Exploration of new catalytic methodologies for heterocyclic synthesis and C-C Bond Formation.

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Exploration of New Catalytic Methodologies for Heterocyclic Synthesis and C-C Bond Formation.

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Declaration

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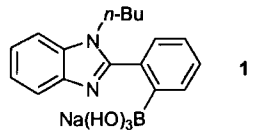
Abstract:

Amino boronate based bifunctional molecules have the potential to be powerful catalysts.[53,54,55] Herein, a number of synthetic approaches to the bifunctional benzimidazole catalyst **1** are described, and the synthesis of a number of analogues are explored. Investigations into the potential of 2-(2-boronobenzene)-N-*n*-butylbenzimidazole sodium hydroxide salt **1** as a catalyst for a number of synthetic transformations, including an aza-version of the Baeyer-Villiger reaction (**Equation 1**), are described.



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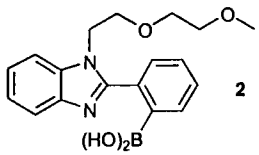

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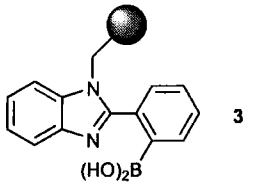

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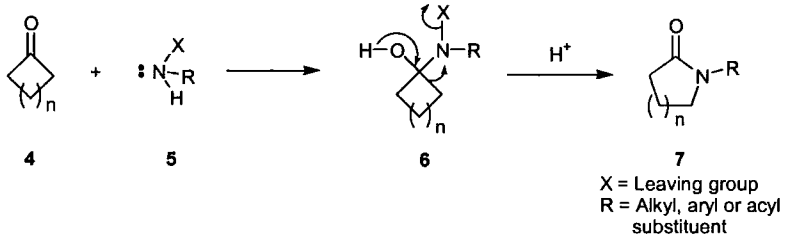
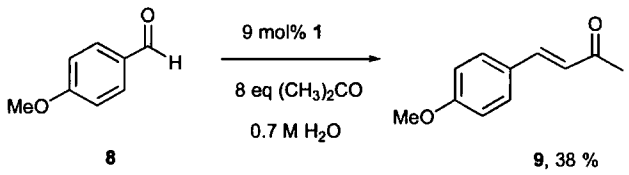


Equation 1

The 2-(2-boronobenzene)-N-*n*-butylbenzimidazole sodium hydroxide salt **1** is shown to be active in the aldol condensation reaction (**Equation 2**), Knoevenagel reaction, and evidence for the promotion of the Michael reaction by **1** is presented. The mechanism by which the aldol condensation reaction is promoted by **1** is explored through kinetic studies.



Equation 2

Abbreviations

Ac	Acetyl group
Ar	Aryl group
BINOL	2,2'-Dihydroxyl-1,1'-binaphthyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl group
BOC	*t*-Butoxycarbonyl group
DCM	Dichloromethane
DMAP	4-N,N-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EI	Electron impact
ES	Electrospray
GC	Gas chromatography
HOSA	Hydroxylamine-O-sulfonic acid
HPLC	High-performance liquid chromatography
IR	Infrared spectroscopy
LCMS	Liquid Chromatography-Mass spectrometry
MB	Mixed bed
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mp	Melting point
MSH	Mesitylene sulfonic acid
NBS	N-bromosuccinamide
NMR	Nuclear magnetic resonance
Ns	4-Nitrobenzene sulfonyl, nosyl group
Oxone™	Potassium peroxomonosulfate
PEG	Polyethylene glycol

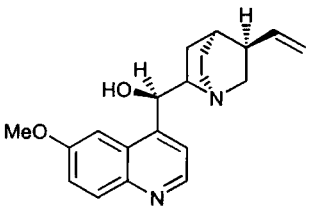
PLE	Pig liver esterase
PMA	Polymolybdic acid
PPh_3	Triphenylphosphine
PTC	Phase transfer catalyst
Pyr	Pyridine
Salen	N,N-Disalicylidene-ethylenediaminato
SPE	Solid phase extraction
Tf	Trifluoromethanesulfonyl group
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl group
Ts	Toluenesulfonyl, tosyl group
Uv	Ultra violet

Contents:

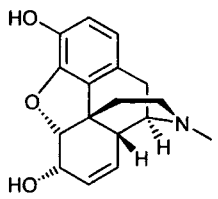
Chapter 1

Section 1.1

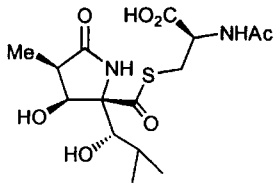
Nitrogen containing heterocyclic compounds are found extensively in natural products, and are incorporated in many medically important compounds such as quinine **1**, morphine **2** and lactacystin **3** (**Figure 1**).[1,2,3] Due to this, research into the effective syntheses of these compounds has attracted considerable interest, and has led to the development of a number of both creative and efficient processes.[4]



1 Quinine: An anti malarial drug



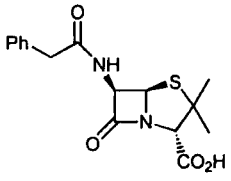
2 Morphine: An opium analgaesic



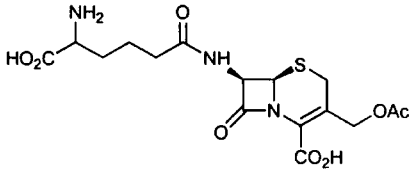
3 (+)-Lactacystin: A proteasome inhibitor

Figure 1

However, despite the amount of interest that the synthesis of nitrogen containing heterocycles has attracted, an intriguing problem remains; the development of a robust and mild synthesis of cyclic amides.[4,5] Lactams, or cyclic amides, are present in many medically important, nitrogen containing compounds.[6,7] Examples of which include lactacystin **3** and the antibiotics penicillin **4** and cephalosporin **5**.[2,3] Currently, syntheses of cyclic amides are often problematic and in many cases employ harsh reaction conditions which can be incompatible with other functional groups.[5,6,7]

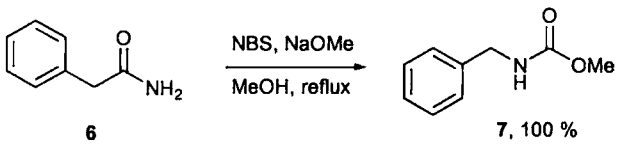


4 Penicillin G



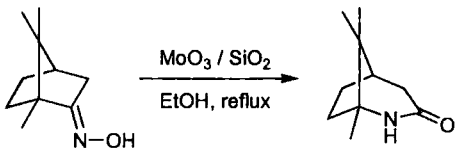
5 Cephalosporin C

Of the techniques available for the synthesis of lactams, one of the most important is through nitrogen insertion reactions. These reactions are widely documented in the literature, and well known examples include the Beckmann, Curtius, Hofmann, Schmidt and Wolff reactions (**Equations 1, 2** and **3**).[5,6,7,8,9,10] Although these reactions allow the *in situ* preparation of lactams and other nitrogen containing compounds, many of them employ azides. This has lead to them falling out of favour due to the safety implications associated with azides.[11]



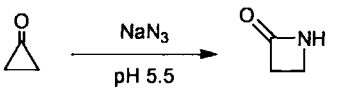
6 **7**, 100 %

Equation 1: *Example of a modified Hofmann rearrangement.*[8]



8 **9**, 96%

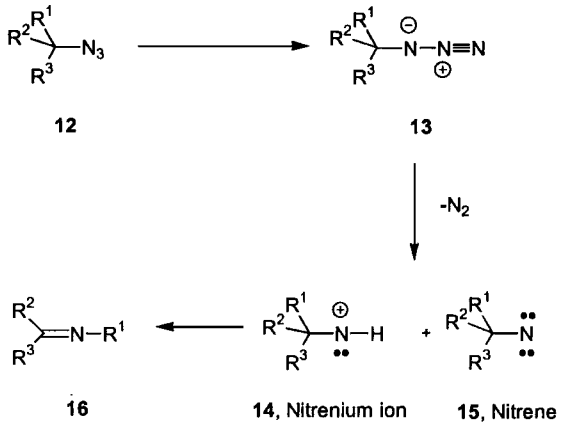
Equation 2: *Example of a Beckmann rearrangement catalysed by silica supported MoO_3.*[9]



10 **11**

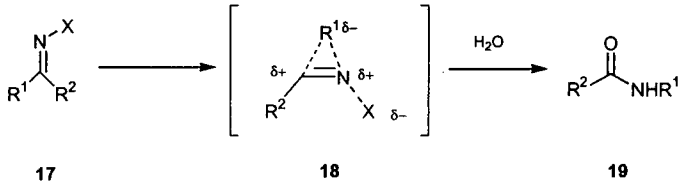
Equation 3: *Example of N-insertion reaction of cyclopropanone using sodium azide.*[10]

Although there is still some controversy surrounding the mechanism of a number of nitrogen insertion reactions, they are generally well understood.[6,7] Typically, these reactions involve the migration of a hydride or an alkyl or aromatic group to an electron deficient nitrogen atom. This species can be either a nitrene or nitrenium ion (**Scheme 1**), or can be formed transiently during the reaction.[6,7,12] In reactions such as the Stieglitz rearrangement, the mechanism involves the loss of a leaving group, to form a discrete nitrenium ion **14** or nitrene **15** (**Scheme 1**).[12] The rearrangement then occurs through the migration of a hydride or carbanion to the nitrenium ion or nitrene as shown in **Scheme 1**.[12]



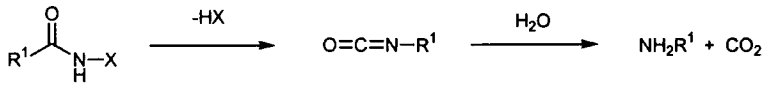
Scheme 1

Alternatively, the rearrangement can occur through the concerted loss of the leaving group and migration. Rearrangements such as these are thought to proceed without the formation of a discrete nitrene or nitrenium ion as shown in **Scheme 2**.[13] An example of this is the Beckmann rearrangement which it is accepted proceeds through a concerted mechanism (**Equation 2**).[6]



Scheme 2

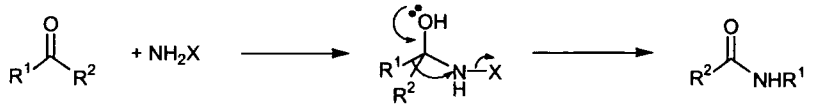
A number of nitrogen insertion reactions are known which proceed through a concerted rearrangement in a similar way to that described above (**Scheme 2**) but that result in the formation of an isocyanate **21**.[14,15] In many cases the isocyanate product is not observed as it is hydrolysed under the reaction conditions (**Scheme 3**).[14] An example of this type of rearrangement is the Curtius reaction which involves the formation and subsequent rearrangement of acyl azides.[15]



