0; FTIR (film): 3486 (br), 2977 (m), 2929 (m), 1558 (w), 1372 (s), 1142 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{24}H_{30}BO_3$ 377.2288 found 377.2291.

- *Synthesis of 2-butyl-5-cyclohexenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **202**



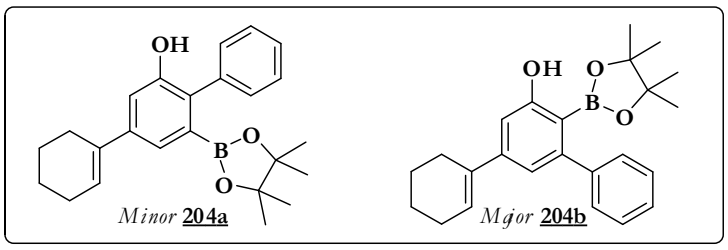
Following the general procedure, addition of $Ni(COD)_2$ (9 mg, 0.03 mmol, 10 mol%) to a mixture of 3-cyclohexenylcyclobutenone **142** (50 mg, 0.34 mmol) and *n*-butylalkynylboronate **95** (141 mg, 0.67 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **202** as a solid (111 mg, 92%, 96:4). M.pt.: 107-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.37 (12H, s, PinC**H**$_3$), 1.39-1.47 (4H, m, C**H**$_2$), 1.65-1.69 (2H, m, C**H**$_2$), 1.75-1.81 (2H, m, C**H**$_2$), 2.19-2.24 (2H, m, C**H**$_2$), 2.38-2.43 (2H, m, C**H**$_2$), 2.83-2.89 (2H, m, C**H**$_2$), 4.64 (1H, bs, O**H**), 6.10-6.13 (1H, m, C**H**), 6.91 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.42 (1H, d, *J* = 2.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.4, 22.6, 23.4, 23.5, 25.3, 26.2, 27.8, 28.3, 34.0, 83.8, 115.0, 124.7, 125.6, 133.6, 136.5, 141.5, 153.5; FTIR (film): 3397 (br), 2930 (s), 2858 (m), 1602 (w), 1573 (w), 1412 (m), 1372 (s), 1143 (s); HRMS (EI): m/z [MH^+] calcd for $C_{22}H_{34}BO_3$ 357.2601 found 357.2610.

- *Synthesis of 5-cyclohexenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trimethylsilyl)phenol* **203**



Following the general procedure, addition of $Ni(COD)_2$ (9 mg, 0.03 mmol, 10 mol%) to a mixture of 3-cyclohexenylcyclobutenone **142** (50 mg, 0.34 mmol) and trimethylsilylalkynylboronate **96** (152 mg, 0.67 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound 203 as a solid (74 mg, 59%, > 96:4). M.pt.: 158-160°C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.41 (9H, s, SiC**H**$_3$), 1.38 (12H, s, PinC**H**$_3$), 1.64-1.69 (2H, m, C**H**$_2$), 1.74-1.80 (2H, m, C**H**$_2$), 2.17-2.23 (2H, m, C**H**$_2$), 2.36-2.39 (2H, m, C**H**$_2$), 5.01-5.02 (1H, m, O**H**), 6.12-6.14 (1H, m, C**H**), 6.74 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.33 (1H, d, *J* = 1.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 0.0, 20.3, 21.2, 23.3, 24.0, 25.4, 82.0, 111.9, 122.7, 123.5, 124.9, 134.2, 142.6, 158.8; FTIR (film): 3396 (br), 2978 (m), 2930 (m), 1586 (s), 1418 (m), 1381 (s), 1381 (s), 1143 (s); HRMS (EI): m/z [MH^+] calcd for $C_{21}H_{34}BO_3Si$ 373.2370 found 373.2377.

- *Synthesis of 4-cyclohexenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) biphenyl-2-ol* **204a** *& 5-cyclohexenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **204b**

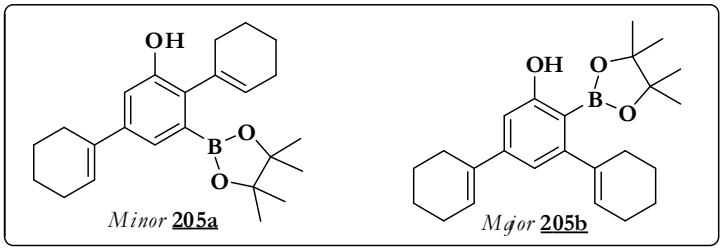


Minor **204a** *Major* **204b**

Following the general procedure, addition of $Ni(COD)_2$ (9 mg, 0.03 mmol, 10 mol%) to a mixture of 3-cyclohexenylcyclobutenone **142** (50 mg, 0.34 mmol) and phenylalkynylboronate **94** (154 mg, 0.67 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **204a** and **204b** as oils (80 mg, 63%, 44:56). *Major regioisomer* **204b**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (12H, s, PinC**H**$_3$), 1.64-1.70 (2H, m, C**H**$_2$), 1.75-1.81 (2H, m, C**H**$_2$), 2.20-2.25 (2H, m, C**H**$_2$), 2.40-2.44 (2H, m, C**H**$_2$), 6.25-6.27 (1H, s, C**H**),

6.92 (2H, s, Ar**H**), 7.33 (5H, bs, Ar**H**), 8.33 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.1, 23.0, 24.5, 25.9, 27.1, 83.8, 110.8, 118.7, 126.3, 126.6, 127.2, 129.3, 136.1, 143.6, 146.8, 150.3, 164.1; FTIR (film): 3406 (br), 2930 (s), 2861 (w), 1615 (s), 1541 (m), 1374 (s), 1142 (s); HRMS (EI): m/z [MH^+] calcd for $C_{24}H_{30}BO_3$ 377.2288 found 377.2276; *Minor regioisomer* **204a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (12H, s, PinC**H$_3$**), 1.64-1.71 (2H, m, C**H$_2$**), 1.76-1.84 (2H, m, C**H$_2$**), 2.20-2.27 (2H, m, C**H$_2$**), 2.43-2.47 (2H, m, C**H$_2$**), 5.00 (1H, s, O**H**), 6.19-6.21 (1H, m, C**H**), 7.08 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.35-7.37 (3H, m, Ar**H**), 7.45-7.47 (3H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.2, 23.1, 24.5, 25.9, 27.4, 83.5, 114.0, 123.3, 125.1, 127.7, 128.6, 129.0, 130.3, 131.3, 136.2, 137.0, 152.1; FTIR (film): 3544 (br), 2979 (m), 2930 (s), 1604 (w), 1558 (w), 1411 (m), 1373 (s), 1142 (s); HRMS (EI): m/z [MH^+] calcd for $C_{24}H_{30}BO_3$ 377.2288 found 377.2276.

- *Synthesis of 2,5-dicyclohexenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenol* **205a** *& 3,5-dicyclohexenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol* **205b**

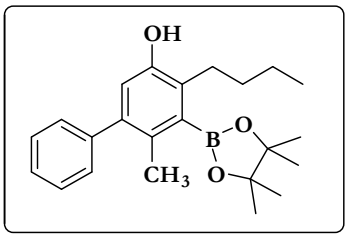


Minor **205a** *Major* **205b**

Following the general procedure, addition of $Ni(COD)_2$ (9 mg, 0.03 mmol, 10 mol%) to a mixture of 3-cyclohexenylcyclobutenone **142** (50 mg, 0.34 mmol) and cyclohexenylalkynylboronate **97** (157 mg, 0.67 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **205a** and **205b** as oils (73 mg, 61%, 31:69). *Major regioisomer* **205b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (12H, s, PinC**H$_3$**), 1.64-1.71 (4H, m, C**H$_2$**), 1.74-1.80 (4H, m, C**H$_2$**), 2.11-2.15 (2H, m, C**H$_2$**), 2.19-2.26 (4H, m, C**H$_2$**), 2.38-2.42 (2H, m,

C**H**$_2$), 5.43-5.46 (1H, m, C**H**), 6.21-6.24 (1H, m, C**H**), 6.74 (1H, d, *J* = 1.5 Hz, Ar**H**), 6.79 (1H, d, *J* = 1.5 Hz, Ar**H**), 8.30 (1H, s, O**H**) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.0, 22.1, 23.0, 23.2, 24.7, 25.6, 25.9, 27.1, 31.3, 83.6, 110.2, 116.8, 124.1, 125.9, 136.3, 141.2, 147.0, 153.6, 164.0; FTIR (film): 3420 (br), 2970 (m), 2927 (s), 1613 (s), 1542 (s), 1418 (m), 1374 (s), 1142 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{24}H_{34}BO_3$ 381.2601 found 381.2599; *Minor regioisomer* **205a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (12H, s, PinC**H**$_3$), 1.64-1.69 (2H, m, C**H**$_2$), 1.72-1.84 (6H, m, C**H**$_2$), 2.21-2.22 (6H, m, C**H**$_2$), 2.40-2.44 (2H, m, C**H**$_2$), 5.67 (1H, bs, O**H**), 5.72-5.73 (1H, m, C**H**), 6.14-6.16 (1H, m, C**H**), 7.05 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.37 (1H, d, *J* = 2.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.4, 22.6, 23.4, 23.5, 25.2, 26.0, 26.3, 27.8, 31.4, 83.8, 114.2, 124.4, 125.2, 128.6, 134.4, 136.2, 136.6, 142.8, 151.9; FTIR (film): 3416 (br), 2978 (m), 2933 (s), 2860 (s), 1693 (w), 1589 (m), 1419 (s), 1380 (s), 1144 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{24}H_{34}BO_3$ 381.2601 found 381.2599.

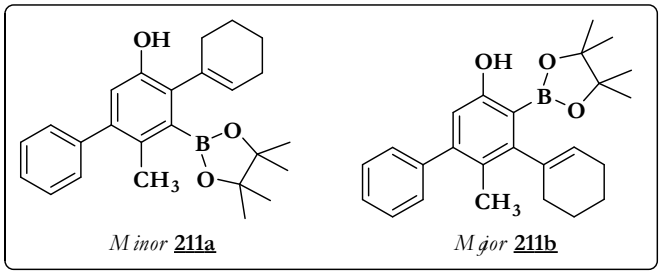
- *Synthesis of 4-butyl-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-ol* **210**



Following the general procedure, addition of $Ni(COD)_2$ (5 mg, 0.02 mmol, 10 mol%) to a mixture of 3-methyl-4-phenylcyclobutenone[24] **155** (30 mg, 0.19 mmol) and *n*-butylalkynylboronate **95** (79 mg, 0.38 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compound **210** as a solid (46.5 mg, 68%, >98/2). M.pt.: 152-154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.41-1.50 (14H, s, PinC**H**$_3$, C**H**$_2$), 1.59-1.67 (2H, m, C**H**$_2$), 2.21 (3H, s, C**H**$_3$), 2.66-2.70 (2H, m, C**H**$_2$), 4.56 (1H, s, O**H**), 6.64

(1H, s, Ar**H**), 7.24-7.28 (2H, m, Ar**H**), 7.30-7.34 (1H, m, Ar**H**), 7.37-7.41 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 19.3, 23.2, 25.1, 30.3, 33.3, 84.0, 117.7, 126.5, 127.9, 129.3, 130.2, 131.1, 140.7, 142.1, 150.7; FTIR (film): 3392 (br), 2956 (s), 2926 (s), 2856(m), 1581 (w), 1544 (s), 1419 (m), 1365 (s), 1140 (s); HRMS (EI): m/z [MH^+] calcd for $C_{23}H_{32}BO_3$ 367.2455 found 367.2445.

- *Synthesis of 4-cyclohexenyl-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) biphenyl-3-ol* **211a** *& 5-cyclohexenyl-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) biphenyl-3-ol* **211b**

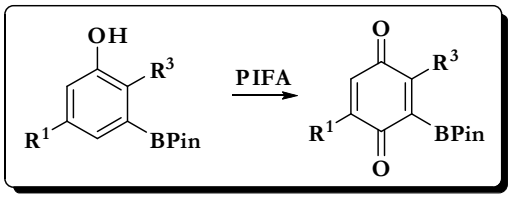


Minor **211a** *Major* **211b**

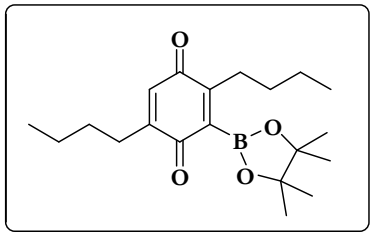
Following the general procedure, addition of $Ni(COD)_2$ (5 mg, 0.02 mmol, 10 mol%) to a mixture of 3-methyl-4-phenylcyclobutenone[24] **155** (30 mg, 0.19 mmol) and cyclohexenylalkynylboronate 97 (88 mg, 0.38 mmol) in Et_2O furnished the crude product. Purification by flash chromatography over silica gel, eluting with pentane/EtOAc (95/5) provided the desired compounds **211a** and **211b** as oils (42 mg, 57%, 80:20). *Major regioisomer* **211b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (12H, s, PinC**H$_3$**), 1.59-1.89 (4H, br, C**H$_2$**), 2.05 (3H, m, C**H$_3$**), 2.07-2.33 (4H, m, C**H$_2$**), 5.37-5.38 (1H, m, C**H**), 6.73 (1H, br, Ar**H**), 7.28 (1H, s, Ar**H**), 7.32-7.37 (2H, m, Ar**H**), 7.40-7.44 (2H, m, Ar**H**), 8.30 (1H, bs, O**H)**; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.4, 22.0, 23.0, 24.6, 25.0, 25.6, 30.3 83.6, 115.4, 123.9, 124.3, 126.8, 127.9, 129.0, 140.3, 142.4, 147.1, 152.7, 161.4; FTIR (film): 3405 (br), 2978 (m), 2928 (s), 2855 (w), 2832(w), 1600 (s), 1547 (m), 1402 (s), 1372 (s), 1140 (s); HRMS (EI): m/z [MH^+] calcd for $C_{25}H_{32}BO_3$ 391.2445 found 391.2462; *Minor regioisomer* **211a**: ^{1}H NMR (400

MHz, $CDCl_3$): δ 1.37 (12H, s, PinC**H**$_3$), 1.70-1.76 (2H, m, C**H**$_2$), 1.79-1.84 (2H, m, C**H**$_2$), 2.19-2.21 (5H, m, C**H**$_2$, C**H**$_3$), 2.31-2.33 (2H, m, C**H**$_2$), 4.97 (1H, s, O**H**) 5.83-5.85 (1H, m, C**H**), 6.79 (1H, s, Ar**H**), 7.28-7.30 (2H, m, Ar**H**), 7.31-7.34 (1H, m, Ar**H**), 7.38-7.42 (2H, m, Ar**H**);^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.2, 22.9, 22.8, 25.1, 25.4, 29.9, 83.7, 117.2, 126.6, 127.9, 129.3, 129.6, 129.8, 133.2, 136.1, 142.0, 142.2, 149.3; FTIR (film): 3404 (br), 2980 (m), 2927 (s), 2862 (m), 1594 (s), 1544 (s), 1415 (m), 1369 (s), 1136 (s); HRMS (EI m/z [MH^+] calcd for $C_{25}H_{32}BO_3$ 391.2445 found 391.2462.