20 **21**

Scheme 3

Nitrogen insertion reactions are also known which proceed through the direct rearrangement of the tetrahedral intermediate **23**, which is formed on nucleophilic attack of the carbonyl compound **19** (**Scheme 4**).[7,16] Instead of losing water, as in the Beckmann reaction resulting in the formation of an oxime, in some cases the intermediate can rearrange through a mechanism similar to that of the Baeyer-Villiger reaction.[17]

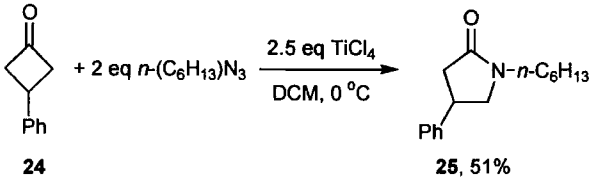


22 **23** **19**

Scheme 4

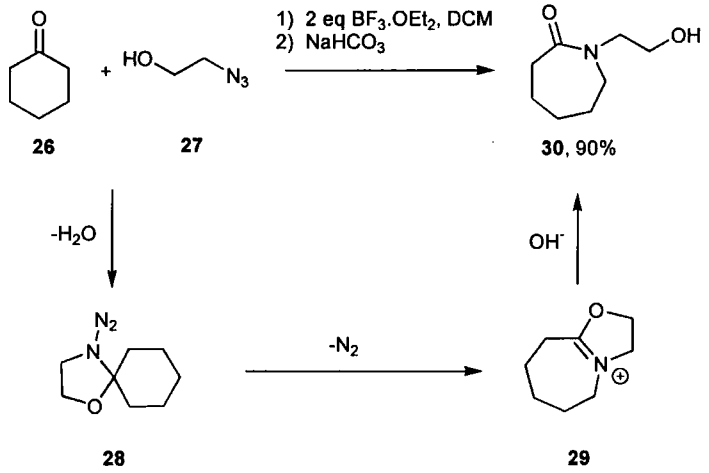
Although there are exceptions, the mechanisms described above represent those of a large number of nitrogen insertion reactions.[6,7,12,16] In a number of nitrogen insertions reactions, for instance the Schmidt reaction, the rearrangements can proceed through a number of these pathways depending on the substrates and reaction conditions.[7]

Traditionally, a limitation of nitrogen insertion reactions is the inability to prepare N-substituted lactams and amides directly using these techniques. Due to the advantages that the development of such a process would offer, a number of research groups have attempted to tackle this problem.[16b-e,18a] Research performed by Aubé *et al.* revealed that N-alkyl lactams and amides could be produced when alkyl azides were reacted with carbonyl compounds in the presence of $TiCl_4$.[16b,c] An example of this reaction is the synthesis of the lactam **25** from the cyclobutanone **24** and *n*-hexylazide as shown in **Equation 4**.[16b]



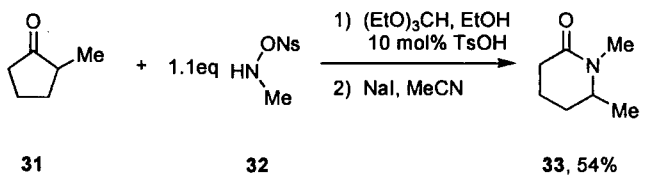
Equation 4

An interesting extension of this chemistry is the reaction of 2-azidoethanol **27** with carbonyl compounds known as the Boyer reaction, shown in **Scheme 5**.[18] In this reaction, instead of attack by the azide, the carbonyl compound is first attacked by the hydroxyl group leading to the formation of the intermediate **28**, rearrangement of which gives the bicyclic compound **29** which can be cleaved to give **30**.[18]



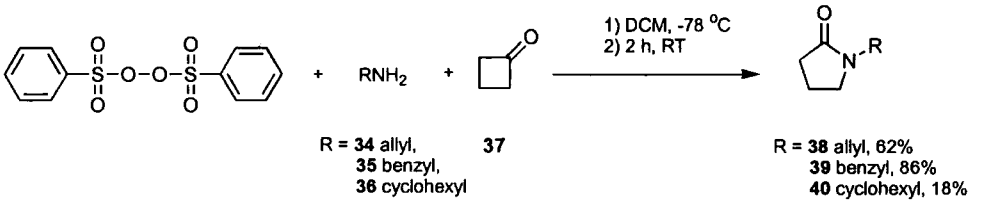
Scheme 5

It was shown by Hoffman *et al.* that N-substituted lactams and amides could also be prepared using N-alkyl-O-arylsulfonylhydroxylamines such as **32** (**Equation 5**).[19] These compounds have similar characteristics to alkyl azides and were shown to allow the preparation of a range of N-substituted lactams and amides, an example of this is shown in **Equation 5**.[19]



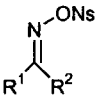
Equation 5[19]

In several cases the N-alkyl-O-arylsulfonylhydroxylamines used by Hoffman *et al.* were reported to have poor thermal stability.[20,13b] This was overcome by the generation of the unstable N-alkyl-O-arylsulfonylhydroxylamines *in situ*, an example of which is shown in **Equation 6**.[20]



Equation 6[20]

The nitrogen insertion reactions of N-alkyl azides and N-alkyl-O-arylsulfonylhydroxylamines, proceed through direct rearrangement of the tetrahedral intermediate **41** (**Scheme 6**).[16,18-21] Due to the presence of alkyl groups on nitrogen, the formation of intermediates such as **43** which are formed in the Beckmann reaction cannot occur. Instead, the reaction proceeds through a mechanism analogous to that of the Baeyer-Villiger reaction.[17,21]



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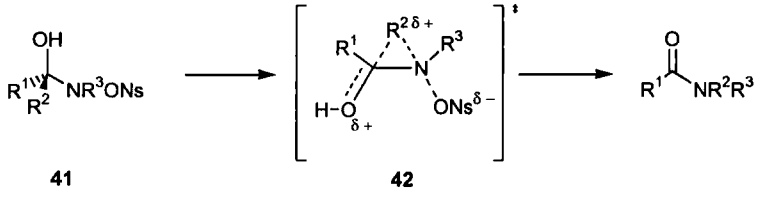


41 **42**

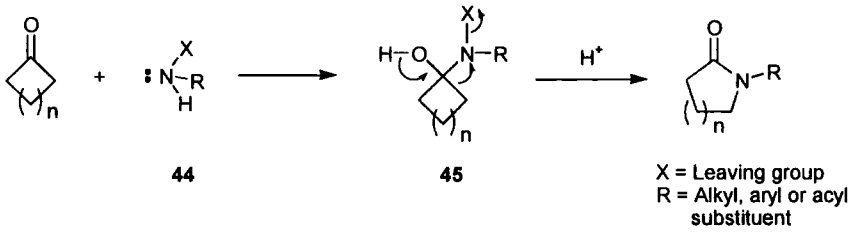
Scheme 6[17]

Mechanistic studies of the reactions of N-alkyl azides and N-alkyl-O-arylsulfonylhydroxylamines with carbonyl compounds were found to support this mechanism.[13b,16c,d,21] The rearrangements of N-alkyl-O-arylsulfonylhydroxylamines in particular, were reported to occur with similar migratory preferences and apparent stereoelectronic effects to those observed in the Baeyer-Villiger reaction.[13b,17,21] It was suggested by Hoffman *et al.* that in a similar way to the primary stereoelectronic effect of the Baeyer-Villiger reaction, the sulfonic acid leaving group must be anti-periplanar to the migrating group of the tetrahedral intermediate **41** (**Scheme 6**) for rearrangement to occur.[13b,21] It was also suggested that as with the secondary stereoelectronic effect of the

Baeyer-Villiger reaction there was a necessity for an anti-periplanar arrangement of the hydroxyl lone pair and the σ-bonding orbital of the migrating group in these rearrangements.[13b,17,21] The preferences for migration of certain groups over others are thought to be due to a combinations of these stereoelectronic effects and the ability of the migrating groups to support a partial positive charge.[21] The striking similarity of this mechanism to that of the Baeyer-Villiger reaction has led to the reactions of N-alkyl-O-arylsulfonylhydroxylamines with carbonyl compounds, often being referred to as aza-Baeyer-Villiger reactions.

Section 1.2

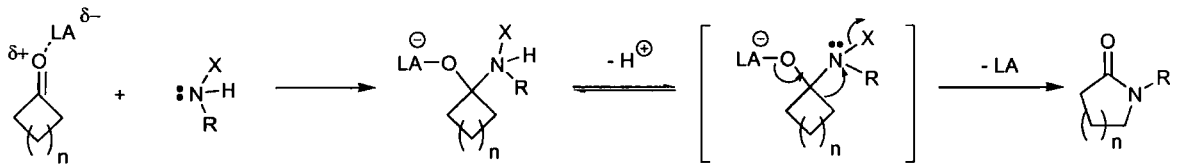
Despite the large number of nitrogen insertion reactions reported in the literature, the development of nitrogen insertion reactions of N-substituted compounds remains a worthwhile objective.[6,7] Such a reaction potentially offers a highly selective method for the synthesis of amides and lactams, and could have enormous potential in organic synthesis. Therefore, we made efforts to develop an aza-version of the Baeyer-Villiger reaction which could be used to selectively prepare amides and lactams. Initially our investigations were focused on the selection of a range of compounds which would behave as nitrogen containing per-acid analogues. Suitable compounds must contain a leaving group, but must also remain nucleophilic at the nitrogen centre. Clearly, the balance between nucleophilicity of the molecule and the leaving group ability is very important. Potential reagents must be nucleophilic enough to allow attack of the carbonyl, but must also contain a leaving group the loss of which, after attack has taken place, is necessary for rearrangement (**Scheme 7**).[13b,16,19,20]



Scheme7

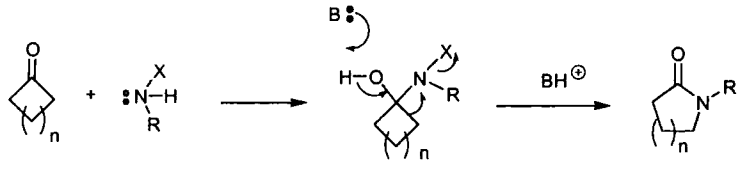
After the selection and synthesis of a number of potential per-acid equivalents, these compounds would then be tested for the desired activity using high through-put screening. After the identification of a number of suitable compounds, our investigations would then focus on the application of catalysis to the aza-Baeyer-Villiger reaction, with particular emphasis on asymmetric and bifunctional catalysts. Due to the mechanism suggested for similar reactions (**Scheme 7**), an aza-Baeyer-Villiger reaction may be susceptible to promotion by both Lewis acids and Lewis bases, potentially allowing the successful application of asymmetric and bifunctional catalysts.[21]

Literature precedents exist for the promotion of nitrogen insertion reactions of N-substituted species by both Lewis and Brønsted acids.[16b,19] Research performed by Aubé *et al.* demonstrated that the insertion of alkyl azides into carbonyls, could be promoted by Lewis acids.[16b] This was also observed in the reactions of N-alkyl-O-arylsulfonylhydroxylamines with carbonyl compounds reported by Hoffman *et al.*, which were shown to be promoted by tosic acid.[19] As the mechanism of an aza-version of the Baeyer-Villiger reaction may proceed in a similar manner to these reactions, this strongly indicates that it may also be possible to promote such a reaction by Lewis acids (**Scheme 8**).[16b]



Scheme 8

Literature reports also suggested that it may be possible to promote an aza-Baeyer-Villiger reaction with bases. It was reported by Hoffman *et al.* that in the reactions of N-alkyl-O-arylsulfonylhydroxylamines, the presence of triethylamine promotes rearrangement by deprotonation of the tetrahedral intermediate formed.[20] The mechanism by which base could promote an aza-version of the Baeyer-Villiger reaction is represented in **Scheme 9**.[20]



44 **48**

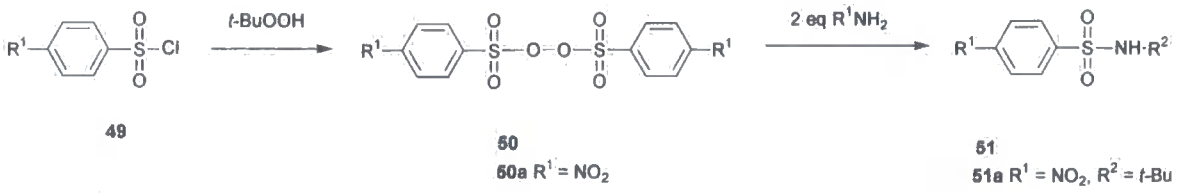
Scheme 9

Therefore, if an aza-Baeyer-Villiger reaction could be developed, then it may be possible to promote it using a catalyst which contains both acidic and basic functionalities. Such 'bifunctional' catalysts have been shown to be effective in a range of reactions including the Michael and Aldol reactions, in many cases giving yields and enantioselectivities to rival those of enzymatic reactions.[22] Although currently they are not widely used in synthesis, a large amount of research is being conducted into the development of bifunctional catalysts and they are becoming recognised as very powerful catalysts.[22]

Section 1.2.1

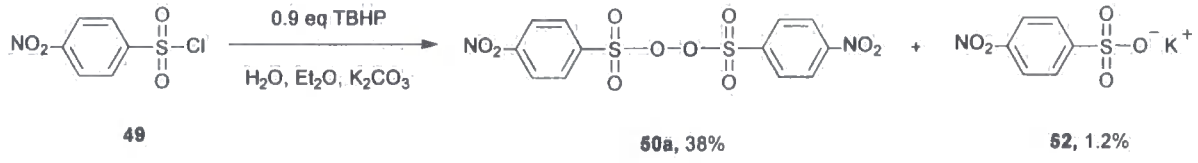
Our investigations initially focused on the selection of a range of compounds that could behave as nitrogen containing per-acid equivalents, which were to be subsequently tested for the desired reactivity. Potential per-acid equivalents were identified from literature reports, commercial sources and were also designed for the purpose. The first compounds investigated were the N-alkyl-O-arylsulfonylhydroxylamines reported by Hoffman *et al.*[13b,19,20] As these compounds had been shown by Hoffman *et al* to undergo the desired reactions, they offered a promising starting point for our investigations.[13b,19,20]

Hence, attempts were made to prepare a range of N-alkyl-O-arylsulfonylhydroxylamines from sulfonyl peroxides according to the literature procedure reported by Hoffman *et al.* shown in **Scheme 10**.[24]



Scheme 10

The 4-nitrobenzenesulfonyl peroxide **50a** used in this synthesis was prepared according to the literature procedure reported by Dannely *et al.*[25] This was achieved through the treatment of nosyl chloride with an aqueous solution of *t*-butyl hydroperoxide, potassium carbonate and ethanol as shown in **Equation 7**.[25] The crude peroxide was collected on precipitation from the reaction mixture, and was purified by recrystallisation from acetone (-10 °C). The purified **50a** was identified by comparison of the characterisation data with the literature data.[25]



Equation 7

After collection of the crude precipitate by filtration of the reaction mixture, the mother liquors obtained were cooled to -20 °C for 12 hours, after which yellow needle-like crystals were observed in the solution (1.2% yield). Upon analysis the crystals formed were found to be nosic acid potassium salt **52** (**Equation 7**).[26,27,28] The chemical connectivity of **52** was confirmed by single crystal X-ray diffraction analysis **Figure 2**

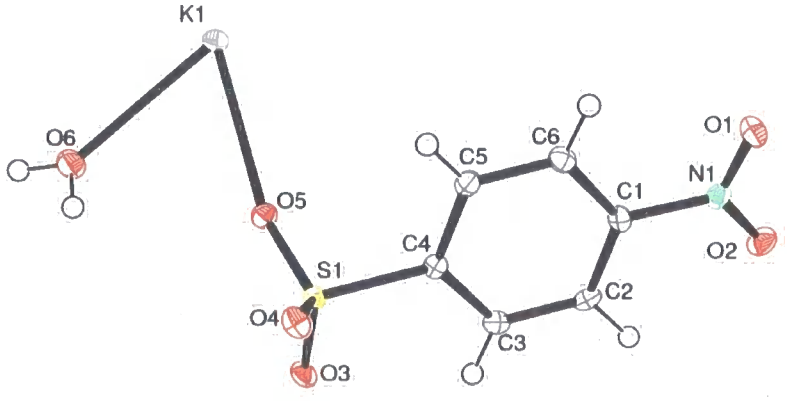
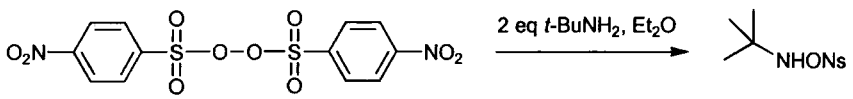


Figure 2: Thermal ellipsoid plot of **52** at 50 % probability.[26,27]

(**Appendix 1**).[27,28] The formation of nosic acid **52** during this reaction may be due to the competing hydrolysis of nosyl chloride under the reaction conditions.

Attempts were made to prepare the N-alkyl-O-benzenesulfonylhydroxylamines from the peroxide **50a**, through reaction with a series of amines according to the synthesis reported by Hoffman *et al.*[24] Unfortunately, despite our efforts to prepare a range of these compounds, only N-*t*-Bu-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a** could be successfully prepared (**Equation 8**).[24] This was achieved through the treatment of a cooled (-20 °C) solution of the peroxide **50a** (diethyl ether), with *t*-butylamine, and stirring at -20 °C for 2 hours and 30 minutes.

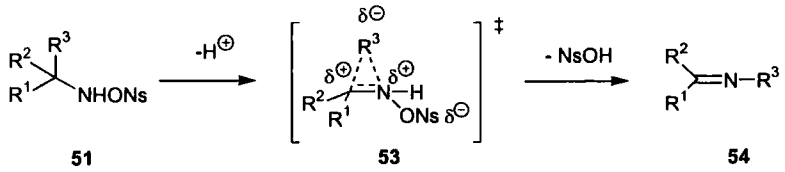


50a **51a**, 60%

Equation 8

Evaporation of the reaction mixture gave a yellow waxy solid which contained **51a**, identified by the characteristic ^{1}H NMR peaks at 8.40 (d, *J* 9 Hz, 2 H), 8.19 (d, *J* 9.2 Hz, 2 H) and 0.97 ppm (s, 9 H).[24] The crude hydroxylamine **51a** was purified by filtration through a short silica column (diethyl ether, -10 °C) to give a white waxy solid. This compound was found to be thermally unstable; after only 2 hours at room temperature the ^{1}H NMR revealed peaks at 8.25 (d, *J* 8.4 Hz, 2 H) and 8.05 ppm (d, *J* 8.4 Hz, 2 H), due to nosic acid formed on decomposition of **51a**.[23]

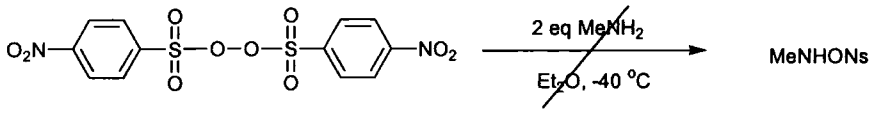
The thermal instability and decomposition of hydroxylamines such as **51a** is well documented in the literature.[29a,c,d] These compounds are known to decompose through a Stieglitz rearrangement to give imines as shown in **Scheme 11**.[29a,c,d] This rearrangement occurs through the concerted migration of the alkyl group from nitrogen to oxygen and loss of nosic acid (**Scheme 11**).[29]



51 **53** **54**

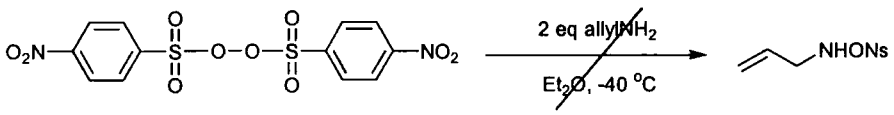
Scheme 11

Attempts were also made to prepare the methyl, allyl and 4-methoxybenzene N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines, through the reaction of methylamine, allylamine and 4-methoxybenzylamine with **50a** according to the literature procedure **Equations 9 and 10**.[24] However, these reactions were not successful, and the desired hydroxylamines **51b** and **51c** could not be isolated.