6.8 Synthesis of quinone boronic esters



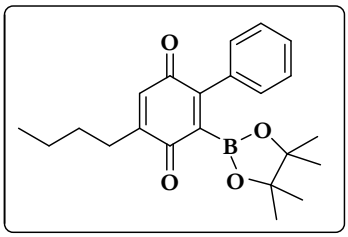
- *Synthesis of 2,5-dibutyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-2,5-diene-1,4-dione* **226**



Phenol **197** (15 mg, 0.05 mmol) was dissolved in a mixture of acetonitrile/water/dichloromethane (2/1/1, 1 mL) and cooled to 0 °C. A solution of PIFA (43 mg, 0.09 mmol) in acetonitrile/water (2/1, 1 mL) was added to the mixture at 0 °C. The reaction reached full conversion within 2 hours. The mixture was extracted with dichloromethane. The resulting organic layer was washed with $NaHCO_{3(aq)}$, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by flash chromatography over

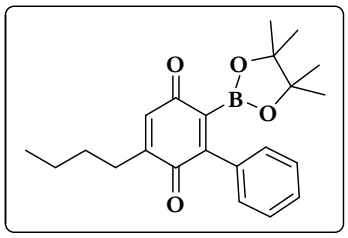
silica gel eluting with pentane/Et_2O (95/5) provided the desired compound **226** as an oil (16 mg, 100%).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92-0.96 (6H, m, C**H**$_3$), 1.33-1.43 (16H, m, PinC**H**$_3$, C**H**$_2$), 1.44-1.53 (4H, m, C**H**$_2$), 2.37-2.46 (4H, m, C**H**$_2$), 6.52 (1H, s, C**H**) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.2, 14.3, 22.8, 23.5, 25.2, 28.9, 30.1, 30.2, 32.7, 85.3, 133.0, 150.1, 154.2, 187.8, 191.5; FTIR (film): 2959 (m), 2930 (m), 1645 (s), 1374(s), 1140 (s); HRMS (EI m/z [MH^+] calcd for $C_{20}H_{32}BO_4$ 346.2430 found 346.2428.

- *Synthesis of 5-butyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-2,5-diene-1,4-dione* **227**



Phenol **200a** (15 mg, 0.04 mmol) was dissolved in a mixture of acetonitrile/water (2/1, 1 mL) and cooled to 0 °C. A solution of PIFA (55 mg, 0.13 mmol) in acetonitrile/water (2/1, 1 mL) was added to the mixture at 0 °C. The reaction was stirred overnight. The mixture was extracted with dichloromethane. The resulting organic layer was washed with $NaHCO_{3(aq)}$, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by flash chromatography over silica gel eluting with pentane/Et_2O (95/5) provided the desired compound **227** as an oil (11 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 7.5 Hz, C**H**$_3$), 1.18 (12H, m, PinC**H**$_3$), 1.35-1.44 (2H, m, C**H**$_2$), 148-1.57 (2H, m, C**H**$_2$), 2.46-2.50 (2H, m, C**H**$_2$), 6.63 (1H, s, C**H**), 7.36-7.42 (5H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 22.4, 24.4, 28.6, 29.8, 85.0, 128.0, 129.3, 129.6, 132.5, 133.7, 149.9, 150.5, 186.6, 191.0; FTIR (film): 2978 (s), 2956 (s), 1645 (s), 1374 (m), 1140 (s); HRMS (EI m/z [MH^+] calcd for $C_{22}H_{28}BO_4$ 367.2081 found 367.2093.

- *Synthesis of 5-butyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexa-2,5-diene-1,4-dione* **228**



Phenol **200b** (15 mg, 0.04 mmol) was dissolved in a mixture of acetonitrile/water (2/1, 1 mL) and cooled to 0 °C. A solution of PIFA (43 mg, 0.09 mmol) in acetonitrile/water (2/1, 1 mL) was added to the mixture at -10 °C to 5 °C. The reaction reached full conversion within 2 hours. The mixture was extracted with dichloromethane. The resulting organic layer was washed with $NaHCO_{3(aq)}$, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by flash chromatography over silica gel eluting with pentane/Et_2O (95/5) provided the desired compound **228** as an oil (8 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.21 (12H, m, PinC**H**$_3$), 1.40-1.47 (2H, m, C**H**$_2$), 1.52-1.60 (2H, m, C**H**$_2$), 2.46-2.50 (2H, m, C**H**$_2$), 6.65 (1H, s, C**H**), 7.38-7.43 (5H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 22.4, 24.5, 29.1, 29.7, 84.9, 127.9, 129.2, 129.6, 132.8, 134.2, 149.6, 151.0, 186.4, 190.7; FTIR (film): 2960 (m), 2933 (m), 1708 (s), 1654 (s), 1645 (s), 1450 (m), 1381 (m), 1175 (s); HRMS (EI m/z [MH^+] calcd for $C_{22}H_{28}BO_4$ 367.2081 found 367.2099.

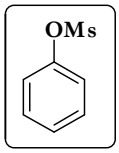
6.9 Synthesis of aryl acceptors

General procedure for the synthesis of aryl mesylates

A solution of phenol (1 eq) in dichloromethane was cooled to 0 °C. Triethylamine (3 eq), *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (2.5 eq) were added sequentially. The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was separated between dichloromethane and water. The organic layer was then

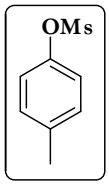
washed with a saturated solution of sodium bicarbonate, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography afforded the desired mesylated compound.

- *Synthesis of phenyl methanesulfonate* **214**



Following the general procedure phenol (1.0 g, 11 mmol) was dissolved in dichloromethane (50 mL). Addition of triethylamine (4.5 mL, 32 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (2.1 mL, 27 mmol) afforded compound **214** as a colourless solid (1.8 g, 100%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[24]. M.pt.: 62-65 °C. {*lit.*[25] 62-63 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16 (3H, s, C**H**$_3$), 7.28-7.37 (3H, m, Ar**H**), 7.42-7.47 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 37.4, 122.0, 127.4, 130.0, 149.3.

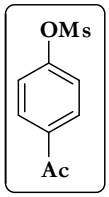
- *Synthesis of p-tolyl methanesulfonate* **217**



Following the general procedure 4-methylphenol (1.0 g, 9 mmol) was dissolved in dichloromethane (50 mL). Addition of triethylamine (3.9 mL, 28 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (1.8 mL, 23 mmol) afforded compound **217** as a colourless solid (1.7 g, 97%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[25]. M.pt.: 47-49 °C. {*lit.*[24] 46-48 °C}. ^{1}H NMR (400

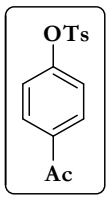
MHz, $CDCl_3$): δ 2.37 (3H, s, C**H**$_3$), 3.11 (3H, s, C**H**$_3$), 7.17-7.23 (4H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.8, 37.1, 121.7, 130.5, 137.4, 147.2.

- *Synthesis of 4-acetylphenyl methanesulfonate* **219**



Following the general procedure 4-acetylphenol (500 mg, 4 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.6 mL, 11 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (713 μL, 9 mmol) afforded compound **219** as a colourless solid (719 mg, 91%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[24]. M.pt.: 69-71 °C. {*lit.*[25] 71-72 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (3H, s, C**H**$_3$), 3.22 (3H, s, C**H**$_3$), 7.41 (2H, d, J = 9.0 Hz, Ar**H**), 8.05 (2H, d, J = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.6, 37.9, 122.1, 130.4, 136.0, 152.4, 196.4.

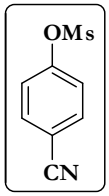
- *Synthesis of 4-acetylphenyl 4-methylbenzenesulfonate* **221**



Following the general procedure 4-acetylphenol (500 mg, 4 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.6 mL, 11.02 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and tosyl chloride (1.8 g, 9 mmol) afforded compound **221** as a colourless solid (761 mg, 71%). The product showed satisfactory spectroscopic and analytical data in

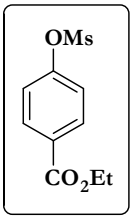
comparison to the literature[25]. M.pt.: 67-70 °C. {*lit.*[26] 66-68 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (3H, s, C**H**$_3$), 2.59 (3H, s, C**H**$_3$), 7.11 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.73 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.91 (2H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.7, 26.6, 122.5, 128.5, 129.9, 130.0, 132.2, 135.7, 145.8, 153.0, 196.6.

- *Synthesis of 4-cyanophenyl methanesulfonate* **223**



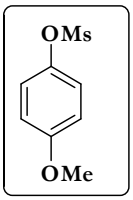
Following the general procedure 4-cyanophenol (500 mg, 4 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.8 mL, 13 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (815 μL, 11 mmol) afforded compound **223** as a colourless solid (604 mg, 73%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[25]. M.pt.: 89-92 °C. {*lit.*[24] 89-90 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (3H, s, C**H**$_3$), 7.44 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.76 (2H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.2, 111.5, 117.6, 123.0, 134.2, 151.9.

- *Synthesis of ethyl 4-(methyl sulfonyloxy) benzoate* **224**



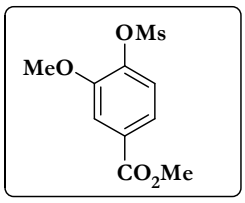
Following the general procedure ethyl 4-hydroxybenzoate (500 mg, 3 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.3 mL, 9 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (585 μL, 8 mmol) afforded compound **224** as a colourless solid (544 mg, 74%). M.pt.: 36-38 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 3.20 (3H, s, C**H**$_3$), 4.38-4.44 (2H, m, C**H**$_2$), 7.37 (2H, d, *J* = 9.0 Hz, Ar**H**), 8.13 (2H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.3, 37.8, 61.3, 121.8, 129.6, 131.6, 152.4, 165.5; FTIR (film): 3430 (br), 2953 (w), 1721 (s), 1642 (m), 1412 (m), 1370 (s), 1159 (s); HRMS (EI): m/z [MH^+] calcd for $C_{10}H_{13}O_5S$ 245.0484 found 245.0492.

- *Synthesis of 4-methoxyphenyl methanesulfonate* **222**



Following the general procedure 4-methoxyanisol (500 mg, 4 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.7 mL, 12 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (782 μL, 10 mmol) afforded compound **222** as a colourless solid (554 mg, 68%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[24]. M.pt.: 76-79 °C. {*lit.*[24] 78-80 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (3H, s, C**H**$_3$), 3.83 (3H, s, C**H**$_3$), 6.93 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.23 (2H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 37.0, 55.7, 114.9, 123.0, 142.7, 158.6.

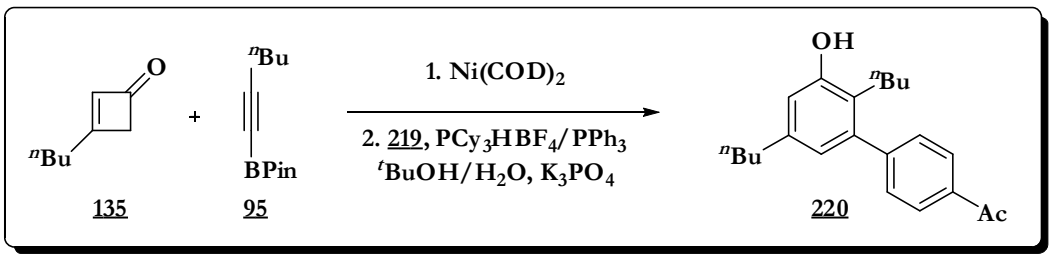
- *Synthesis of methyl 3-methoxy-4-(methyl sulfonyloxy) benzoate* **225**



Following the general procedure ethyl vanillate (500 mg, 3 mmol) was dissolved in dichloromethane (25 mL). Addition of triethylamine (1.2 mL, 8 mmol) and *N*,*N*-dimethylaminopyridine (few crystals) and methanesulfonyl chloride (533 μL, 7 mmol) afforded compound **225** as a colourless solid (429 mg, 60%). M.pt.: 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (3H, s, C**H**$_3$), 3.95 (3H, s, C**H**$_3$), 3.97 (3H, s, C**H**$_3$), 7.38 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.68-7.71 (2H, m, Ar**H**), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 37.7, 52.4, 56.3, 114.0, 122.8, 124.4, 130.1, 141.7, 151.4, 165.9; FTIR (film): 3430 (br), 2953 (w), 1721 (s), 1642 (m), 1412 (m), 1370 (s), 1159 (s); FTIR (film): 3422 (br), 3030 (w), 2986 (m), 2941 (m), 1718 (s), 1603 (s), 1500 (m), 1413 (m), 1370 (s), 1154 (s); HRMS (EI): m/z [MH$^+$] calcd for $C_{10}H_{12}O_6S$ 260.0355 found 260.0347.

6.10 "One-Pot" Cycloaddition/Cross-coupling

- *Synthesis of 1-(2',5'-dibutyl-3'-hydroxybiphenyl-4,4')ethanone* **220**

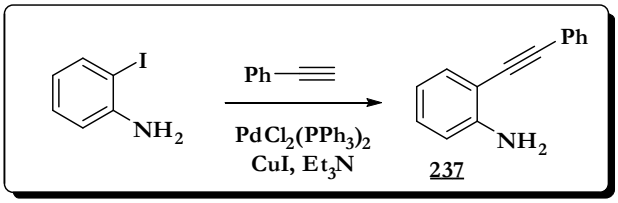


A flame dried Schlenk tube was charged with 3-*n*-butylcyclobutenone **135** (20 mg, 0.16 mmol), *n*-butylalkynylboronate **95** (67 mg, 0.32 mmol) and anhydrous diethyl ether (0.5 mL) under an argon atmosphere. The mixture was cooled to 0 °C before addition of $Ni(COD)_2$ (9 mg, 20 mol%). The mixture was stirred

at 0 °C for 45 min. Mesylate **219** (35 mg, 0.16 mmol) was added followed by sequential addition of PCy_3HBF_4 (30 mg, 0.08 mmol), PPh_3 (21 mg, 0.08 mmol), K_3PO_4 (103 mg, 0.48 mmol) and $^tBuOH/H_2O$ (1/1, 1.6 mL). The mixture was stirred overnight at 110 °C. The reaction mixture was cooled to room temperature, extracted with EtOAc, washed with brine and dried over $MgSO_4$. The volatiles were removed *in vacuo*. The crude mixture was purified by flash chromatography over silica gel eluting petrol/EtOAc (90/10) providing the desired compound as an oil. Recrystallisation from petrol gave the desired compound **220** as a solid (27 mg, 51%). M.pt.: 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 0.94 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.18-1.28 (2H, m, C**H**$_2$), 1.34-1.50 (4H, m, C**H**$_2$), 1.57-1.65 (2H, m, C**H**$_2$), 2.50-2.59 (4H, m, C**H**$_2$), 2.69 (3H, s, C**H**$_3$), 5.20 (1H, br, O**H**), 6.62 (1H, d, *J* = 1.0 Hz, Ar**H**), 6. 70 (1H, d, *J* =1.0 Hz, Ar**H**), 7.43 (2H, d, *J* = 8.5 Hz, Ar**H**), 8.03 (2H, d, *J* = 8.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 14.0, 22.4, 22.8, 26.5, 26.7, 32.2, 33.4, 35.1, 114.9, 122.3, 123.9, 128.1, 129.5, 135.5, 141.4, 142.2, 147.4, 153.9, 198.2; FTIR (film): 3380 (b), 2957 (s), 2928 (s), 2855 (m), 1605 (s), 1582 (m), 1404 (w), 1360 (w), 1128 (s); HRMS (EI): m/z [M^+] calcd for $C_{22}H_{28}O_2$ 324.2089 found 324.2088.

6.11 Synthesis of *o*-alkynylanilines

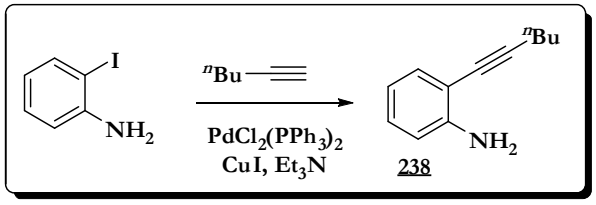
- *Synthesis of 2-(2'-phenylethynyl) aniline* **237**



2-Iodoaniline (2.0 g, 9 mmol) and triethylamine (25 mL) were introduced into a 250 mL flask. $PdCl_2(PPh_3)_2$ (320 mg, 0.5 mmol) and CuI (174 mg, 0.9 mmol) were added. The reaction mixture was stirred at room temperature for 15-20 minute before dropwise addition of phenylacetelene (5 mL, 45.6 mmol). The mixture was stirred overnight at room temperature. The mixture was filtered

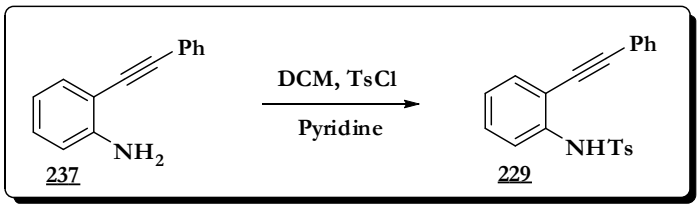
through silica gel and volatiles were evaporated *in vacuo* to give the crude product. Purification by flash chromatography over silica gel, eluting petrol/EtOAc (90/10) provided the desired compound **237** as a solid (1.2 g, 67%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[26]. M.pt.: 83-85 °C. {*lit.*[26] 85-87 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (2H, s, N**H**$_2$), 6.73-6.77 (2H, m, Ar**H**), 7.14-7.19 (1H, m, Ar**H**), 7.36-7.40 (4H, m, Ar**H**), 7.54-7.57 (2H, m, Ar**H**) ; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 85.9, 94.7, 107.9, 114.3, 118.0, 123.3, 128.2, 128.4, 129.7, 131.5, 132.2, 147.8.

- *Synthesis of 2-(hex-1'-ynyl) aniline* **238**



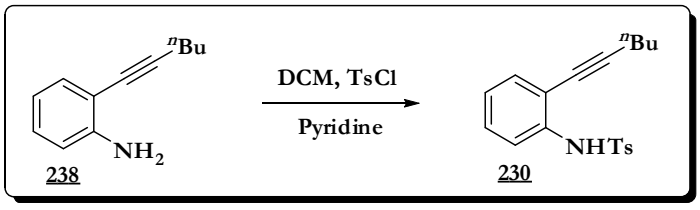
2-Iodoaniline (1.0 g, 5 mmol) and triethylamine (15 mL) were introduced into a 250 mL flask. $PdCl_2(PPh_3)_2$ (160 mg, 0.2 mmol) and CuI (87 mg, 0.5 mmol) were added. The reaction mixture was stirred at room temperature for 15-20 minute before dropwise addition of 1-hexyne (2.6 mL, 23 mmol). The mixture was stirred overnight at 60 °C. The mixture was filtered through silica gel and volatiles were evaporated *in vacuo* to give the crude product. Purification by flash chromatography over silica gel, eluting petrol/EtOAc (90/10) provided the desired compound **238** as an oil (0.5 g, 60%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[27]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.49-1.74 (4H, m, C**H**$_2$), 2.54 (2H, t, *J* = 7.0 Hz, C**H**$_2$), 4.23 (2H, s, N**H**$_2$), 6.70-6.76 (2H, m, Ar**H**), 7.11-7.18 (1H, m, Ar**H**), 7.30-7.35 (1H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 19.4, 22.2, 31.1, 77.2, 95.8, 109.0, 114.2, 117.8, 128.9, 132.1, 147.8.

- *Synthesis of 2-(2'-phenylethynyl)-N-tosylaniline* **229**



To a solution of compound **237** (200 mg, 1.0 mmol) in DCM (10 mL) was introduced TsCl (237 mg, 1.2 mmol) and pyridine (167 μL, 2.1 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography eluting petrol/EtOAc (85/15) providing the desired compound **229** as a solid (302 mg, 84%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[26]. M.pt.: 106-108 °C. {*lit.*[27] 105-106 °C}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (3H, s, C**H**$_3$), 7.07-7.11 (1H, m, Ar**H**), 7.18-7.24 (3H, m, Ar**H**), 7.30-7.34 (1H, m, Ar**H**), 7.39-7.43 (4H, m, Ar**H**), 7.48-7.51 (2H, m, Ar**H**), 7.64-7.70 (2H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5, 83.7, 96.1, 114.6, 120.3, 122.0, 124.6, 127.3, 128.6, 129.1, 129.6, 131.6, 132.1, 136.1, 137.5, 139.5, 144.0.

- *Synthesis of 2-(hex-1'-ynyl)-N-tosylaniline* **230**

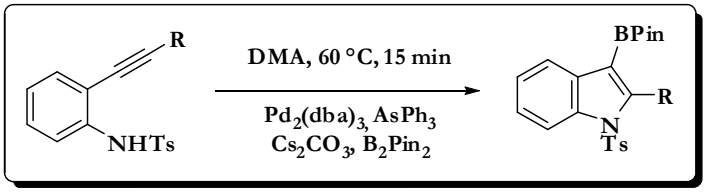


To a solution of compound **238** (500 mg, 2.9 mmol) in DCM (25 mL) was introduced TsCl (660 mg, 3.5 mmol) and pyridine (467 μL, 5.8 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography

eluting petrol/EtOAc (85/15) providing the desired compound **230** as an oil (558 mg, 59%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[27]. NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.5 Hz, C**H**$_3$), 1.44-1.53 (2H, m, C**H**$_2$), 1.56-1.65 (2H, m, C**H**$_2$), 2.38 (3H, s, C**H**$_3$), 2.44 (2H, t, *J* = 7.5 Hz, C**H**$_2$), 7.00 (1H, dd, *J* = 1.0, 7.5 Hz, Ar**H**), 7.21-7.27 (4H, m, Ar**H**), 7.58 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.68 (2H, d, *J* = 8.0 Hz, Ar**H**; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.6, 19.2, 21.5, 22.1, 30.7, 75.3, 97.9, 114.9, 119.3, 124.2, 127.2, 128.8, 129.4, 131.9, 136.2, 137.6, 143.9.

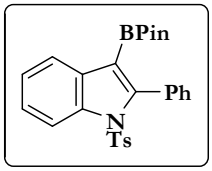
6.12 Synthesis of indole boronic ester derivatives

General procedure for the synthesis of indole boronic esters



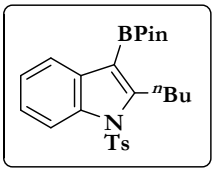
A solution of amino alkyne (1 eq) in DMA (1 mL) was treated with Cs_2CO_3 (2 eq) and 4Å MS (50 mg) and stirred at 60 °C under inert atmosphere for 10 minutes before adding Pd_2dba_3 (10 mol%), B_2Pin_2 (2 eq) and $AsPh_3$ (20 mol%). The reaction mixture was stirred under air at 60 °C for **15 minutes**. *Extra caution was required during the work up in order to reduce the protodeboronation.* Et_2O and water were added to the warm mixture. The organic layer was washed with water (2 times) – at this stage a small portion of brine was added to the aqueous layer to speed up the difficult separation of the two layers. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo* to provide the crude mixture. Purification by flash chromatography provided the desired products.

- *Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-tosyl-2-phenylindole* **231**



Following the general procedure a mixture of amino alkyne **229** (50 mg, 0.14 mmol), Cs_2CO_3 (94 mg, 0.29 mmol), 4Å MS (50 mg), Pd_2dba_3 (13 mg, 10 mol%), B_2Pin_2 (73 mg, 0.29 mmol) and $AsPh_3$ (9 mg, 0.03 mmol, 20 mol%) afforded the crude mixture. Purification by flash chromatography over silica gel, eluting petrol/EtOAc (90/10) provided the desired compound **231** as a solid (49 mg, 72%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[28]. M.pt.: 122-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (12H, s, PinC**H**$_3$), 2.32 (3H, s, C**H**$_3$), 7.07 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.32-7.49 (9H, m, Ar**H**), 7.87-7.90 (1H, m, Ar**H**), 8.31-8.35 (1H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5, 24.6, 83.3, 115.5, 122.2, 124.0, 124.6, 126.6, 126.9, 128.6, 129.3, 131.7, 132.2, 133.4, 135.7, 137.6, 144.6, 148.7.

- *Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-tosyl-2-butylindole* **232**



Following the general procedure a mixture of amino alkyne **230** (50 mg, 0.15 mmol), Cs_2CO_3 (100 mg, 0.29 mmol), 4ÅMS (50 mg), Pd_2dba_3 (14 mg, 10 mol%), B_2Pin_2 (78 mg, 0.29 mmol) and $AsPh_3$ (9 mg, 0.03 mmol, 20 mol%) afforded the crude mixture. Purification by flash chromatography over silica

gel, eluting petrol/EtOAc (90/10) provided the desired compound **232** as a solid (42 mg, 63%). The product showed satisfactory spectroscopic and analytical data in comparison to the literature[28]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.0 Hz, C**H**$_3$), 1.36 (12H, s, PinC**H**$_3$), 1.36-1.47 (2H, m, C**H**$_2$), 1.67-1.74 (2H, m, C**H**$_2$), 2.35 (3H, s, C**H**$_3$), 3.29-3.33 (2H, m, C**H**$_2$), 7.19 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.23-7.25 (2H, m, Ar**H**), 7.65 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.93-7.96 (1H, m, Ar**H**), 8.12-8.16 (1H, m, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 21.5, 22.7, 24.9, 28.1, 34.2, 83.1, 114.5, 122.1, 123.5, 123.6, 126.4, 126.5, 129.8, 134.4, 136.5, 137.2, 144.6, 153.0.

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[24]3-methyl-4-phenylcyclobutenone **155** was obtained as a mixture (1:1) with 2-methyl-3-phenylcyclobutenone **156**. Therefore, the mass of cyclobutenone **155** used in the experiment was corrected and adjusted to 1 eq of compound **155**.

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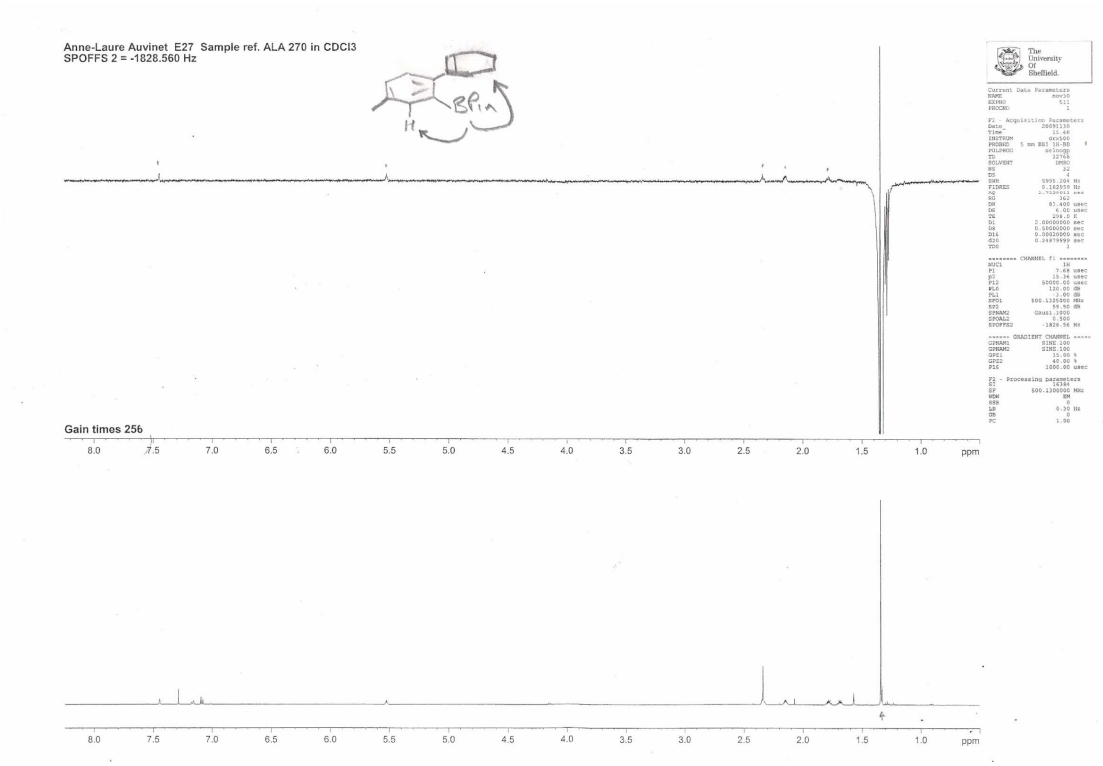
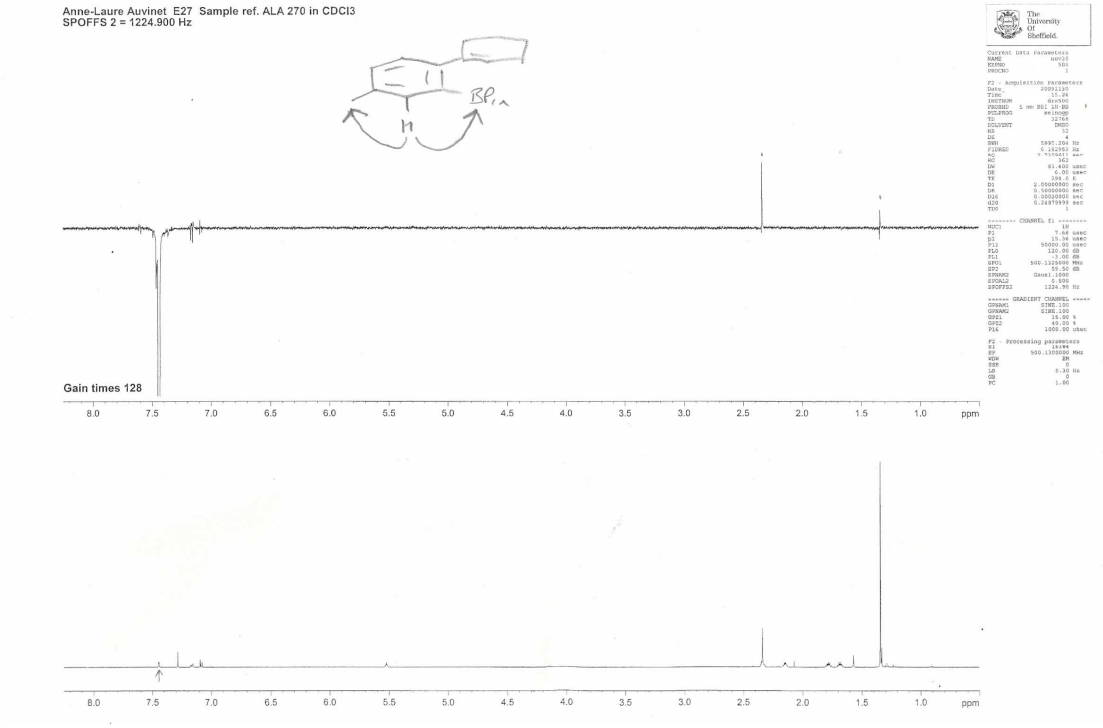
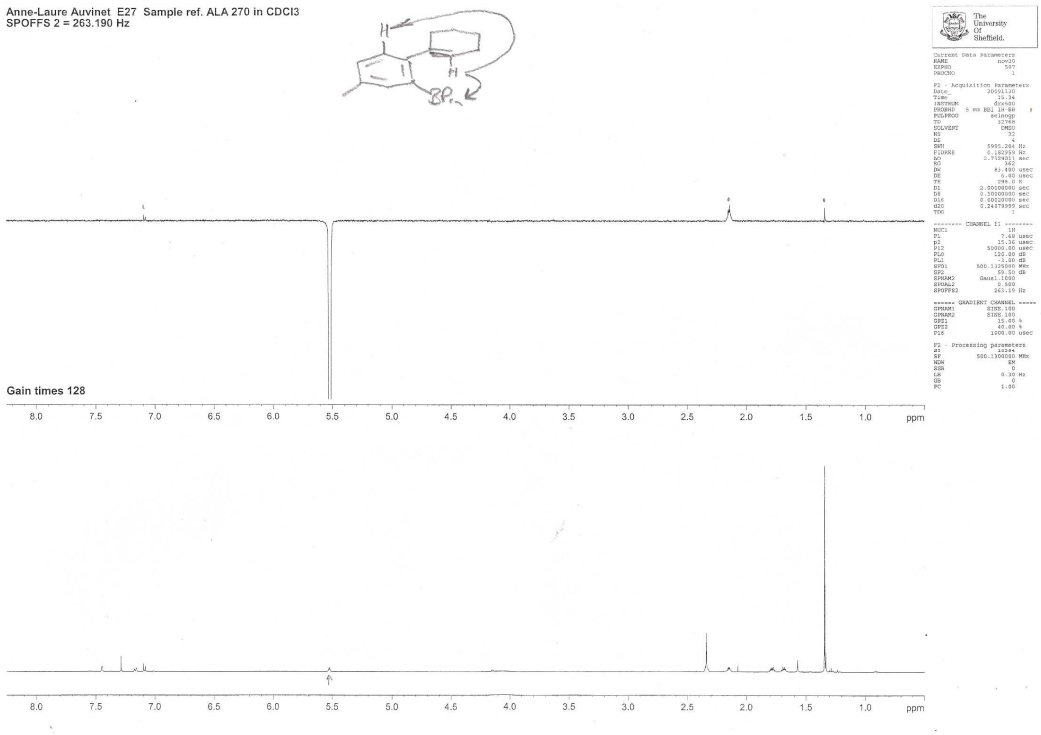
Appendices