50a **51b**

Equation 9



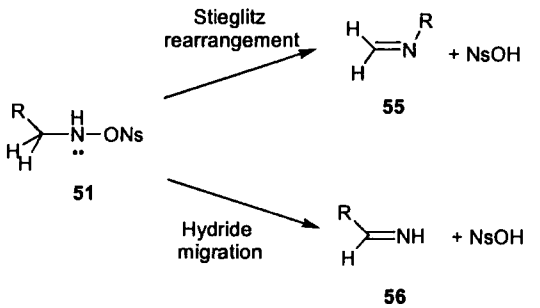
50a **51c**

Equation 10

After stirring at -78 °C for two hours, the reactions described above (**Equations 9** and **10**) were worked-up through the filtration of the reaction mixtures through short silica columns (diethyl ether, -10 °C), followed by evaporation. Unfortunately, the crude products obtained from these reactions were not found by ^{1}H NMR to contain the desired compounds **51b** and **51c**.[24] The crude product isolated on work-up of the reaction of methylamine with the peroxide **50a** (**Equation 9**), was found to contain peaks in the aromatic region of the ^{1}H NMR spectrum due to nosic acid, indicating that the product had been formed during the reaction but had decomposed.[22,24,29]

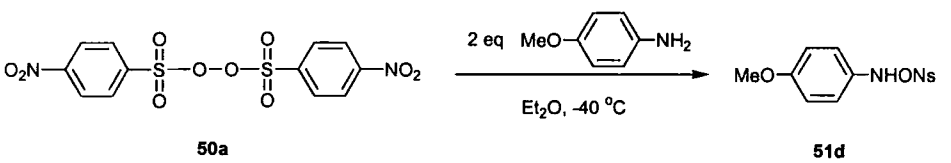
The crude product obtained on work-up of the reaction of allylamine with the peroxide **50a** (**Equation 10**), was also found by ^{1}H NMR to contain none of the desired compound **51c**.[24]

In this residue, evidence for the presence of nosic acid was obtained by ^{1}H NMR, indicating that the desired product **51c** had been formed, but had decomposed either during the reaction, work-up or analysis.[29] The difficulty encountered in the synthesis of **51b** and **51c** was presumably due to these compounds being less stable than the hydroxylamine **51a**. These compounds can decompose through the migration of a hydride from the α-position to form an imine as shown in **Scheme 12**, as well as through a Stieglitz rearrangement.[29,30]



Scheme 12

When 4-nitrobenzenesulfonyl peroxide **50a** was reacted with 4-methoxybenzylamine the reaction was found to be more successful (**Equation 11**). The reaction was performed according to the literature procedure (**Equations 8**, **9** and **10**), and resulting solution was stirred at -40 °C for 2 hours after which no remaining **50a** was observed in the reaction mixture by TLC.



Equation 11

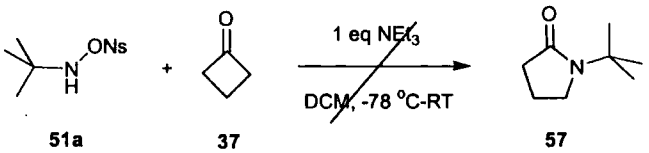
The crude product obtained on filtration of the reaction mixture through a short silica column (diethyl ether, -10 °C), and evaporation (-20 °C) was found by ^{1}H NMR to contain a number of compounds of which only nosic acid could be accurately identified due to the complexity of the spectrum.[23] However, mass spectrometry (ES +) of the crude material

provided evidence for the formation of **51d** (325.6, MH) as well as for the presence of nosic acid (*m/z* 226.0, NsONa) formed on decomposition of **51d**.[29]

Section 1.2.2

The poor thermal stability of these compounds would seriously compromise their potential as reagents for an aza-Baeyer-Villiger reaction. It was understood that the most effective way to develop aza-version of the Baeyer-Villiger reaction would be to run a large number of reactions in parallel through a series of screening experiments. This would hopefully allow potential reagents and catalysts to be identified, which could then be developed further. However, in order to do this large quantities of reagents would need to be prepared, stored and handled. Therefore, potential per-acid equivalents would be required to have reasonable levels of thermal stability.

Despite the unsuitability of the compounds prepared so far for use in an investigation of this type, it was decided that the reactions reported by Hoffman *et al.* would be reproduced, as they may give some insight into the aza-Baeyer-Villiger reaction and the type of reagents suitable for this reaction.[13b,19,20] Attempts to reproduce these reactions focused on the reaction of the N-*t*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a** with cyclobutanone as shown in **Equation 12** according to the literature procedure described by Hoffman *et al.*[20]



51a **37** **57**

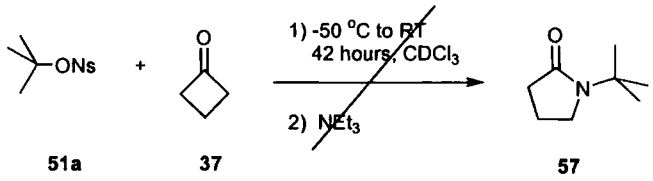
Equation 12

This reaction was performed through the treatment of a cooled (-78 °C) solution of **51a** (DCM) with cyclobutanone. The resultant solution was slowly warmed to room temperature whilst being gently shaken in accordance with the literature procedure, before triethylamine was added and the solution mixed for a further 10 minutes.[20] The crude product obtained on evaporation of the material obtained was found by ^{1}H NMR to contain

a number of products. Of these it was possible to tentatively identify the nosic acid triethylamine salt due to, amongst others, peaks at δ_H 8.24 (d, *J* 8.8 Hz, 2 H), 8.05 (d, *J* 8.4 Hz, 2 H), 3.24-3.09 (m, 6 H) and 1.38 ppm (t, *J* 7.4 Hz, 9 H).[23] A complex pattern of peaks were also observed between δ_H 3.04 and 1.09 ppm, potentially indicating the presence of the lactam product **57** (**Equation 12**).[30] However, when the crude material was further analysed (^{13}C, IR) there was no further evidence for the presence of **57**.[30]

Attempts were made to isolate the product **57**, which may have been formed during the reaction of **51a** and cyclobutanone (**Equation 12**), through Krugelröhr distillation. Unfortunately, this was unsuccessful, as no evidence of the product **57** was observed by ^1H NMR in any of the distillation fractions collected.[30] The apparent loss of **57** during purification was not due the volatility of **57**, as the literature value for the boiling point of this compound reported to be 202 °C, and during the distillation precautions had been taken to prevent the loss of volatile materials occurring, including the collection and analysis of all fractions including material collected in the cold trap (N_2).[30] The most plausible explanation for the absence of **57** after purification was that this product had not been formed during the reaction. The only evidence for the formation of the product had been low level, partially obscured peaks in the ^1H NMR spectrum, and no evidence had been seen in the IR or ^{13}C spectral data.[30]

To eliminate the possibility that the product **57** had been lost during purification, the reaction was repeated on an NMR scale (~0.7 ml) as shown in **Equation 13**. This involved the treatment of a cooled (-50 °C) solution of **51a** in $CDCl_3$ with cyclobutanone according to the literature procedure, described previously.[20] The reaction was slowly warmed to room temperature, mixed by gentle shaking, and triethylamine was added.[20] After 10 minutes the reaction was analysed by ^1H NMR, and from this it could be seen that the nosic acid triethylamine salt had been formed.[23] Apart from the signals due to the salt and the starting materials, there were very few other signals observed and none which corresponded to the desired compound.[30] Even after 42 hours at room temperature there was still no further change observed in the ^1H NMR of the reaction mixture.



51a **37** **57**

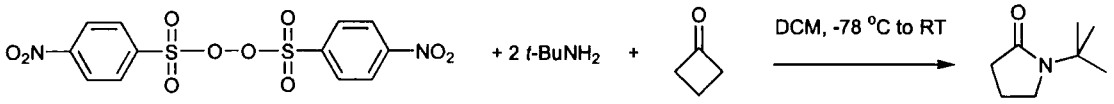
Equation 13

The lack of reactivity displayed in these reactions was intriguing. Although they had been carefully carried out according to the literature procedure, in our hands there had been no evidence of reaction.[19,30] This may be due to the poor nucleophilicity of **51a**, caused by the bulky *t*-butyl group, or due to the cyclobutanone not being activated.[29] In a number of reactions reported by Hoffman *et al.*, it had been suggested that even when no additional acid was added to the reactions, they may be promoted by residual acid present in the reaction mixture carried through as impurities from the hydroxylamine starting materials.[16b,19,20] Therefore, it was possible that if activation of cyclobutanone was not occurring in the reactions performed in our hands, **51a** may be so poorly nucleophilic that it may decompose before reaction took place.

Therefore, attempts were made to perform the nitrogen insertion reaction of cyclobutanone using **51a** generated *in situ* according to the procedure reported by Hoffman *et al.* (**Equation 14**).[19] By performing the reaction in this way the problems associated with instability of **51a,** and the lack of activation of cyclobutanone should be avoided as the reaction proceeds with production of acid.[19] Although, the reactions of ketones with N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines generated *in situ* would avoid the problems associated with the poor thermal stability of these compounds, they are unsuitable for the investigations into the development of an aza-Baeyer-Villiger reaction. These reactions would contain numerous species which may prevent a clear picture of the mechanism of these reactions being obtained, and could hinder attempts to develop catalytic systems. However, by reproducing these reactions further insight into the desired reactivity may be acquired.

Attempts were made to repeat the reaction of cyclobutanone with N-*t*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a** generated *in situ* from the reaction of 4-

nitrobenzenesulfonyl peroxide **50a** with *t*-butylamine as shown in **Equation 14**.[19] The reaction was performed in a similar way to those performed previously, through the treatment of a cooled (-78 °C) solution of the peroxide **50a** and cyclobutanone (DCM) with 2 equivalents of *t*-butylamine.[19] The reaction mixture was then slowly warmed (-20 °C) and stirred for 2 hours.



50a **37** **57**

Equation 14

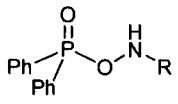
The crude material obtained after aqueous work-up of this reaction was analysed (^{1}H, ^{13}C, TLC, IR, MS), but was not found to contain the nitrogen inserted product **57**.[19,30] The major constituents of the crude product were instead nosic acid and other decomposition products of the starting materials, indicated by a complex pattern of peaks in the ^{1}H NMR spectrum.[24,29] However, it was possible that these peaks may be obscuring signals due to the nitrogen insertion product **57**, and to avoid this possibility, separation of the components of the crude product was attempted through Krugelröhr distillation. Unfortunately, despite strenuous efforts to prevent the loss of the nitrogen insertion product, if formed, during distillation, the product was not found. It appeared that, as in the reactions of **51a** with cyclobutanone (**Equations 12** and **13**), the decomposition of **51a** had occurred before the attack of cyclobutanone took place, due to the low nucleophilicity of **51a**.

During our attempts to prepare N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines for use as reagents in the aza-Baeyer-Villiger reaction, it had become clear that these compounds were unsuitable for our purposes. Only the N-*t*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a** had been stable enough to be isolated and despite literature reports of the reaction, in our hands the reaction of **51a** with cyclobutanone was found to be inactive.[19] Even if the reactivity **51a** towards carbonyl compounds could be improved, perhaps by the use of stronger acids, the use of **51a** would only allow the synthesis of *t*-butyl-substituted lactams. For these reasons the search for potential reagents

for the aza-Baeyer-Villiger reaction moved away from N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines.

Section 1.2.3

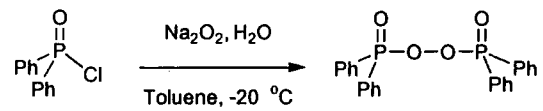
The search for more stable compounds for use as reagents in the aza-version of the Baeyer-Villiger reaction now focused on N-alkyl-O-(diphenylphosphoryl)hydroxylamines **58**, considered to be phosphorous analogous of N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines **51**.