nOe spectra of compound 164

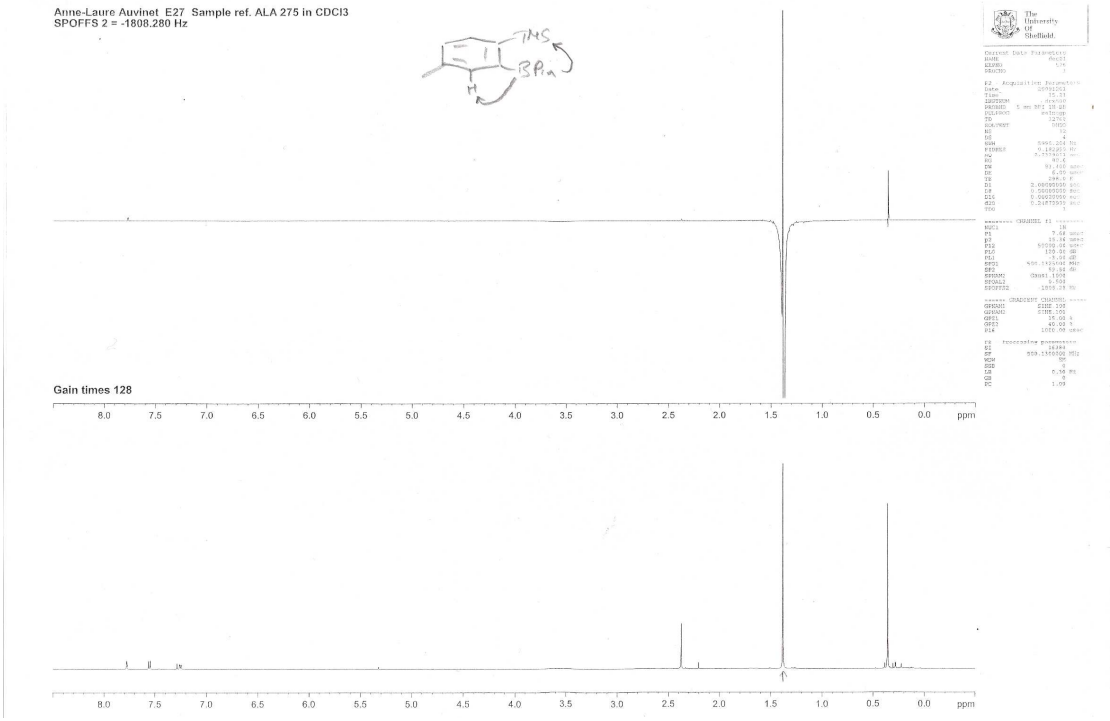


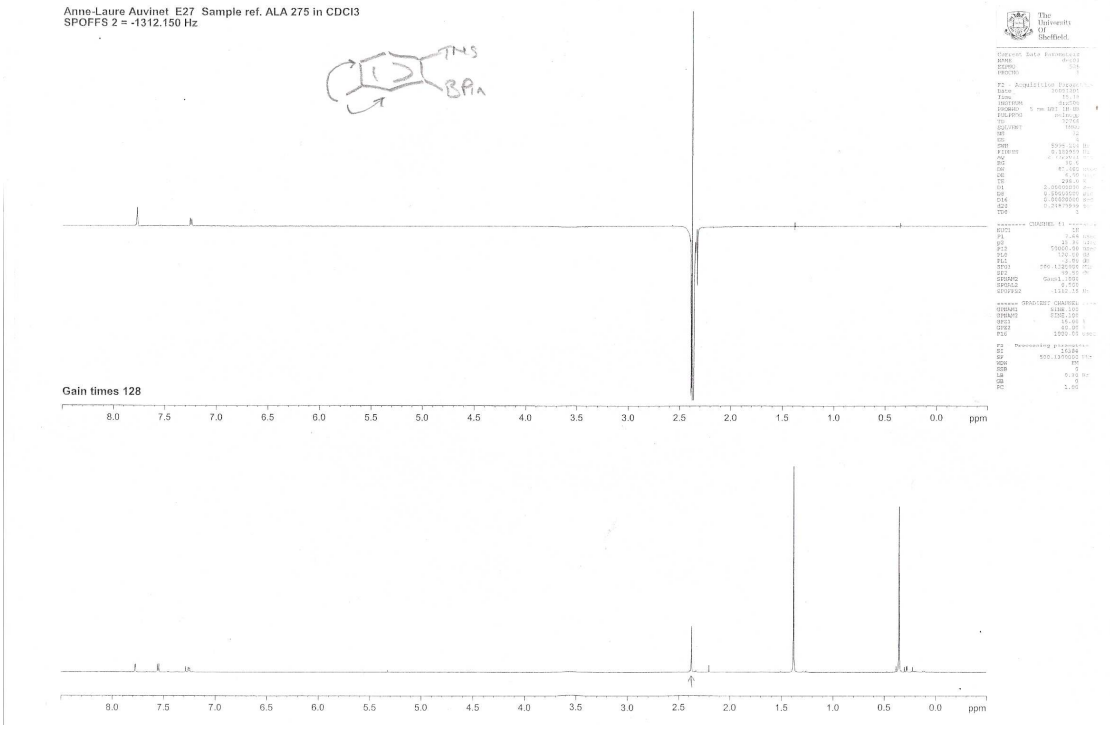


nOe spectra of compound 164

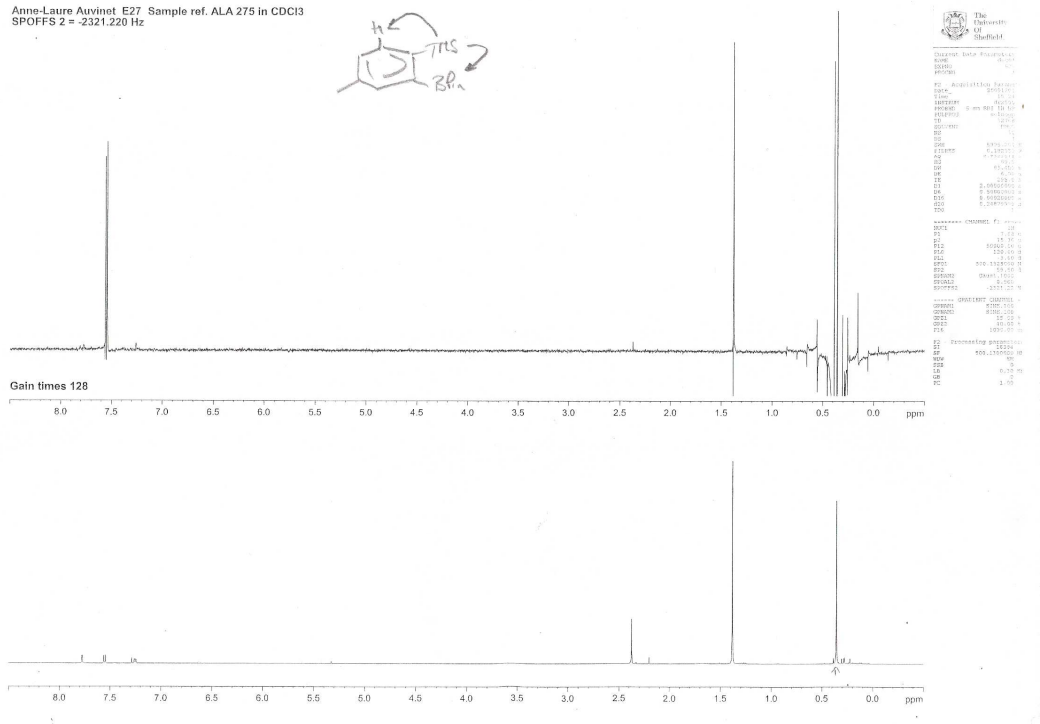


nOe spectra of compound 166

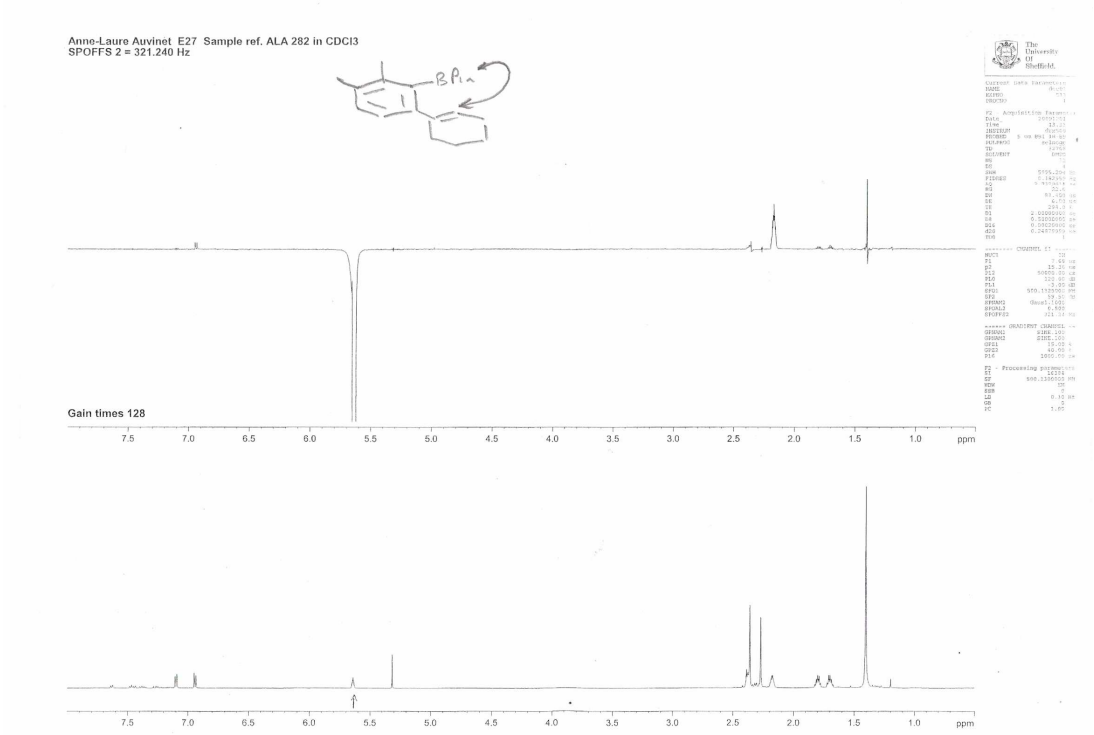


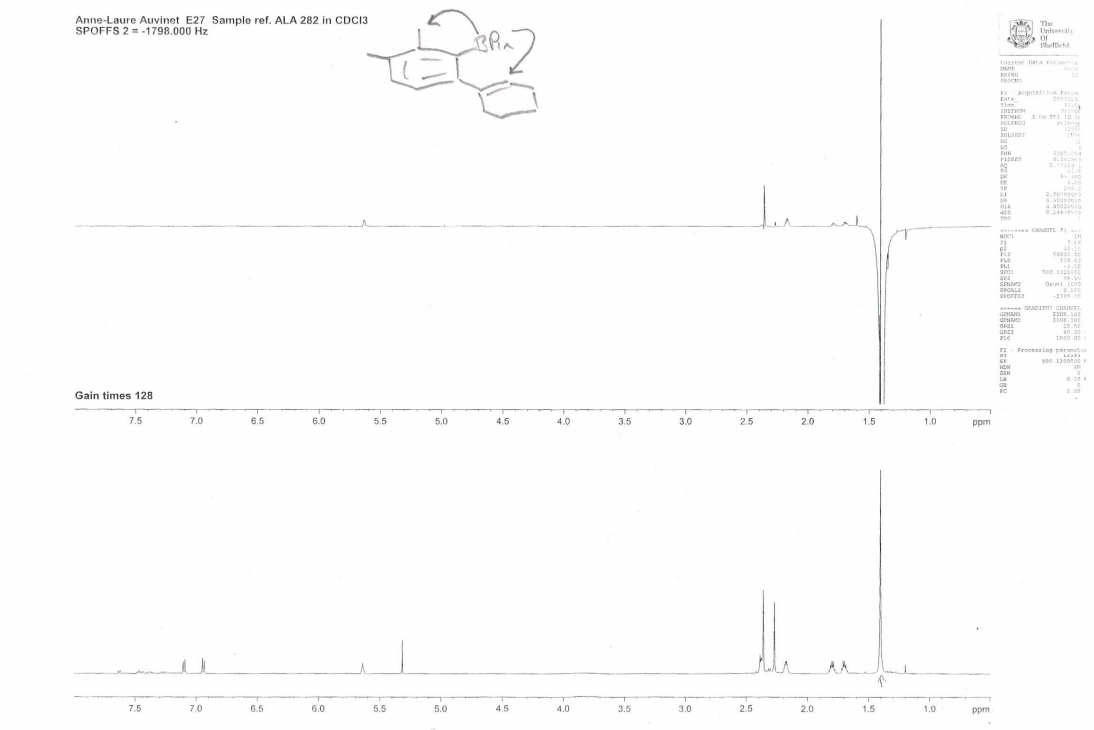


nOe spectra of compound <u>166</u>

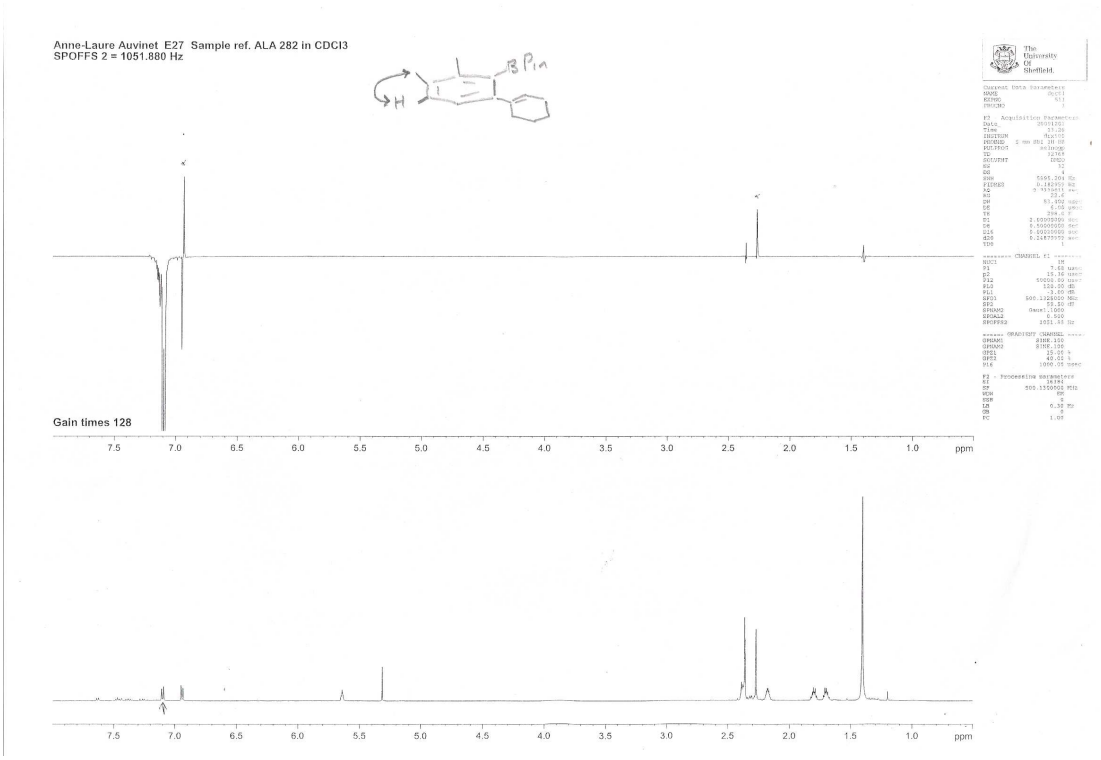


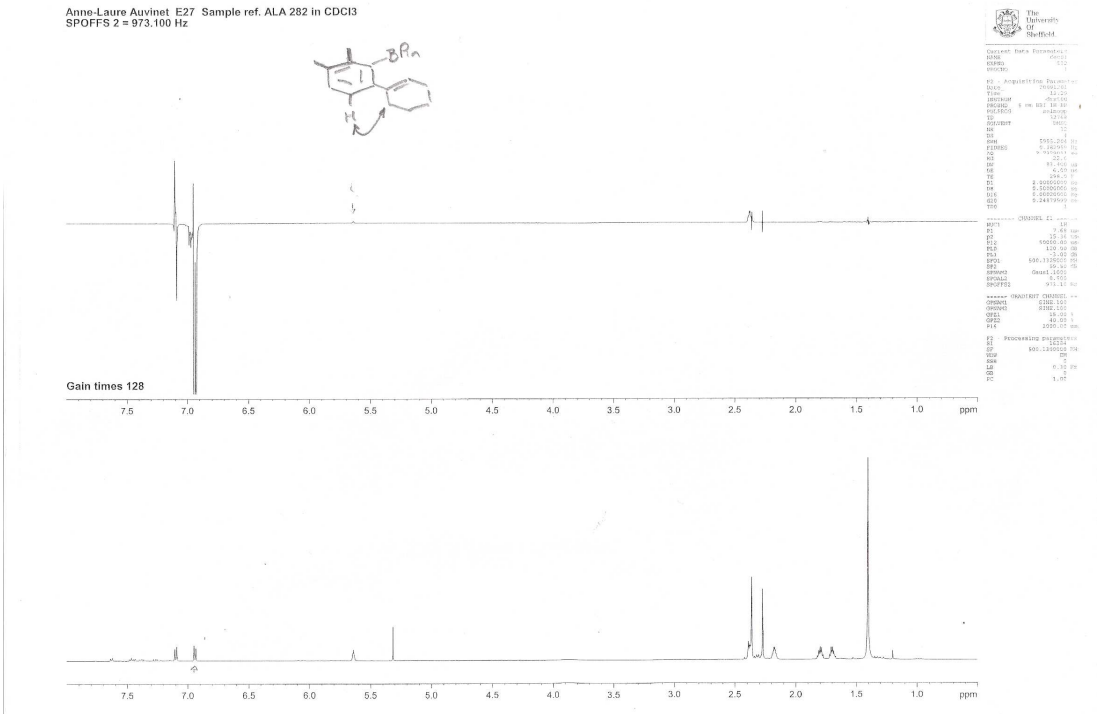
nOe spectra of compound <u>168</u>



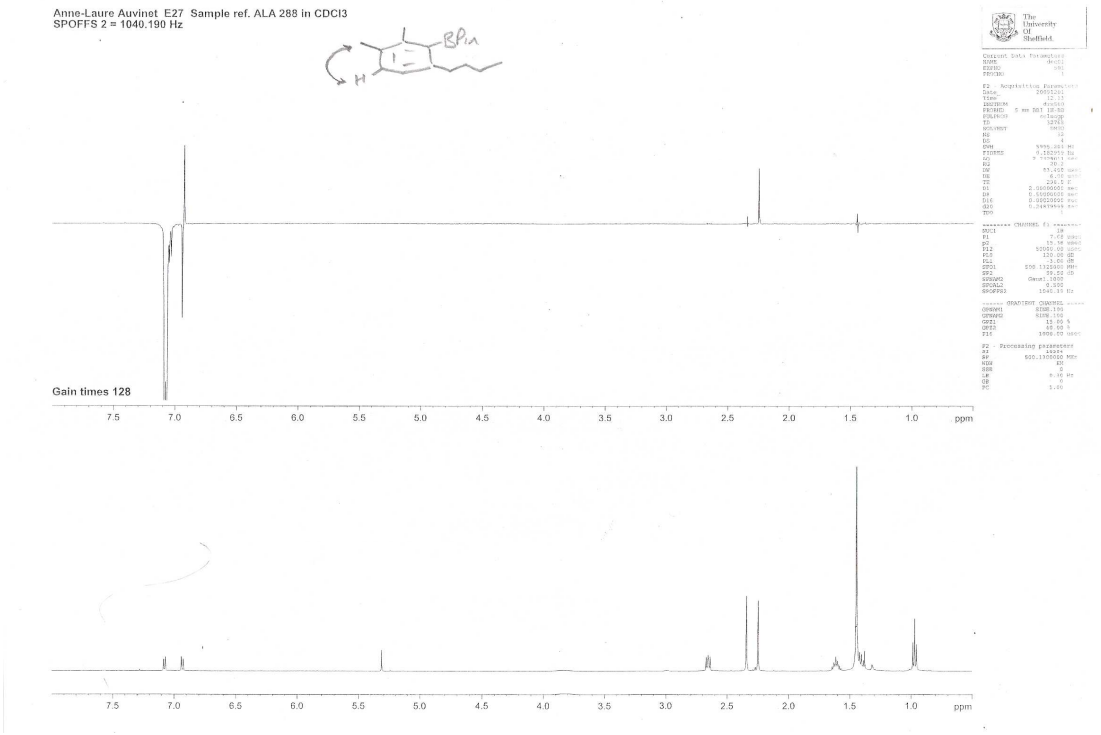


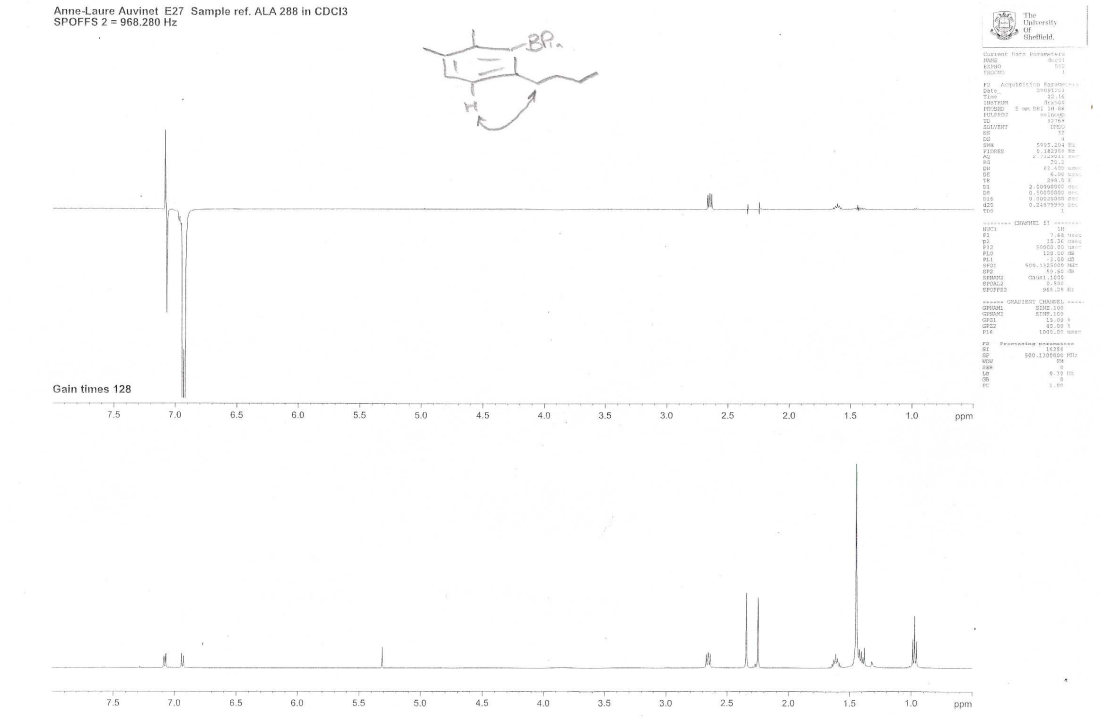
nOe spectra of compound <u>168</u>