58

These species appeared to be more stable than the sulfur containing compounds, due to the reduced lability of the phosphoryl leaving group, evident in the propensity of these compounds to rearrange without loss of phosphinic acid, as well as through Stieglitz and imine forming reactions.[29,30,33] The N-alkyl-O-(diphenylphosphoryl)hydroxylamines **58** have been reported in the literature to display similar chemistry to their sulfur containing equivalents, including electrophilic amination reactions and Schmidt reactions.[33] The reported behaviour of these compounds, including the formation of potassium nitrenoids, indicated that these species may posses the necessary characteristics which would allow them to be effective per-acid equivalents.[31,32,33]

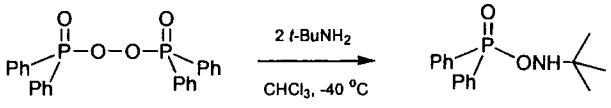
These compounds were prepared in a similar way to the analogous sulfur containing compounds, according to the literature procedure reported by Masse and Sturtz *et al.*[31,32] The peroxide **60** was prepared through the reaction of diphenylphosphinic chloride with sodium peroxide according to the procedure reported by Dannley *et al.* (**Equation 15**).[34] The isolation of **60** was achieved, even on a 10 g scale, through the recrystallisation (diethyl ether:hexane) of the crude product obtained on evaporation. Using this method it should be possible to prepare the large quantities of **60** that would be required for the hydroxylamine compound **58** derived from it to be used in screening experiments.



59 **60, 47%**

Equation 15

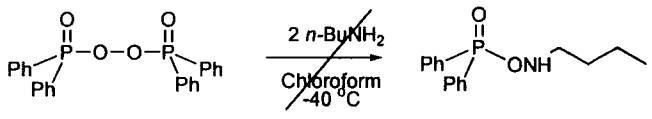
Attempts were then made to prepare the N-*t*-butyl-O-(diphenylphosphoryl)hydroxylamine **58a** according to the literature procedure reported by Masse, Sturtz *et al.*[31,32] This reaction was performed through the treatment of a solution of the peroxide **60** with 2 equivalents of *t*-butylamine in HPLC grade chloroform (-78 °C) as shown in **Equation 16**. After 3 hours the solvent was removed from the reaction mixture under reduced pressure at -20 °C, and the residue obtained was passed through a short Florasil® column using cooled (-40 °C) dichloromethane as the solvent. The product obtained on evaporation was identified by comparison of the characterisation data with that reported in the literature.[31,32] The ^{1}H NMR spectrum of **58a** (-20 °C) revealed peaks at 7.79-7.71 (m, 4 H), 7.47-7.32 (m, 6 H) and 1.02 ppm (s, 9 H), characteristic of the desired hydroxylamine **58a**, as well as low levels of decomposition products for example the peaks at 6.97 and 1.31-1.14 ppm.[31] The ^{31}P NMR of **58a**, which contained a peak at 35.2 ppm, was also found to be consistent with that reported in the literature.[31,32]



60 **58a**

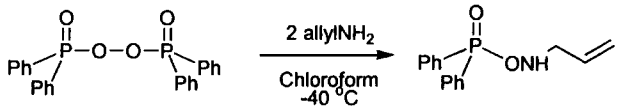
Equation 16

When attempts were made to prepare the N-*n*-butyl and N-allyl-O-(4-nitrobenzenesulfonyl)hydroxylamines in this way, the reactions were found to be less successful.[31,32] The reactions of *n*-butylamine and allylamine with the peroxide **60** were performed as described previously and are shown in **Equations 17 and 18**.



60 **58b**

Equation 17



60 **58c**

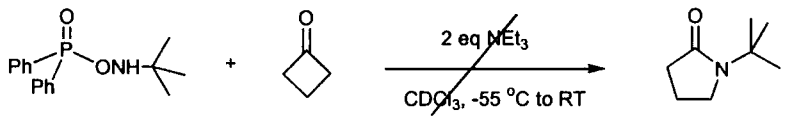
Equation 18

The ^{1}H NMR spectra of the crude products obtained from the reaction of *n*-butylamine with **60** (**Equation 17**) was found to contain signals due the peroxide and *n*-butylamine starting materials as well as low levels of a product shifted up-field at δ_H 1.43-4.60 (m, 2 H, $CH_2CH_2CH_2$), 1.70-1.92 (m, 2 H, CH_2NH) and 3.09 ppm (heptet, *J* 7 Hz, 2 H, CH_3CH_2). The triplet signal due to the terminal methyl group of the *n*-butyl chain of **58b** was not observed, and may have been obscured by that of the starting material which had become distorted.[23,31,32] However, attempts to purify **58b** through the filtration of the crude product through short, cooled (-20 °C) columns packed with either silica gel, alumina or Florasil®, were unsuccessful. The manipulation of the material was found to result in the appearance of new signals in the ^{1}H NMR spectra which were due to decomposition products.

The crude product obtained from the reaction of allylamine and **60** (**Equation 18**), was also found by ^{1}H NMR to contain signals due the allylamine and peroxide starting materials as well as those that were thought may be due to the desired product **58c**, which were shifted from those of the starting materials.[23,31,32,34] The formation of the hydroxylamine **58c** was supported by the mass spectrometry (ES +) data which revealed a signal consistent with the desired product **58c** (*m/z* 296.1, MNa^+), as well as a fragment which may have been formed by decomposition of **58c** (*m/z* 219.1, MH-(NC_3H_5)). However, due to the low levels of product formed and the poor thermal stability of these compounds, attempts to purify and isolate it through chromatography were mot made.

Section 1.2.4

Despite the unsuitability of N-alkyl-O-(diphenylphosphoryl)hydroxylamines as nitrogen containing per-acid equivalents due to their poor thermal stability, if the desired nitrogen insertion reaction could be performed using **58a**, then this would provide a starting point from which more stable analogues of these compounds could be developed. Due to the reduced lability of the phosphoryl group, these compounds may be more nucleophilic than the sulfur analogues, and therefore may undergo the desired nitrogen insertion reaction before decomposition occurs. Therefore, the nitrogen insertion reaction of cyclobutanone with N-*t*-butyl-O-(diphenylphosphoryl)hydroxylamine **58a** was performed in a similar way to the nitrogen insertion reactions previously attempted using N-*t*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a** (**Equation 19**).[20] The reaction was performed on an NMR scale (~0.7 ml), and to prevent decomposition of **58a**, the solution was initially cooled to -55 °C. Cyclobutanone was added to the solution, which was then warmed from -55 °C to room temperature, and treated with triethylamine whilst being shaken gently.



58a **37** **57**

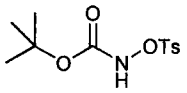
Equation 19

However, even after 3 days the ^{1}H NMR spectrum revealed only cyclobutanone, triethylamine, **58a** and a number signals due to decomposition products.[24,30,31,32] The lack of reactivity observed in this reaction was thought to be an indication that **58a** was not nucleophilic enough to undergo the desired chemistry. Instead of continuing the investigation into the use of **58a** as a reagent for the nitrogen insertion reaction, it was decided that our investigations should move onto the use of other species as potential reagents for the aza-Baeyer-Villiger reaction. This was partially due to the handling problems associated with these compounds, but also due to the fact that if a nitrogen insertion reaction could be developed using **58a** this would only allow the synthesis of *t*-butyl-substituted lactams and amides. One of the aims in developing an aza-version of the

Baeyer-Villiger reaction had been the potential to easily generate N-substituted-amides and lactams. To prepare other N-substituted compounds from **57** would first require the cleavage of the *t*-butyl group followed by selective alkylation. This approach would result in a less effective route to these compounds than is already offered by the use of MSH and related reagents.[35]

Section 1.2.5

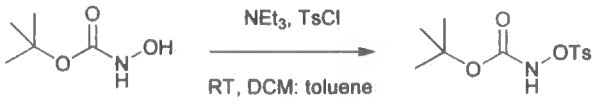
The investigation into the aza-Baeyer-Villiger reaction now turned towards the consideration of more stable compounds as potential per-acid equivalents. Compounds which contained less labile leaving groups than those of the N-alkyl-O-(diphenylphosphoryl)hydroxylamines and N-alkyl-O-(4-nitrobenzenesulfonyl)hydroxylamines were considered, as well as those with more stabilising alkyl groups. Therefore, the N-Boc-O-arylsulfonylhydroxylamine ester **61** was selected as a potential reagent for the aza-Baeyer-Villiger reaction, and the preparation and screening of this compound was planned.[36] This compound is reported in the literature to form metal nitrenoids, and therefore may display the desired chemistry.[36,37] This was more stable than the compounds previously studied due to the involvement of the nitrogen lone pair in the amide bond, reducing the electron density at the nitrogen centre and preventing decomposition. It was hoped that although **61** may be less nucleophilic than the compounds **51a** and **58a**, the increased stability would allow it to react rather than decompose. Unfortunately, if this reagent was found to be an effective per-acid equivalent, the production of a range of N-substituted insertion products would require further synthetic transformations. However, this approach would have an advantage over established methods, as it could allow the development of catalytic systems, including asymmetric catalysts, which would be incompatible with other reagents such as MSH and HOSA.[35]



61

The N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** was prepared as shown in **Equation 20** in 38 % yield.[36,37] This reaction involved the treatment of a cooled (0 °C)

solution of N-Boc-hydroxylamine and tosyl chloride in anhydrous dichloromethane with triethylamine, followed by stirring at room temperature for 1 hour, after which the reaction was quenched by the addition of water.[36,37]



62 **61, 38%**

Equation 20

After aqueous work-up the crude product obtained was recrystallised (diethyl ether:hexane) to give pale yellow crystals. The characterisation data obtained for this material found to be consistent with literature values, and the material was found to be stable when stored at room temperature in small quantities.[37] However, even at 4 °C quantities above 5 g were found to be unstable and were therefore unsuitable for storage. The crystals of **61** obtained were found to be suitable for single crystal X-ray diffraction analysis.[27] As well as confirming the structure of **61**, the crystal structure obtained may reflect the electron density at the nitrogen centre through the lengths of the bonds connected to this atom, for instance, the lability of the tosyloxy group may lead to a lengthening of the bond between nitrogen and the oxygen atom of this group.