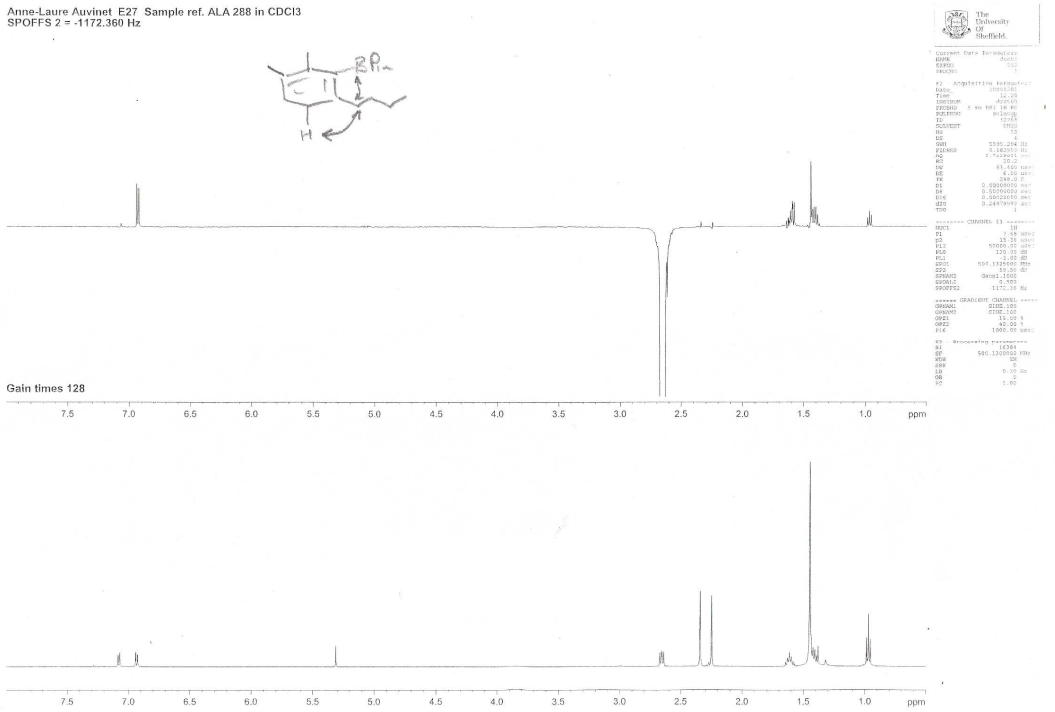


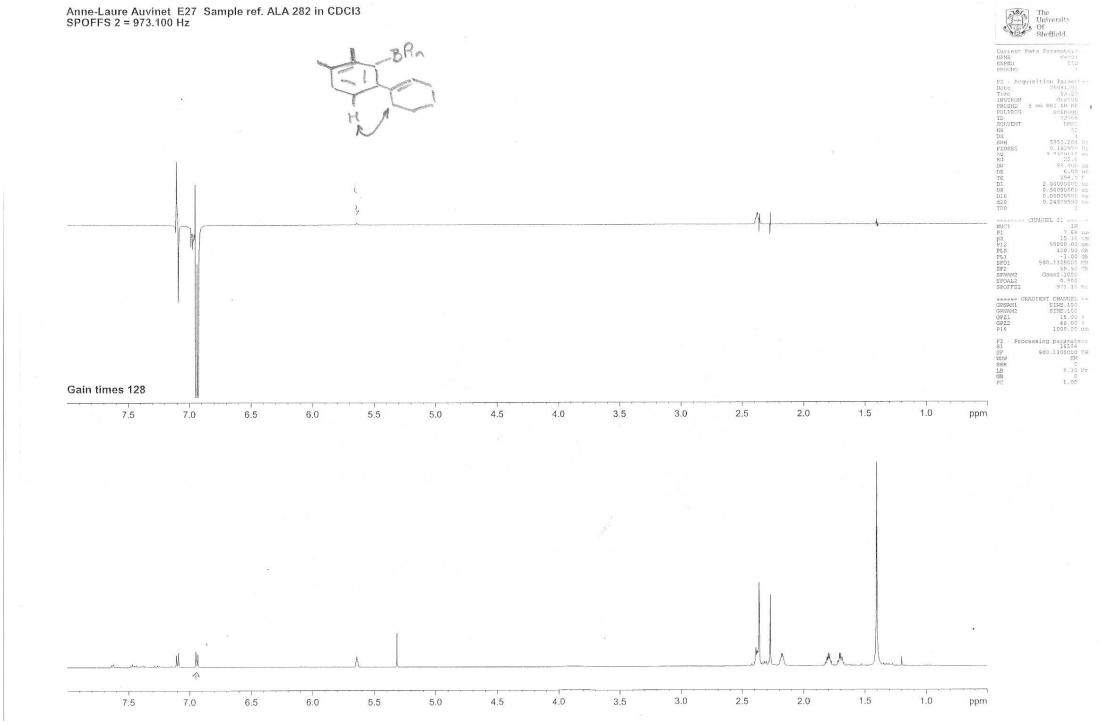
nOe spectra of compound <u>169</u>



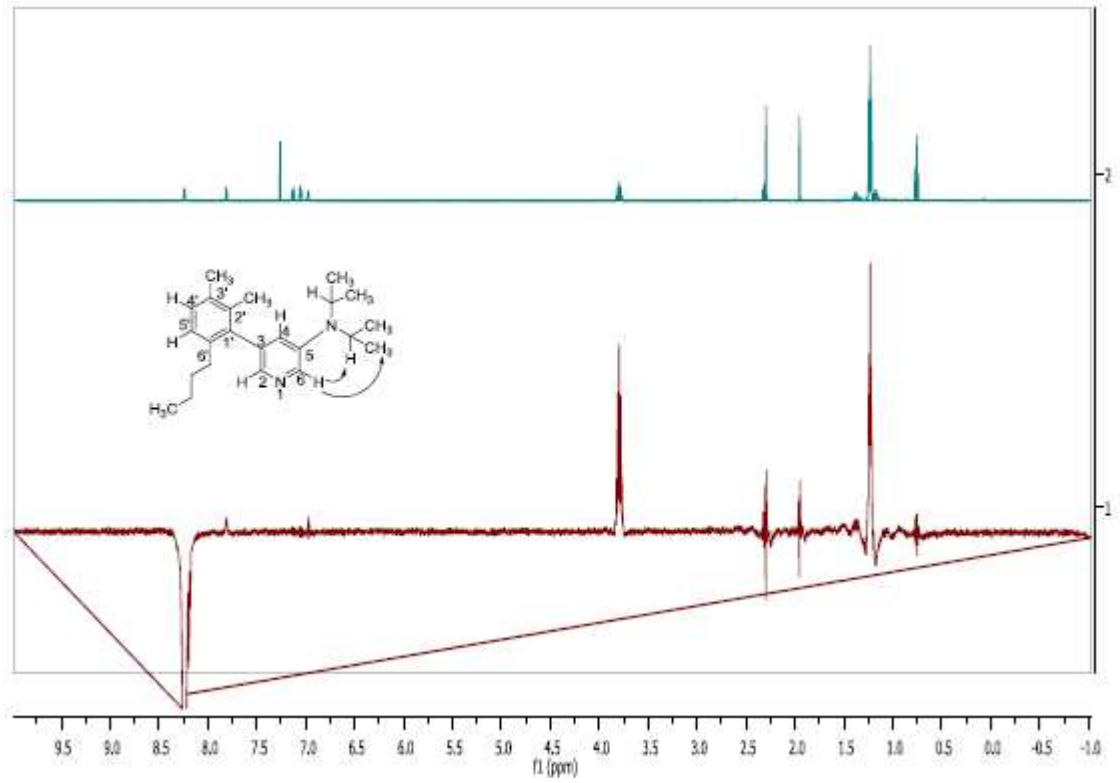


nOe spectra of compound <u>169</u>

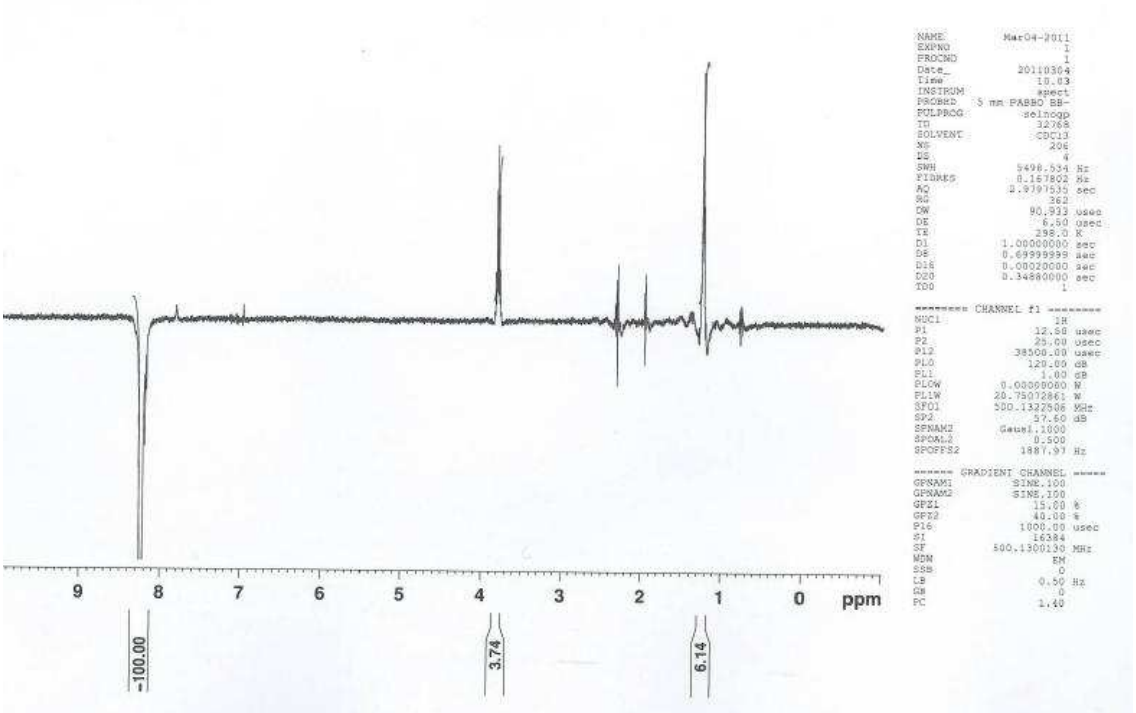




nOe spectra of compound <u>185</u>

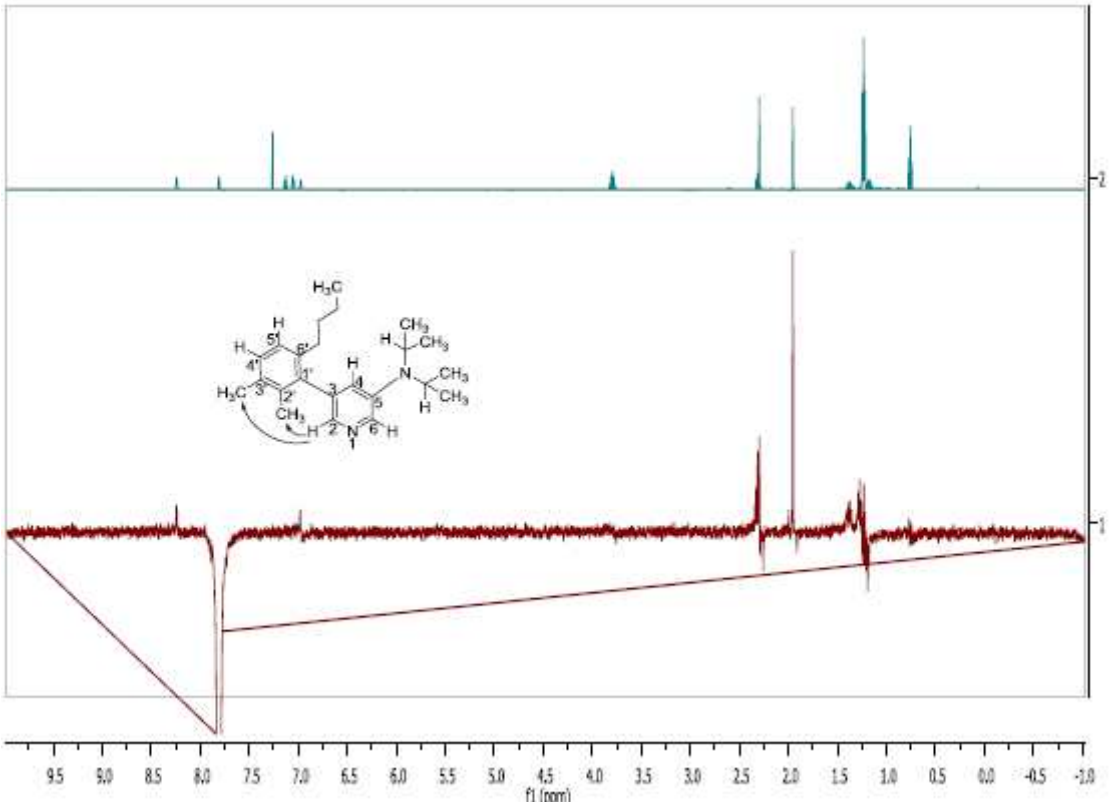


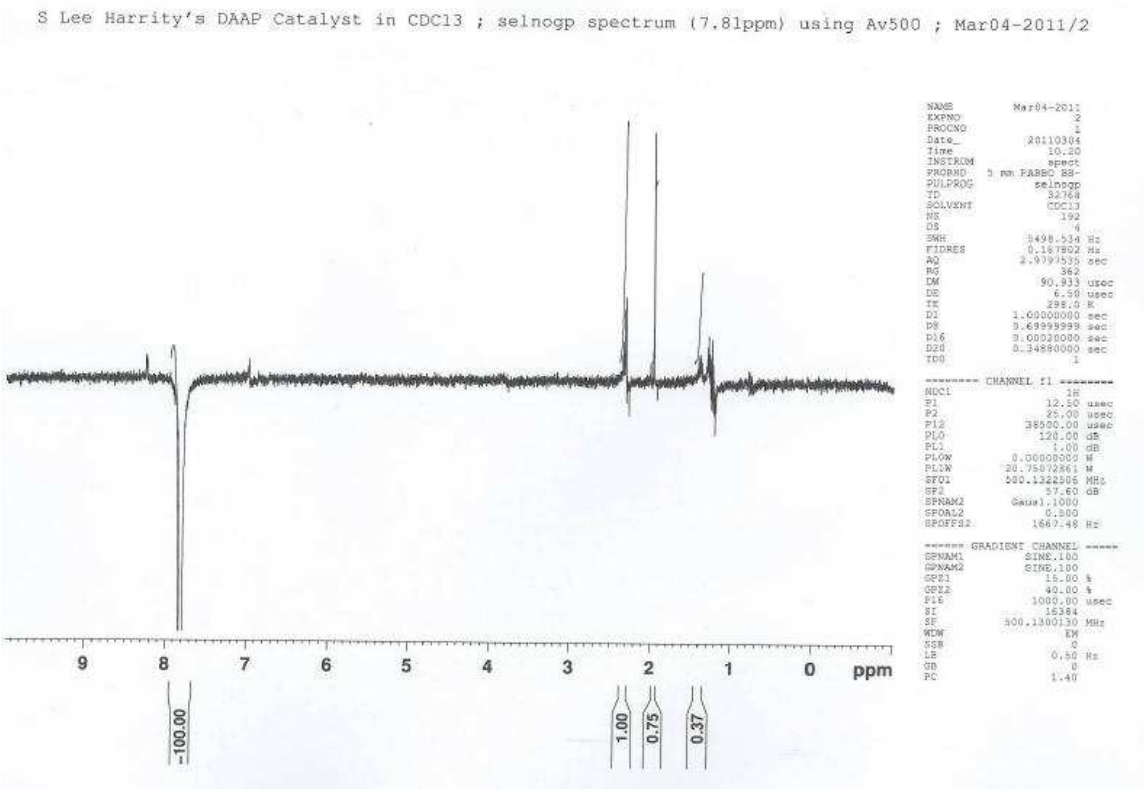
S Lee Harrity's DAAP Catalyst in CDCl3 ; selnogp spectrum (8.24ppm) using Av500 ; Mar04-2011/1



NAME	Mar04-2011
EXPNO	1
PROCNO	1
Date_	20110304
Time	10.03
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	selnogp
TD	32768
SOLVENT	CDCl3
NS	206
DS	4
SWH	5498.534 Hz
FIDRES	0.167802 Hz
AQ	2.9797535 sec
RG	362
DW	90.933 usec
DE	6.50 usec
TE	298.0 K
D1	1.00000000 sec
D8	0.69999999 sec
D16	0.00020000 sec
D20	0.34880000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	12.50 usec
P2	25.00 usec
P12	38500.00 usec
PL0	120.00 dB
PL1	1.00 dB
PLOW	0.00000000 W
PL1W	20.75072861 W
SFO1	500.1322506 MHz
SP2	57.60 dB
SPNAM2	Gaus1.1000
SPOAL2	0.500
SPOFFS2	1887.93 Hz
======= GRADIENT CHANNEL =======	
GPNAM1	SINE.100
GPNAM2	SINE.100
GPZ1	15.00 %
GPZ2	40.00 %
P16	1000.00 usec
SI	16384
SF	500.1300130 MHz
WDW	EM
SSB	0
LB	0.50 Hz
GB	0
PC	1.40

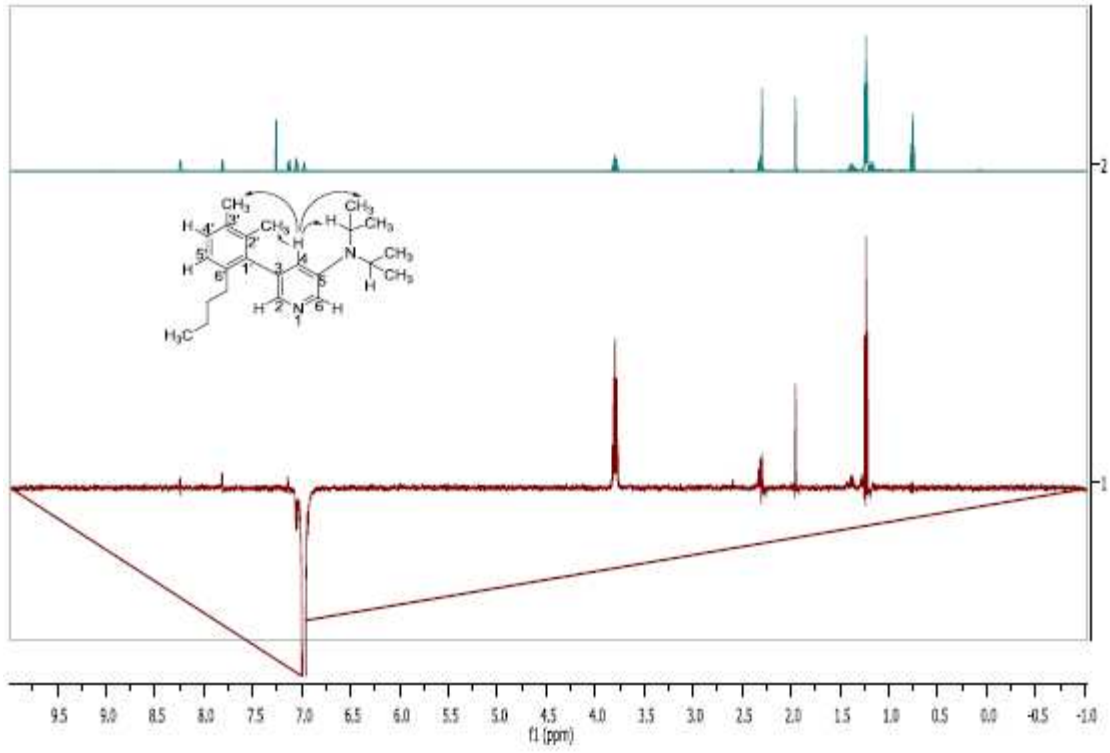
nOe spectra of compound <u>185</u>

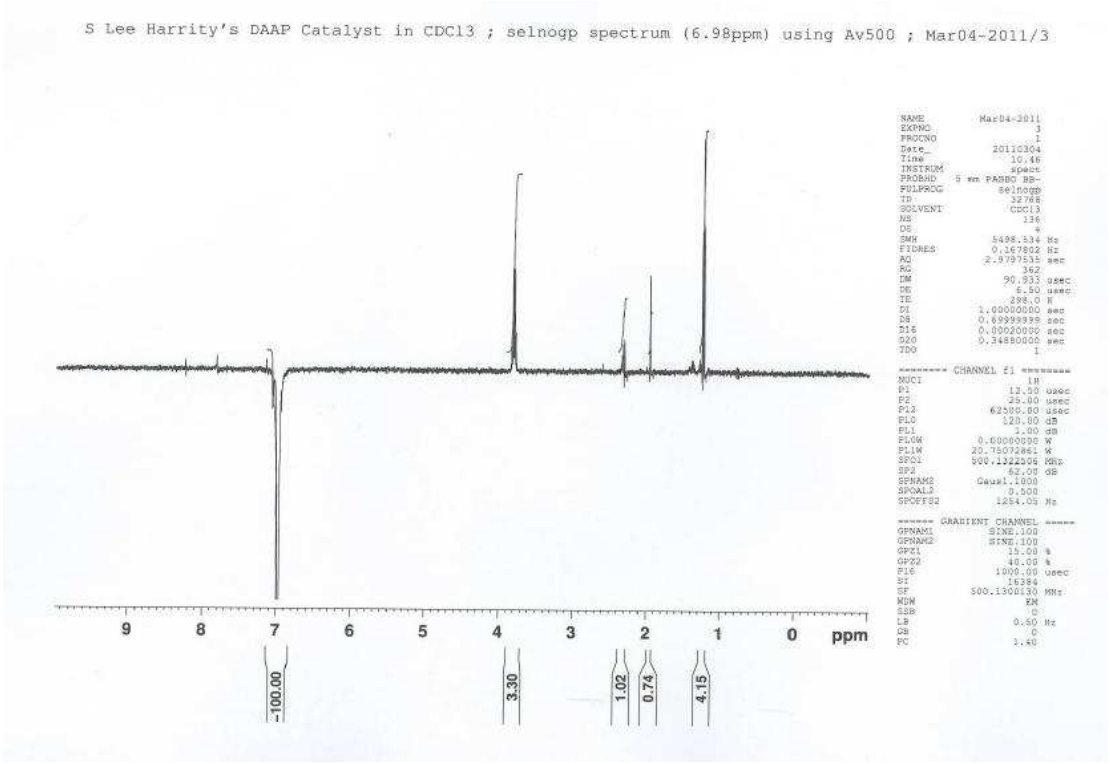




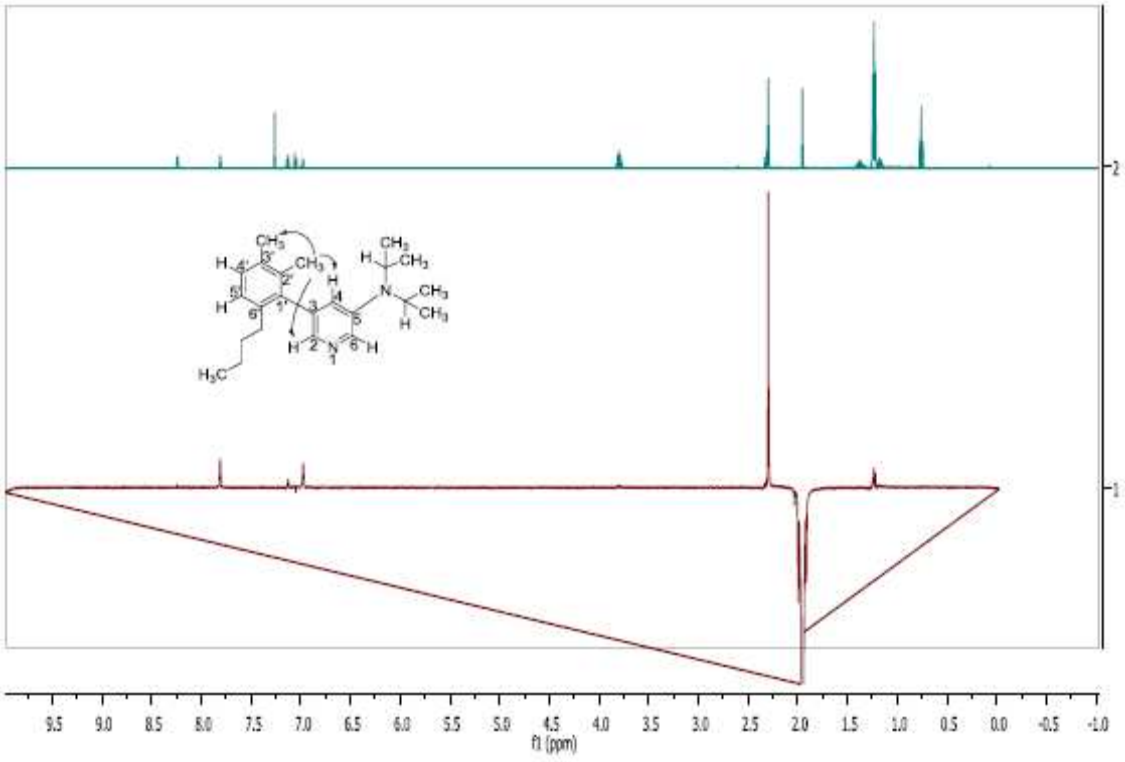
I

nOe spectra of compound <u>185</u>

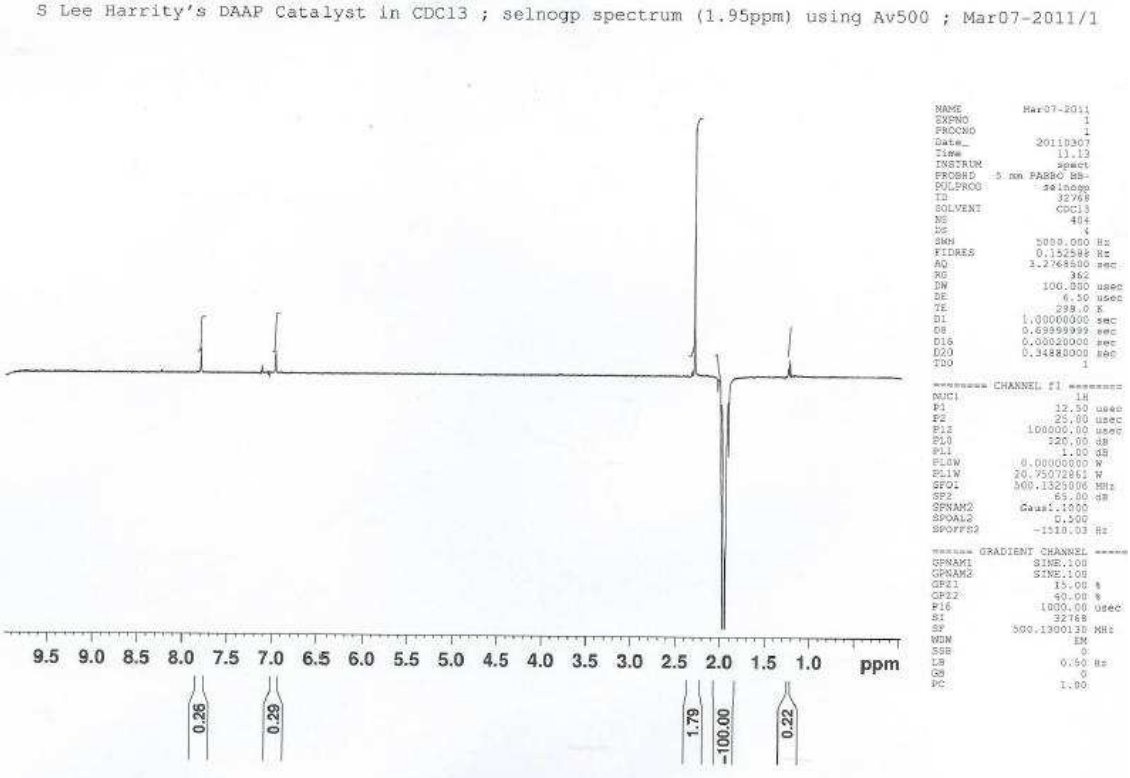




nOe spectra of compound 185



S Lee Harrity's DAAP Catalyst in CDCl3 ; selnogp spectrum (1.95ppm) using Av500 ; Mar07-2011/1



NAME	Mar07-2011
EXPNO	1
PROCNO	1
Date_	20110307
Time	11.12
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	selnogp
TD	32768
SOLVENT	CDCl3
NS	404
DS	4
SWH	5050.000 Hz
FIDRES	0.152598 Hz
AQ	3.2768000 sec
RG	362
DW	100.000 usec
DE	6.50 usec
TE	299.0 K
D1	1.00000000 sec
D8	0.69999999 sec
D16	0.00020000 sec
D20	0.34888000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	12.50 usec
P2	25.00 usec
P12	100000.00 usec
PL0	120.00 dB
PL1	1.00 dB
PL0W	0.00000000 W
PL1W	20.75072861 W
SFO1	500.1325006 MHz
SP2	65.00 dB
SPNAM2	Gaus1.1000
SPOAL2	0.500
SPOFFS2	-1510.03 Hz
====== GRADIENT CHANNEL =====	
GPNAM1	SINE.100
GPNAM2	SINE.100
GPZ1	15.00 %
GPZ2	40.00 %
P16	1000.00 usec
SI	32768
SF	500.1300135 MHz
WDW	EM
SSB	0
LB	0.50 Hz
GB	0
PC	1.00

X-ray Cristal structure data

2,5-Dibutyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **197**

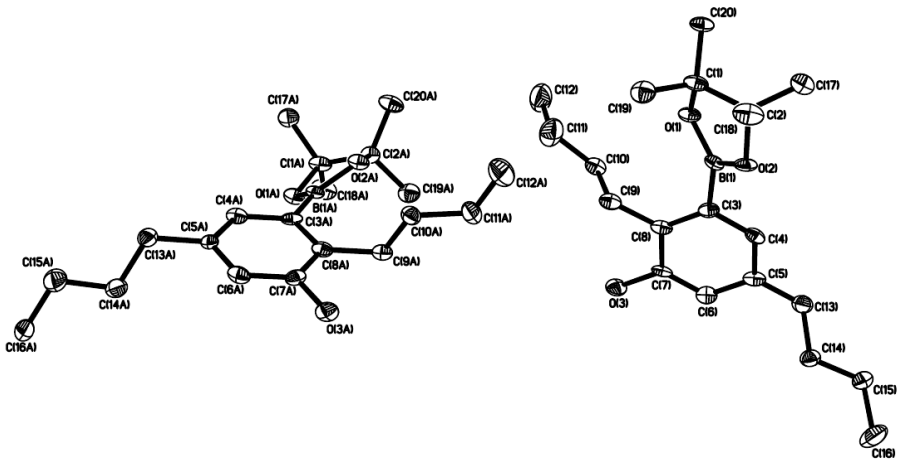


Table 1. Crystal data and structure refinement for ohj197pca21.

Identification code	ohj197pca21	
Empirical formula	C20 H33 B O3	
Formula weight	332.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pca2_1$	
Unit cell dimensions	a = 12.3938(10) Å	α= 90°.
	b = 8.1673(7) Å	β= 90°.
	c = 39.754(3) Å	γ = 90°.
Volume	4024.0(6) $Å^3$	
Z	8	
Density (calculated)	1.097 Mg/m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	1456	
Crystal size	0.18 x 0.10 x 0.05 mm^3	
Theta range for data collection	2.49 to 25.00°.	
Index ranges	-14<=h<=14, -9<=k<=9, -47<=l<=47	
Reflections collected	59862	
Independent reflections	3605 [R(int) = 0.1006]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9965 and 0.9874
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3605 / 1 / 447
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1433
R indices (all data)	R1 = 0.0689, wR2 = 0.1518
Absolute structure parameter	0(10)
Largest diff. peak and hole	0.337 and -0.228 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for ohj197pca21. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
B(1)	6250(4)	3203(6)	5923(1)	18(1)
O(1)	5402(2)	3257(4)	6147(1)	22(1)
O(2)	6336(2)	4590(4)	5732(1)	23(1)
O(3)	8877(3)	-885(4)	6360(1)	27(1)
C(1)	5004(4)	4971(5)	6150(2)	23(2)
C(2)	5389(4)	5621(6)	5796(1)	24(1)
C(3)	7060(3)	1733(5)	5883(1)	20(1)
C(4)	7305(3)	1237(5)	5553(1)	21(1)
C(5)	8065(4)	-1(5)	5483(2)	21(1)
C(6)	8588(4)	-693(6)	5761(1)	24(1)
C(7)	8360(4)	-194(5)	6086(2)	19(1)
C(8)	7567(4)	990(5)	6155(1)	21(1)
C(9)	7335(4)	1436(5)	6518(1)	23(1)
C(10)	6526(5)	233(7)	6683(2)	28(1)
C(11)	6107(5)	864(9)	7018(2)	50(2)
C(12)	5263(6)	-222(10)	7166(2)	57(2)
C(13)	8303(4)	-518(7)	5133(1)	29(1)
C(14)	9425(4)	-69(6)	5008(2)	26(2)
C(15)	9584(4)	-485(8)	4638(1)	34(1)
C(16)	10702(6)	-78(9)	4498(2)	50(2)
C(17)	4591(5)	5310(7)	5514(2)	31(1)
C(18)	5757(4)	7391(6)	5796(2)	34(1)
C(19)	5556(4)	5805(6)	6446(1)	32(1)
C(20)	3791(4)	4934(5)	6202(2)	25(2)
B(1A)	8671(4)	1821(7)	8415(1)	19(1)
O(1A)	8739(3)	432(4)	8604(1)	25(1)
O(2A)	7813(2)	1749(3)	8190(1)	20(1)
O(3A)	11298(3)	5893(4)	7980(1)	26(1)
C(1A)	7803(4)	-606(6)	8533(1)	24(1)
C(2A)	7415(4)	35(5)	8189(2)	19(1)

C(3A)	9465(3)	3280(5)	8456(1)	19(1)
C(4A)	9719(4)	3747(5)	8786(1)	22(1)
C(5A)	10460(4)	4981(5)	8848(2)	19(1)
C(6A)	11004(4)	5688(5)	8578(1)	22(1)
C(7A)	10752(4)	5218(6)	8251(2)	21(1)
C(8A)	9986(4)	4035(5)	8182(1)	20(1)
C(9A)	9721(4)	3641(5)	7819(1)	21(1)
C(10A)	8960(5)	4912(6)	7664(2)	24(1)
C(11A)	8567(5)	4427(8)	7312(1)	38(1)
C(12A)	7770(6)	5693(9)	7167(2)	58(2)
C(13A)	10714(4)	5535(7)	9206(1)	26(1)
C(14A)	11828(5)	5062(6)	9336(2)	29(2)
C(15A)	11996(5)	5490(8)	9701(2)	36(1)
C(16A)	13104(5)	5073(8)	9829(2)	38(2)
C(17A)	6997(4)	-305(7)	8820(2)	29(1)
C(18A)	8170(4)	-2383(6)	8534(2)	34(1)
C(19A)	7951(4)	-777(6)	7889(1)	30(1)
C(20A)	6204(4)	80(6)	8141(2)	32(2)

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Table 3. Bond lengths [Å] and angles [°] for ohj197pca21.

B(1)-O(2)	1.368(6)
B(1)-O(1)	1.378(6)
B(1)-C(3)	1.573(6)
O(1)-C(1)	1.484(5)
O(2)-C(2)	1.467(5)
O(3)-C(7)	1.384(7)
O(3)-H(3)	0.8400
C(1)-C(20)	1.518(7)
C(1)-C(19)	1.523(9)
C(1)-C(2)	1.576(9)
C(2)-C(18)	1.515(7)
C(2)-C(17)	1.516(8)
C(3)-C(8)	1.389(7)
C(3)-C(4)	1.407(7)
C(4)-C(5)	1.410(7)
C(4)-H(4)	0.9500
C(5)-C(6)	1.401(9)
C(5)-C(13)	1.483(9)
C(6)-C(7)	1.382(8)
C(6)-H(6)	0.9500
C(7)-C(8)	1.407(6)
C(8)-C(9)	1.515(7)
C(9)-C(10)	1.550(8)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.518(10)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.492(9)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.521(7)
C(13)-H(13A)	0.9900

C(13)-H(13B)	0.9900
C(14)-C(15)	1.522(9)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.531(8)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
B(1A)-O(1A)	1.363(7)
B(1A)-O(2A)	1.390(6)
B(1A)-C(3A)	1.554(7)
O(1A)-C(1A)	1.464(6)
O(2A)-C(2A)	1.484(5)
O(3A)-C(7A)	1.388(7)
O(3A)-H(3A)	0.8400
C(1A)-C(18A)	1.521(6)
C(1A)-C(17A)	1.536(8)
C(1A)-C(2A)	1.542(9)
C(2A)-C(20A)	1.514(7)
C(2A)-C(19A)	1.517(8)
C(3A)-C(4A)	1.400(7)
C(3A)-C(8A)	1.410(7)
C(4A)-C(5A)	1.386(7)
C(4A)-H(4A)	0.9500

C(5A)-C(6A)	1.392(8)
C(5A)-C(13A)	1.525(8)
C(6A)-C(7A)	1.393(8)
C(6A)-H(6A)	0.9500
C(7A)-C(8A)	1.382(7)
C(8A)-C(9A)	1.513(7)
C(9A)-C(10A)	1.532(7)
C(9A)-H(9A1)	0.9900
C(9A)-H(9A2)	0.9900
C(10A)-C(11A)	1.534(9)
C(10A)-H(10C)	0.9900
C(10A)-H(10D)	0.9900
C(11A)-C(12A)	1.542(8)
C(11A)-H(11C)	0.9900
C(11A)-H(11D)	0.9900
C(12A)-H(12D)	0.9800
C(12A)-H(12E)	0.9800
C(12A)-H(12F)	0.9800
C(13A)-C(14A)	1.524(7)
C(13A)-H(13C)	0.9900
C(13A)-H(13D)	0.9900
C(14A)-C(15A)	1.505(9)
C(14A)-H(14C)	0.9900
C(14A)-H(14D)	0.9900
C(15A)-C(16A)	1.503(8)
C(15A)-H(15C)	0.9900
C(15A)-H(15D)	0.9900
C(16A)-H(16D)	0.9800
C(16A)-H(16E)	0.9800
C(16A)-H(16F)	0.9800
C(17A)-H(17D)	0.9800
C(17A)-H(17E)	0.9800
C(17A)-H(17F)	0.9800
C(18A)-H(18D)	0.9800
C(18A)-H(18E)	0.9800
C(18A)-H(18F)	0.9800
C(19A)-H(19D)	0.9800
C(19A)-H(19E)	0.9800

C(19A)-H(19F)	0.9800
C(20A)-H(20D)	0.9800
C(20A)-H(20E)	0.9800
C(20A)-H(20F)	0.9800

O(2)-B(1)-O(1)	113.1(4)
O(2)-B(1)-C(3)	121.8(4)
O(1)-B(1)-C(3)	125.1(4)
B(1)-O(1)-C(1)	106.8(4)
B(1)-O(2)-C(2)	108.4(4)
C(7)-O(3)-H(3)	109.5
O(1)-C(1)-C(20)	108.2(4)
O(1)-C(1)-C(19)	106.1(5)
C(20)-C(1)-C(19)	110.3(5)
O(1)-C(1)-C(2)	102.2(4)
C(20)-C(1)-C(2)	115.4(5)
C(19)-C(1)-C(2)	113.7(4)
O(2)-C(2)-C(18)	107.9(4)
O(2)-C(2)-C(17)	107.2(4)
C(18)-C(2)-C(17)	110.9(5)
O(2)-C(2)-C(1)	101.8(4)
C(18)-C(2)-C(1)	114.4(5)
C(17)-C(2)-C(1)	113.8(4)
C(8)-C(3)-C(4)	120.2(4)
C(8)-C(3)-B(1)	123.0(4)
C(4)-C(3)-B(1)	116.7(4)
C(3)-C(4)-C(5)	122.3(5)
C(3)-C(4)-H(4)	118.9
C(5)-C(4)-H(4)	118.9
C(6)-C(5)-C(4)	116.3(6)
C(6)-C(5)-C(13)	122.2(4)
C(4)-C(5)-C(13)	121.5(6)
C(7)-C(6)-C(5)	121.6(5)
C(7)-C(6)-H(6)	119.2
C(5)-C(6)-H(6)	119.2
C(6)-C(7)-O(3)	121.3(4)
C(6)-C(7)-C(8)	121.9(5)
O(3)-C(7)-C(8)	116.7(5)