Single crystal X-ray diffraction analysis (120 K) of **61** gave bond lengths for the nitrogen to oxygen bond (N_1-O_2) and nitrogen to carbon bond (N_1-C_8) of **61** of 1.4227(15) and 1.381(2) Å respectively (**Figure 3, Appendix 2**).[27,28] These values are very close to those of other carbamates reported in the Cambridge Structural Database (CSD), which were calculated to have average nitrogen to carbon bond

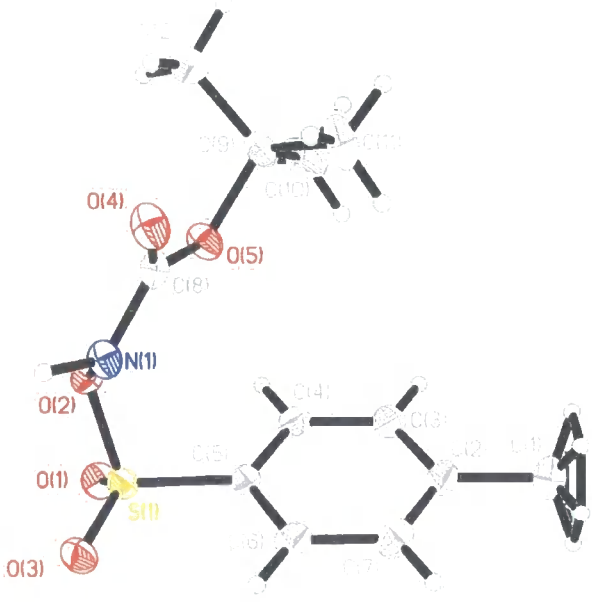


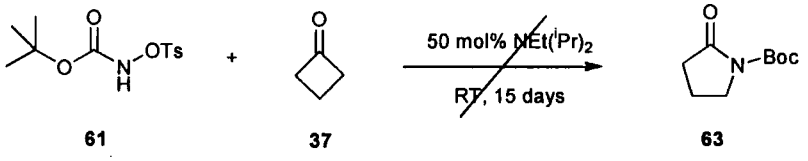
Figure 3: 50% probability thermal ellipsoid plot of **61**

lengths of 1.3729 Å and nitrogen to oxygen bond lengths of 1.4223 Å.

Although the single crystal X-ray diffraction analysis of the compounds from which these average values were calculated were reported to have been performed at a range of temperatures, and therefore must be treated with care, the similarity between these average bond lengths and those calculated for **61** is striking. Although this was unexpected, it was not known whether this would mean that the compound **61** was unsuitable as a reagent for the aza-Baeyer-Villiger.

Section 1.2.6

Initially attempts to assess the potential of **61** to undergo nitrogen insertion reaction were focused on small scale discrete reactions. N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** was reacted with cyclobutanone in the presence of diisopropylethylamine (50 mol%) with anhydrous MeCN as the solvent as shown in **Equation 21**. The reaction was carried out at room temperature under argon and was stirred for 15 days, during which samples were taken and analysed by ^{1}H NMR. The spectra obtained revealed that there had been no reaction between **61** and cyclobutanone.[24,39]

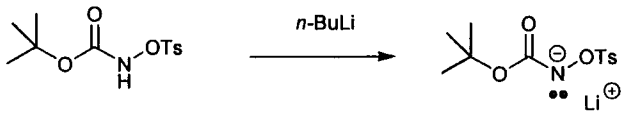


61 **37** **63**

Equation 21

The lack of activity observed in this reaction, presumably due to the electron withdrawing nature of the urethane, may be improved by the use of an acid as well as a base. Although an acid could potentially bind to the carbonyl oxygen of **61** reducing the electron density at the nitrogen centre and therefore reducing its reactivity, it may instead activate the cyclobutanone to attack. It was also possible that the presence of a Lewis acid may activate **61** to the desired activity through the formation of a metal nitrenoid. The formation of

metal nitrenoids and nitrogen based anions of **61** are described in the literature.[37] These species have found application in amination reactions, and are often generated by lithiation **(Equation 22)**.[37]



61 **64**

Equation 22

Investigations were then made into the effects that combinations of Lewis acids and bases had on the reaction of **61** with cyclobutanone. The best approach to this investigation was decided to be through a series of screening experiments which would hopefully allow an effective investigation of the reactivity of **61** under a variety of conditions. Potentially, this could allow the efficient identification of suitable conditions for the nitrogen insertion reaction of **61** to be determined which could then be studied in depth and developed further. To perform an effective screening experiment a method of following the reactions was needed, which would allow the rapid determination of whether reaction had occurred in each of the individual reactions. GC and LCMS were seen as the most appropriate methods of analysis at our disposal; by following the planned screening experiments using these analysis methods, accurate profiles of the reactions could potentially be generated. However, although GC and LCMS appeared initially to be the analysis methods of choice, problems were soon encountered when attempting to follow screening experiments using these methods. Analysis by either LCMS or GC was found to take a long time; as well as the running time of the analysis method, the samples had to be prepared for analysis, which involved purification and dilution of the samples. In the screening experiments that were planned, purification by chromatography through short silica columns was necessary to remove Lewis acids present which may otherwise poison the LCMS and GC columns leading to a reduced lifetime and loss of function. This meant that although the results obtained were of a high quality, analysis of the screening experiments by these methods was often inefficient. In the screening experiments planned a large number of reactions would be performed, the majority of which were expected to display no activity. Due to this a method of analysis was required which would allow a fast way of determining in which reactions activity had occurred, so that only these could be examined further.

Although following the screening experiments by TLC does not provide as accurate a method of analysis as GC or LCMS, in some experiments it was more appropriate as activity could be quickly and easily identified.

Therefore, a screening experiment was performed in which N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** was reacted with a number of carbonyl compounds in the presence of a range of Lewis acids and bases, and the reactivity assessed by TLC. The carbonyl compound selected were benzophenone, cyclobutanone and chalcone and the reactions were performed in the presence of the copper salts $Cu(OTf)_2$ and $CuCl_2$ and with pyridine as the base. The copper complexes were chosen as the Lewis acids for this experiment as a number of copper nitrenoids, and their insertion reactions into alkenes are reported in the literature.[38,40] Triphenylphosphine was also added to the reactions as, it was hoped, that in the event of the copper complexes being inactive PPh_3 may serve as a ligand to the copper salts, activating them to the desired reactivity.[40] The reactions in this screening experiment were performed in small screw-top vials (1.5 ml), which were first charged with the copper salts, followed by the additive, carbonyl compound, and finally **61** as solutions (DCM) (**Table 1**). The reactions were stirred at room temperature for one week during which they were analysed directly by TLC.

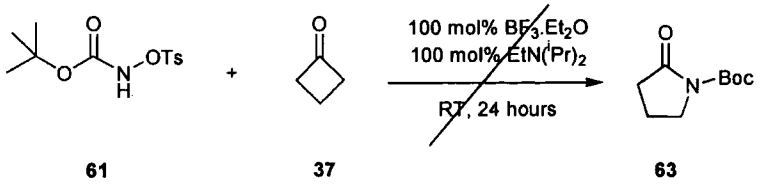
Analysis of this screening experiment by TLC proved effective, and it was found that although in the majority of reactions there was no activity, in some there was a complete loss of at least one of the starting materials (**Entries 5, 8, 11** and **12** in **Table 1**). In order to discover what had occurred, these reactions (**Entries 8, 11** and **12, Table 1**) were repeated on a larger scale (0.06 g). The reaction shown in **Entry 5** (**Table 1**) was not repeated as the TLC of this reaction had revealed a large number of spots, indicating the presence of a numerous compounds. Repetition of these reactions was performed through the addition of the carbonyl reagents to a suspension containing the copper salt and additives (DCM) followed by the addition of **61**. The resulting mixtures were stirred at room temperature for 6 days, and after aqueous work-up the crude materials were analysed by ^1H, ^{13}C NMR and IR. In most of the repeated reactions the ^1H NMR spectra revealed the presence of only the starting materials. However, in the reaction of benzophenone (**Entry 8**) the ^1H NMR of the crude material revealed an increase in the complexity of the signals in the aromatic region. This was thought to be due to side reactions of

triphenylphosphine or pyridine, as there was no loss of intensity of the *t*-butyl-signal or the signal due to the methyl group of **61**.

Entry	Reagent	Complex	Additive
1	Benzophenone	25 mol% $CuCl_2$	-
2			25 mol% pyridine
3			100 mol% PPh_3
4			25 mol% pyridine, 100 mol% PPh_3
5		10 mol% $Cu(OTf)_2$	-
6			25 mol% pyridine
7			100 mol% PPh_3
8			25 mol% pyridine, 100 mol% PPh_3
9	Cyclobutanone	25 mol% $CuCl_2$	-
10			25 mol% pyridine
11			100 mol% PPh_3
12			25 mol% pyridine, 100 mol% PPh_3
13		10 mol% $Cu(OTf)_2$	-
14			25 mol% pyridine
15			100 mol% PPh_3
16			25 mol% pyridine, 100 mol% PPh_3
17	Chalcone	25 mol% $CuCl_2$	-
18			25 mol% Pyridine
19			100 mol% PPh_3
20			25 mol% Pyridine, 100 mol% PPh_3
21		10 mol% $Cu(OTf)_2$	-
22			25 mol% Pyridine
23			100 mol% PPh_3
24			25 mol% Pyridine, 100 mol% PPh_3

Table 1: Reactions of **61** with benzophenone, cyclobutanone and chalcone in the presence of copper(II) complexes, pyridine and triphenylphosphine at room temperature.

The lack of reactivity observed in the screening experiment described above (**Table 1**), indicated to us that the copper complexes, even when in combination with bases, were not capable of promoting the nitrogen insertion reaction of **61** into carbonyl compounds. Although this lack of activity was disappointing, it was seen as an indication that our investigations should move towards the use of other, possibly harder, Lewis acids. Hence, a discrete reaction was performed in which the carbamate **61** and cyclobutanone were reacted in the presence of $BF_3.OEt_2$ and diisopropylethylamine as shown in **Equation 23**. This reaction was intended to allow the effect that the combination of a hard Lewis acid and a base would have on the reaction of **61** with cyclobutanone without the need for a large quantity of **61** to be prepared.

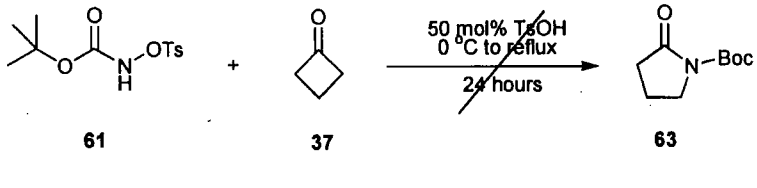


61 **37** **63**

Equation 23

The reaction was performed through the treatment of a solution of **61** and cyclobutanone in dichloromethane with 1 equivalent of $BF_3.OEt_2$ and 1 equivalent of diisopropylethylamine. The reaction was stirred at room temperature for 24 hours during which samples were taken and analysed by ^1H and ^{13}C NMR. Unfortunately, there was no evidence obtained during this time that any reaction had occurred. The NMR data obtained revealing only the **61**, cyclobutanone and diisopropylethylamine starting materials.[24,39]

From the experiments performed so far with **61**, no evidence of the desired reactivity had been observed. It was therefore unlikely that **61** was capable of behaving as a reagent for an aza-version of a Baeyer-Villiger reaction. However, as a final attempt to encourage the reaction of **61** with carbonyl compounds, the possibility that these reactions may be promoted by protic acids was considered. In the reactions of N-alkyl-O-arylsulfonylhydroxylamines reported by Hoffman *et al.* it had been suggested that the reactions could be promoted by protic acids, either as added to the reactions or carried through as impurities from the starting materials.[19,20] Although our attempts to replicate the *in situ* reactions described by Hoffman *et al.* had been unsuccessful, similar conditions may promote the reactions of **61**, and therefore, the effect that protic acids have on the reaction of **61** with cyclobutanone was tested. In the reaction shown in **Equation 24**, 50 mol% of tosic acid was added to a cooled (0 °C) solution of cyclobutanone and **61** in dichloromethane. The solution was then stirred at room temperature for 2 hours after which no change was observed in the reaction mixture by TLC.



61 **37** **63**

Equation 24

To encourage the reaction, the solution was refluxed for 8 hours after which a complete loss of starting material was observed by TLC. After aqueous work-up the crude product was found by ^{1}H NMR to contain a complex pattern of signals including what appeared to be heptets and quintets around 2-3 ppm, thought to be a possible indication that the product **63** had been formed.[39] The crude product was therefore subjected to column chromatography, however, when the fractions were collected and analysed, no evidence was found for the presence of the desired product **63**. Due to this the complex pattern of peaks that had been observed in the ^{1}H NMR of the crude material were attributed to a number of compounds.

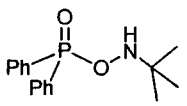
The reaction of **50** with cyclobutanone was repeated in the presence of 10 mol% of tosic acid, but was stirred at room temperature rather than heated to reflux. It was hoped that this would limit the number of products formed in the reaction and encourage the production of **50**. The reaction was performed according to the procedure described above (**Equation 24**) however, even after 1 month under these conditions there was still no significant change observed by ^{1}H NMR or TLC. The reaction was quenched by addition of water, and after aqueous work-up the crude product was found by ^{1}H NMR to contain only signals corresponding to the starting materials and tosic acid.[23,39]

During our investigations into the potential of **61** as a reagent for the aza-Baeyer-Villiger reaction, there had been no evidence that N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** was capable of undergoing the desired chemistry. The presence of the urethane unit in this compound, despite improving the stability of **61**, had had the disadvantage of reducing the nucleophilicity of the nitrogen centre. The balance between electron density at the nitrogen centre, leaving group ability and stability of possible per-acid equivalents was very subtle, and it appeared that in **61** the balance was tipped too far towards low electron density at the nitrogen centre, which although it improved stability, it prevented the desired reactivity. Even when attempts had been made to activate the molecule through the addition of Lewis acids, bases and strong protic acids there had still been no activity observed. Due to these factors, the problems associated with **61** were felt to be insurmountable. Only very harsh reaction conditions could be expected to promote the reaction of **61** with carbonyl compounds and it was very unlikely that these conditions would be compatible with other functional groups and may even prevent the development of catalytic systems.

Section 1.2.7

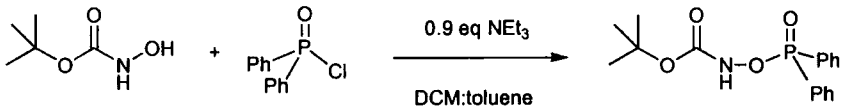
Our attention was now turned towards the selection of other compounds as potential reagents for the aza-Baeyer-Villiger reaction. The selection of suitable molecules was guided by our experience of the behaviour of the previous candidates, and those with higher electron density at the nitrogen centre were chosen. Rather than alter the Boc group, as the presence of this group had been found to give stability, it was decided that the electron density at nitrogen would be adjusted by altering the leaving group. It was hoped that by installing a leaving group which would draw less electron density away from the nitrogen centre, a more nucleophilic candidate could be prepared.

51a



58a

During the synthesis of the possible nitrogen containing per-acid equivalents such as **51a** and **58a**, the N-alkyl-O-(diphenylphosphoryl)hydroxylamines were found to be more stable than their sulfur containing counterparts. This was thought to be due to the phosphoryl leaving group of **58a** being less labile than the arylsulfonyl leaving groups of the analogous **51a**, resulting them being less prone to decomposition.[29,33] Therefore, if N-Boc-O-(diphenylphosphoryl)hydroxylamine could be prepared, then the balance between leaving group ability and nucleophilicity in this molecule may allow it to behave as a per-acid equivalent for the aza-Baeyer-Villiger reaction. Therefore, attempts were made to prepare N-Boc-O-(diphenylphosphoryl)hydroxylamine **65** using similar chemistry to that used in the synthesis of **61** (**Equation 20**). The synthesis of **65** was successfully performed as shown in **Equation 25** through the treatment of a cooled (0 °C) solution of N-Boc-hydroxylamine (DCM) with a solution of diphenylphosphinic chloride (toluene) and triethylamine under argon.



62 **59** **65, 76%**

Equation 25

The reaction was stirred for 4 hours, after which a second portion of toluene was added to the slurry, and stirred for a further 8 hours. The ^{1}H NMR spectrum of the crude product obtained on aqueous work-up revealed signals attributable to the diphenylphosphinic chloride starting material, triethylamine hydrochloride salt and also signals shifted from the starting materials which were thought to be due to the N-Boc-O-(diphenylphosphoryl)hydroxylamine product **65**.[23] Recrystallisation of the crude product (DCM) gave **65** as white crystals (76 %), which were found to be suitable for single crystal X-ray diffraction analysis (**Figure 4, Appendix 3**).[28]

By single crystal X-ray diffraction analysis 3 molecules of **65** were found in the repeating unit represented in **Figure 4**.[27,28] Of the 3 molecules, one differed from the others in the orientation of the substituents at the oxygen centre (O3) as shown in **Figure 5**.[27,28] The average nitrogen to carbon (N1-C5) and nitrogen to oxygen bond lengths calculated for these molecules were 1.4364(14) and 1.3847(18) Å respectively. Once again, these are very similar to the average values calculated from similar structures reported in the Cambridge Structural Database (CSD), and this may indicate that **65** was not capable of undergoing the desired aza-Baeyer-Villiger reaction.

The ^{1}H NMR of this compound, as well as revealing peaks due to the aromatic protons and a peak at 1.39 (s, 9 H) due to the *t*-butyl group, revealed a signal at 8.63 ppm (broad s, 1 H) that was thought to be due to the amine proton. This was confirmed by a D_2O-shake experiment during which the signal at 8.63 ppm in the ^{1}H NMR (D_2O:$CDCl_3$) disappeared and no other peaks were altered. The appearance of the amine

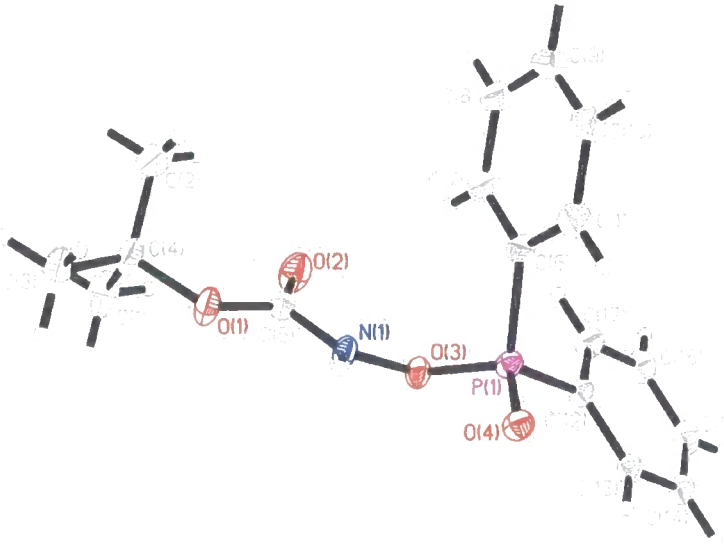


Figure 4: Thermal ellipsoid plot at 50 % probability of **65**.[118]

proton so far up-field was intriguing; the signals corresponding to the amine proton of **61** was observed at δ_H 7.6 ppm, very much lower than that of **65**. This may indicate that the amine proton in **65** is more acidic than that of **61**, due to low electron density at the nitrogen centre making it better able to support a negative charge. It was hoped that the acidity of this proton would allow **65** to be activated through deprotonation and formation of a metal nitrenoid, rather than preventing this molecule behaving as an effective per-acid analogue.[37,38]

Section 1.2.8

Investigation of the reactivity of the phosphoryl compound **65** was conducted through a series of screening experiments in which the reaction of **65** with cyclobutanone was performed in the presence of combinations of Lewis acids and bases. Due to the relative stability of **65**, synthesis of large quantities of this material could be achieved, allowing an extensive investigation into the ability of **65** to behave as a reagent for the aza-Baeyer-Villiger to be made. Therefore, an experiment was planned in which the reactions of **65** and cyclobutanone were performed in a range of solvents including polar solvents, polar protic solvents and water (**Table 2**), and in the presence of a much larger range of Lewis acids than had been attempted in our previous investigations. Rather than following the reactions of this screening experiment by TLC, it was instead decided to use LCMS. Although this method of analysis potentially allows a large number of high quality results to be generated, in reactions involving metal components an additional work-up step is required to remove these residues prior to analysis and if a large number of reactions are performed this can take considerable time. Therefore, a way of working-up the reactions in parallel was devised using a modified Robbins block™, in which the wells had been packed with plugs of wet silica. This reduced the time taken for analysis by LCMS, and made this method of analysis advantageous.

Entry	Solvent	Complex (100 mol%)	Entry	Solvent	Complex (100 mol%)
1[a]	DCM	AgI	25[b]	DCM	$Pd(0)(PPh_3)_3$
2[a]	MeOH		26[b]	MeOH	
3[a]	MeCN		27[b]	DCM	$Pd(OAc)_2$
4[a]	MeCN:H_2O 1:1		28[b]	MeOH	
5[a]	DCM	Cu(OTf)	29[b]	DCM	$PtBr_2$
6[a]	MeOH		30[b]	MeOH	
7[a]	MeCN		31[b]	DCM	$PtCl_4$[b]
8[a]	MeCN:H_2O 1:1		32[b]	MeOH	
9[a]	DCM	CuBr	33[b]	DCM	$MnBr_2$
10[a]	MeOH		34[b]	MeOH	
11[a]	MeCN		35[b]	DCM	$MnCO_3$
12[a]	MeCN:H_2O 1:1		36[b]	MeOH	
13[a]	DCM	$Cu(OTf)_2$	37[b]	DCM	$Fe(OAc)_2$
14[a]	MeOH		38[b]	MeOH	
15[a]	MeCN		39[b]	DCM	$FeBr_2$
16[a]	MeCN:H_2O 1:1		40[b]	MeOH	
17[a]	DCM	$CuBr_2$	41[b]	DCM	$FeBr_3$
18[a]	MeOH		42[b]	MeOH	
19[a]	MeCN		43[a]	DCM	$BF_3.OEt_2$
20[a]	MeCN:H_2O 1:1		44[a]	MeOH	
21[b]	DCM	$RuCl_2(PPh_3)_3$	45[a]	MeCN	
22[b]	MeOH		46[a]	MeCN:H_2O 1:1	
23[b]	DCM	$RuCl_3$			
24[b]	MeOH				

Table 2: Reactions of **65** with cyclobutanone in the presence of a range of Lewis acids at room temperature both with and without the addition of either [a] 100 mol% of diisopropylethylamine or [b] 100 mol% of triethylamine.