C(3)-C(8)-C(7)	117.6(5)
C(3)-C(8)-C(9)	123.4(4)
C(7)-C(8)-C(9)	119.0(5)
C(8)-C(9)-C(10)	111.9(4)
C(8)-C(9)-H(9A)	109.2
C(10)-C(9)-H(9A)	109.2
C(8)-C(9)-H(9B)	109.2
C(10)-C(9)-H(9B)	109.2
H(9A)-C(9)-H(9B)	107.9
C(11)-C(10)-C(9)	112.2(5)
C(11)-C(10)-H(10A)	109.2
C(9)-C(10)-H(10A)	109.2
C(11)-C(10)-H(10B)	109.2
C(9)-C(10)-H(10B)	109.2
H(10A)-C(10)-H(10B)	107.9
C(12)-C(11)-C(10)	112.6(6)
C(12)-C(11)-H(11A)	109.1
C(10)-C(11)-H(11A)	109.1
C(12)-C(11)-H(11B)	109.1
C(10)-C(11)-H(11B)	109.1
H(11A)-C(11)-H(11B)	107.8
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(5)-C(13)-C(14)	114.7(5)
C(5)-C(13)-H(13A)	108.6
C(14)-C(13)-H(13A)	108.6
C(5)-C(13)-H(13B)	108.6
C(14)-C(13)-H(13B)	108.6
H(13A)-C(13)-H(13B)	107.6
C(13)-C(14)-C(15)	112.3(5)
C(13)-C(14)-H(14A)	109.1
C(15)-C(14)-H(14A)	109.1
C(13)-C(14)-H(14B)	109.1
C(15)-C(14)-H(14B)	109.1

H(14A)-C(14)-H(14B)	107.9
C(14)-C(15)-C(16)	114.9(6)
C(14)-C(15)-H(15A)	108.5
C(16)-C(15)-H(15A)	108.5
C(14)-C(15)-H(15B)	108.5
C(16)-C(15)-H(15B)	108.5
H(15A)-C(15)-H(15B)	107.5
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(2)-C(17)-H(17A)	109.5
C(2)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(2)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(2)-C(18)-H(18A)	109.5
C(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(1)-C(19)-H(19A)	109.5
C(1)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(1)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(1)-C(20)-H(20A)	109.5
C(1)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(1)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
O(1A)-B(1A)-O(2A)	111.5(4)

O(1A)-B(1A)-C(3A)	122.8(4)
O(2A)-B(1A)-C(3A)	125.7(4)
B(1A)-O(1A)-C(1A)	109.1(4)
B(1A)-O(2A)-C(2A)	107.2(4)
C(7A)-O(3A)-H(3A)	109.5
O(1A)-C(1A)-C(18A)	108.4(4)
O(1A)-C(1A)-C(17A)	106.2(4)
C(18A)-C(1A)-C(17A)	110.2(4)
O(1A)-C(1A)-C(2A)	102.8(4)
C(18A)-C(1A)-C(2A)	114.8(4)
C(17A)-C(1A)-C(2A)	113.7(4)
O(2A)-C(2A)-C(20A)	107.9(4)
O(2A)-C(2A)-C(19A)	105.7(4)
C(20A)-C(2A)-C(19A)	110.3(5)
O(2A)-C(2A)-C(1A)	102.3(4)
C(20A)-C(2A)-C(1A)	115.4(5)
C(19A)-C(2A)-C(1A)	114.4(4)
C(4A)-C(3A)-C(8A)	120.1(4)
C(4A)-C(3A)-B(1A)	116.7(4)
C(8A)-C(3A)-B(1A)	123.0(4)
C(5A)-C(4A)-C(3A)	121.0(5)
C(5A)-C(4A)-H(4A)	119.5
C(3A)-C(4A)-H(4A)	119.5
C(4A)-C(5A)-C(6A)	118.9(6)
C(4A)-C(5A)-C(13A)	121.4(5)
C(6A)-C(5A)-C(13A)	119.7(4)
C(5A)-C(6A)-C(7A)	119.8(4)
C(5A)-C(6A)-H(6A)	120.1
C(7A)-C(6A)-H(6A)	120.1
C(8A)-C(7A)-O(3A)	117.2(5)
C(8A)-C(7A)-C(6A)	122.2(5)
O(3A)-C(7A)-C(6A)	120.5(4)
C(7A)-C(8A)-C(3A)	117.7(5)
C(7A)-C(8A)-C(9A)	119.2(5)
C(3A)-C(8A)-C(9A)	123.1(4)
C(8A)-C(9A)-C(10A)	111.8(4)
C(8A)-C(9A)-H(9A1)	109.3
C(10A)-C(9A)-H(9A1)	109.3

C(8A)-C(9A)-H(9A2)	109.3
C(10A)-C(9A)-H(9A2)	109.3
H(9A1)-C(9A)-H(9A2)	107.9
C(9A)-C(10A)-C(11A)	112.7(4)
C(9A)-C(10A)-H(10C)	109.0
C(11A)-C(10A)-H(10C)	109.0
C(9A)-C(10A)-H(10D)	109.0
C(11A)-C(10A)-H(10D)	109.0
H(10C)-C(10A)-H(10D)	107.8
C(10A)-C(11A)-C(12A)	111.8(5)
C(10A)-C(11A)-H(11C)	109.3
C(12A)-C(11A)-H(11C)	109.3
C(10A)-C(11A)-H(11D)	109.3
C(12A)-C(11A)-H(11D)	109.3
H(11C)-C(11A)-H(11D)	107.9
C(11A)-C(12A)-H(12D)	109.5
C(11A)-C(12A)-H(12E)	109.5
H(12D)-C(12A)-H(12E)	109.5
C(11A)-C(12A)-H(12F)	109.5
H(12D)-C(12A)-H(12F)	109.5
H(12E)-C(12A)-H(12F)	109.5
C(14A)-C(13A)-C(5A)	115.4(5)
C(14A)-C(13A)-H(13C)	108.4
C(5A)-C(13A)-H(13C)	108.4
C(14A)-C(13A)-H(13D)	108.4
C(5A)-C(13A)-H(13D)	108.4
H(13C)-C(13A)-H(13D)	107.5
C(15A)-C(14A)-C(13A)	113.2(5)
C(15A)-C(14A)-H(14C)	108.9
C(13A)-C(14A)-H(14C)	108.9
C(15A)-C(14A)-H(14D)	108.9
C(13A)-C(14A)-H(14D)	108.9
H(14C)-C(14A)-H(14D)	107.8
C(16A)-C(15A)-C(14A)	113.6(5)
C(16A)-C(15A)-H(15C)	108.8
C(14A)-C(15A)-H(15C)	108.8
C(16A)-C(15A)-H(15D)	108.8
C(14A)-C(15A)-H(15D)	108.8

H(15C)-C(15A)-H(15D)	107.7
C(15A)-C(16A)-H(16D)	109.5
C(15A)-C(16A)-H(16E)	109.5
H(16D)-C(16A)-H(16E)	109.5
C(15A)-C(16A)-H(16F)	109.5
H(16D)-C(16A)-H(16F)	109.5
H(16E)-C(16A)-H(16F)	109.5
C(1A)-C(17A)-H(17D)	109.5
C(1A)-C(17A)-H(17E)	109.5
H(17D)-C(17A)-H(17E)	109.5
C(1A)-C(17A)-H(17F)	109.5
H(17D)-C(17A)-H(17F)	109.5
H(17E)-C(17A)-H(17F)	109.5
C(1A)-C(18A)-H(18D)	109.5
C(1A)-C(18A)-H(18E)	109.5
H(18D)-C(18A)-H(18E)	109.5
C(1A)-C(18A)-H(18F)	109.5
H(18D)-C(18A)-H(18F)	109.5
H(18E)-C(18A)-H(18F)	109.5
C(2A)-C(19A)-H(19D)	109.5
C(2A)-C(19A)-H(19E)	109.5
H(19D)-C(19A)-H(19E)	109.5
C(2A)-C(19A)-H(19F)	109.5
H(19D)-C(19A)-H(19F)	109.5
H(19E)-C(19A)-H(19F)	109.5
C(2A)-C(20A)-H(20D)	109.5
C(2A)-C(20A)-H(20E)	109.5
H(20D)-C(20A)-H(20E)	109.5
C(2A)-C(20A)-H(20F)	109.5
H(20D)-C(20A)-H(20F)	109.5
H(20E)-C(20A)-H(20F)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for ohj197pca21. 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}
B(1)	13(2)	16(3)	26(3)	2(2)	-4(2)	3(2)
O(1)	16(2)	15(2)	34(2)	-1(1)	1(1)	3(1)
O(2)	14(2)	22(2)	33(2)	4(2)	5(1)	9(1)
O(3)	23(2)	23(2)	33(2)	2(2)	0(2)	9(1)
C(1)	17(2)	14(3)	39(4)	-1(2)	0(3)	5(2)
C(2)	13(2)	24(3)	36(3)	4(2)	3(2)	8(2)
C(3)	15(2)	17(2)	29(3)	-1(2)	4(2)	-2(2)
C(4)	14(2)	19(2)	30(3)	3(2)	-4(2)	-3(2)
C(5)	15(2)	12(3)	36(4)	-4(2)	3(2)	0(2)
C(6)	22(2)	17(2)	32(3)	-1(2)	2(2)	-1(2)
C(7)	8(2)	17(2)	33(3)	0(2)	0(2)	0(2)
C(8)	13(2)	16(2)	33(3)	-2(2)	1(2)	0(2)
C(9)	18(2)	17(2)	35(3)	1(2)	1(2)	1(2)
C(10)	20(3)	32(3)	33(4)	0(2)	-3(3)	-1(2)
C(11)	50(4)	63(4)	38(3)	2(3)	6(3)	-24(3)
C(12)	52(4)	85(5)	34(4)	3(3)	1(3)	-20(4)
C(13)	22(2)	33(3)	32(3)	-7(3)	-1(2)	2(2)
C(14)	22(3)	29(3)	28(4)	-3(2)	4(3)	4(2)
C(15)	25(3)	50(3)	27(3)	-4(3)	5(2)	4(3)
C(16)	43(4)	67(5)	40(5)	-13(3)	20(4)	-12(3)
C(17)	25(3)	31(3)	37(4)	2(3)	-3(2)	2(2)
C(18)	26(3)	19(3)	56(4)	2(2)	2(3)	1(2)
C(19)	32(3)	26(3)	38(3)	-7(2)	1(2)	1(2)
C(20)	17(3)	20(3)	37(4)	2(2)	3(2)	8(2)
B(1A)	11(2)	22(3)	25(3)	0(2)	0(2)	4(2)
O(1A)	19(2)	22(2)	33(2)	2(2)	-1(2)	2(1)
O(2A)	15(2)	13(2)	33(2)	0(1)	1(1)	-2(1)
O(3A)	22(2)	24(2)	32(2)	0(2)	4(2)	-9(1)
C(1A)	17(2)	14(2)	41(3)	1(2)	3(2)	-1(2)
C(2A)	20(2)	8(2)	28(4)	-1(2)	1(3)	-4(2)
C(3A)	13(2)	16(2)	30(3)	2(2)	5(2)	6(2)
C(4A)	16(2)	17(2)	31(3)	-1(2)	1(2)	0(2)
C(5A)	15(2)	24(3)	19(3)	-1(2)	1(2)	6(2)

C(6A)	17(2)	15(2)	35(3)	-1(2)	-2(2)	-3(2)
C(7A)	19(2)	21(2)	24(3)	2(2)	5(2)	5(2)
C(8A)	16(2)	16(2)	29(3)	1(2)	0(2)	4(2)
C(9A)	16(2)	20(2)	28(3)	-1(2)	2(2)	1(2)
C(10A)	21(2)	24(3)	26(3)	-1(2)	-3(2)	3(2)
C(11A)	32(3)	51(4)	31(3)	-6(3)	-9(2)	11(3)
C(12A)	52(4)	76(5)	46(4)	7(4)	-12(3)	24(4)
C(13A)	23(3)	28(3)	27(3)	-7(2)	2(2)	0(2)
C(14A)	25(3)	33(4)	28(4)	0(2)	5(3)	2(2)
C(15A)	37(3)	37(3)	36(3)	-6(3)	0(3)	10(3)
C(16A)	33(3)	55(4)	26(4)	-11(2)	-2(3)	11(2)
C(17A)	24(3)	32(3)	31(3)	4(3)	4(2)	-9(2)
C(18A)	31(3)	16(2)	56(4)	6(2)	-1(3)	1(2)
C(19A)	28(3)	25(3)	37(3)	-7(2)	2(2)	0(2)
C(20A)	18(3)	26(3)	51(5)	0(2)	-3(3)	-3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ohj197pca21.

	x	y	z	U(eq)
H(3)	9363	-1523	6292	40
H(4)	6944	1754	5371	25
H(6)	9111	-1527	5726	29
H(9A)	7036	2559	6527	28
H(9B)	8019	1427	6647	28
H(10A)	5910	57	6529	34
H(10B)	6885	-836	6719	34
H(11A)	6717	956	7177	60
H(11B)	5802	1972	6985	60
H(12A)	4666	-340	7006	86
H(12B)	4995	262	7375	86
H(12C)	5575	-1300	7213	86
H(13A)	7763	-15	4981	35
H(13B)	8216	-1721	5118	35
H(14A)	9969	-661	5144	32
H(14B)	9542	1120	5041	32
H(15A)	9036	112	4505	41
H(15B)	9451	-1671	4607	41
H(16A)	10843	1095	4526	75
H(16B)	10727	-359	4258	75
H(16C)	11250	-708	4619	75
H(17A)	4922	5596	5299	46
H(17B)	3946	5983	5550	46
H(17C)	4388	4151	5513	46
H(18A)	6353	7525	5956	51
H(18B)	5155	8099	5862	51
H(18C)	6002	7693	5570	51
H(19A)	5420	5176	6651	48
H(19B)	5268	6915	6472	48
H(19C)	6335	5860	6404	48

H(20A)	3457	4242	6030	37
H(20B)	3502	6049	6185	37
H(20C)	3630	4488	6425	37
H(3A)	11758	6566	8050	39
H(4A)	9378	3211	8969	26
H(6A)	11545	6488	8618	27
H(9A1)	9380	2546	7807	26
H(9A2)	10398	3603	7687	26
H(10C)	9338	5977	7651	29
H(10D)	8327	5052	7814	29
H(11C)	8210	3344	7324	46
H(11D)	9196	4328	7160	46
H(12D)	7138	5772	7314	86
H(12E)	7543	5348	6942	86
H(12F)	8124	6764	7153	86
H(13C)	10646	6742	9216	31
H(13D)	10165	5067	9359	31
H(14C)	11929	3868	9307	35
H(14D)	12383	5626	9200	35
H(15C)	11872	6678	9731	44
H(15D)	11454	4901	9838	44
H(16D)	13283	3945	9766	57
H(16E)	13117	5179	10075	57
H(16F)	13633	5823	9730	57
H(17D)	7340	-563	9036	43
H(17E)	6363	-1006	8789	43
H(17F)	6774	846	8819	43
H(18D)	8761	-2524	8373	51
H(18E)	7565	-3090	8470	51
H(18F)	8420	-2680	8760	51
H(19D)	7789	-151	7685	45
H(19E)	7676	-1896	7864	45
H(19F)	8733	-808	7924	45
H(20D)	5876	735	8321	47
H(20E)	5917	-1037	8149	47
H(20F)	6035	573	7922	47