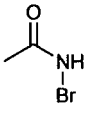
The reactions were performed in parallel using Robbins blocks™ through the addition of the metal complexes to wells containing a solution of **65** and either diisopropylethylamine or triethylamine in the respective solvent or in the solvent alone. The Robbins blocks™ were sealed and shaken to mix the reactions at room temperature for 24 hours. Work-up of these reactions was achieved through the filtration of the reaction mixtures through a complimentary Robbins block™ packed with wet silica gel (MeCN). This was followed by evaporation and dilution of the samples for analysis (0.05 M).

Unfortunately, there was no evidence of reaction observed by LCMS (**Table 2**), and we began to consider the possibility that perhaps **65** was as poor a reagent for the aza-Baeyer-Villiger reaction as **61**. It had become increasingly clear that the hydroxylamine **65** was not capable of behaving as a per-acid analogue for the aza-Baeyer-Villiger reaction. Presumably, the presence of the urethane unit had reduced the electron density at the

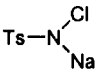
nitrogen centre to a point which rendered the reagent unreactive towards cyclobutanone, even when in the presence of a range of Lewis acids and bases.

Section 1.2.9

The balance between leaving group ability, nucleophilicity of the nitrogen centre and the stability of the molecule is crucial for a molecule to behave as a nitrogen containing per-acid equivalent for an aza-version of the Baeyer-Villiger reaction. However, during our investigations, concerns had grown that the development of a suitable reagent for the reaction would not be possible. A molecule which displayed the desired reactivity would be very prone to decomposition, and conversely, a molecule which was stable would be unlikely to be reactive. When potential reagents for the aza-version of the Baeyer-Villiger reaction were initially considered, as well as the synthesis of potential reagents, commercially available compounds were also investigated. Due to our growing doubts as to whether a molecule which displayed the desired chemistry could be found, these alternatives were now given serious consideration. As well as the compounds **51a**, **58a**, **61** and **65**, the commercially available N-bromoacetamide **66** and the nitrene equivalent precursor chloroamine T **67** had been considered. It was hoped that these stable, storable compounds would either posses the desired reactivity or could be activated to subsequently display this behaviour. The potential of N-bromoacetamide **66** and chloroamine T **67** as reagents for an aza-version of the Baeyer-Villiger reaction was planned to be investigated in a similar way to that of **65**, through a series of screening experiments.

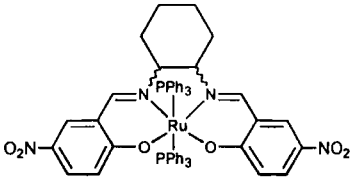


66



67

Our investigations into the ability of the commercially available compounds **66** and **53** were initially focused on the reactions of N-bromoacetamide **66**. As in the screening experiments previously conducted, exploration of the reactivity of **66** was performed through a series of parallel reactions in which **66** was reacted with cyclobutanone in the presence of a range of Lewis acids in combination with



68

bases as shown in **Table 3**. In this initial screening experiment the metal complexes used were $BF_3.OEt_2$, $RuCl_2(PPh_3)_3$ and $CuClO_4.4MeCN$, and the ruthenium complex **68**, which were intended to represent a range of hard and soft Lewis acids.

Entry	Complex	Base	Loading (mol%)	Entry	Complex	Base	Loading (mol%)
1	$BF_3.OEt_2$	2,6-Lutidine	10	**16**	$RuCl_2(PPh_3)_3$	$PhNEt_2$	10
2			50	**17**			50
3			100	**18**			100
4		$^iPr_2NEt$	10	**19**	$CuClO_4.4MeCN$	2,6- Lutidine	10
5			50	**20**			50
6			100	**21**			100
7		$PhNEt_2$	10	**22**		$^iPr_2NEt$	10
8			50	**23**			50
9			100	**24**			100
10	**68**	2,6- Lutidine	10	**25**		$PhNEt_2$	10
11			50	**26**			50
12			100	**27**			100
13		$^iPr_2NEt$	10				
14			50				
15			100				

Table 3: Reactions of **66** with cyclobutanone in the presence of 10, 50 and 100 mol% of a number of bases and metal complexes in DCM.

The reactions shown in **Table 3** were performed in parallel in a similar way to those in the previous screening experiment of **61** (**Table 1**), and stirred at room temperature for 24 hours. The reactions were followed by GC, which like LCMS required the purification of the samples before analysis. As in the previous screens to reduce the time required for this process the reactions were worked-up in parallel, in this case through the filtration of the reaction mixtures through short-plugs of silica gel, Amberlite™ (MB-1) and $MgSO_4$, which were separated by layers of sand using a sample handling station (Supelco Visiprep™ 24, SPE vacuum manifold). In the majority of these reactions no conversion of starting material was observed by GC, however, in some reactions new peaks were observed (**Entries 2, 8, 9, 26** and **27, Table 3**). When these reactions were analysed by ^1H NMR, none were found to have undergone significant levels of reaction, and in the cases were new compounds appeared to have been formed, they were present in very low levels and could not be accurately characterised.

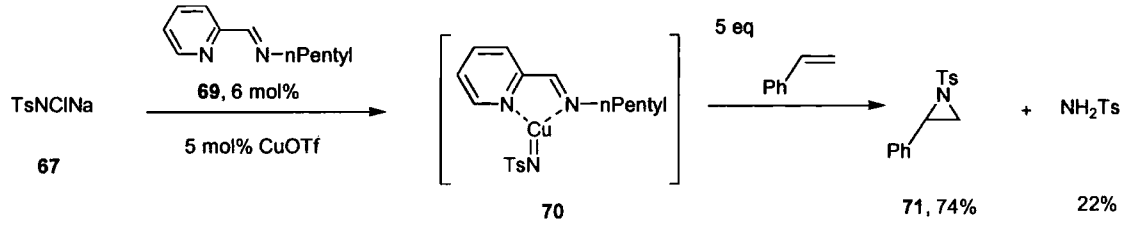
Although following the reactions by GC did provide high quality results, despite our attempts to work up the reaction in parallel this method of analysis was still slow. To thoroughly investigate the potential of **66** to behave as a reagent for the aza-Baeyer-Villiger reaction large numbers of reactions were necessary, the majority of which were expected to be inactive. To enable a fast qualitative determination of whether or not reaction has occurred, future screening experiments of **66** were analysed by TLC. Despite the inaccuracies associated with TLC, using this method allowed the reactions that displayed no reactivity to be identified and excluded from work-up and further analysis. To avoid the problems that had been encountered when following previous screening experiments by TLC, a number of precautions were made including the use of acetophenone which has a stronger chromophore than cyclobutanone and is easier to visualise by TLC. Therefore, further investigations into the potential of **66** as a reagent for an aza-version of the Baeyer-Villiger reaction focused on the reaction of acetophenone with **66** in the presence of a number of Lewis acids and bases as shown in **Table 4**, and was followed by TLC.

Entry	Solvent	Complex	Entry	Solvent	Base
1	DCM	$Yb(OTf)_3$	6	DCM	$^iPr_2NEt$
2	MeOH		7	MeOH	
3	DCM	MgI_2	8	DCM	$PhNEt_2$
4	MeOH		9	MeOH	
5	MeOH	PhCu(I)(OTf)	10	DCM	Pyridine
			11	MeOH	

Table 4: Reactions of **66** with acetophenone in the presence of 10, 50 and 100 mol% of a number of bases and metal complexes in DCM.

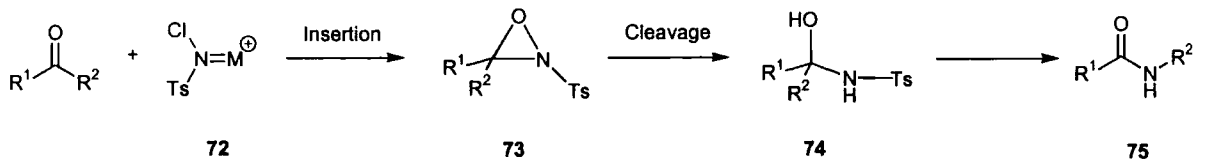
This screening experiment was performed in a similar way to the previous experiments (**Table 1** and **3**) and the reactions were stirred at room temperature for 1 week. The reactions that appeared by TLC to have displayed activity were worked-up by filtration through short plugs of wet silica (DCM) and after evaporation were analysed by ^1H NMR. Although, in the majority of reactions there was no evidence of reaction observed, in the presence of 50 and 100 mol% $^iPrNEt_2$ **Entries 6-8** (**Table 4**) the crude products were found by ^1H NMR to contain a number of new species. These were thought to be derived from $^iPrNEt_2$ and as they were formed in very low levels they could not be accurately identified.

The lack of activity displayed by the compounds investigated so far as reagents for an aza-Baeyer-Villiger reaction led us to consider the possibility that it may not be possible to discover a compound, or a range of compounds capable of displaying the desired behaviour. It was decided that the search for possible reagents for the aza-Baeyer-Villiger should now turn towards the commercially available reagent chloroamine T. This nitrene equivalent precursor is known to undergo nitrogen insertion reactions, including the aziridination of alkenes (**Scheme 13**).[37,38,40] Reactions such as these proceed through the formation of a metal nitrenoid, for example, the reaction of **67**, copper(II) triflate and the ligand **69** reported by Taylor *et al.*, in which the copper nitrenoid **70** is formed *in situ* as shown in **Scheme 13**.[38]



Scheme 13[38d]

Chloroamine T is significantly different from alkyl azides and N-alkyl-O-arylsulfonylhydroxylamines, however, this species may also be capable of undergoing nitrogen insertion reactions into carbonyls.[6,7,13,16,38] If nitrenoids derived from chloroamine T are capable of inserting into carbonyl bonds, then this could offer an alternative route to the desired N-substituted lactam products (**Scheme 14**). If the oxaziridine **73** can be formed by insertion of chloroamine T based nitrenoids **72** into carbonyl bonds (**Scheme 14**), this could be cleaved to give a nitrogen containing product **74**, which it may be possible to induce to rearrange after cleavage of the nosyl group.[38] This would allow the intermediate **74** reminiscent of those thought to form during the insertion reactions of azides into carbonyl compounds, to be prepared without the need to resort to unstable per-acid equivalents.



Scheme 14

Investigation into the ability of chloroamine T **67** to behave as a potential reagent for an aza-version of the Baeyer-Villiger reaction was at first focused on the reaction of **67** with carbonyl compounds under the reaction conditions reported in the literature for the aziridination reactions.[38d] At this investigation was conducted though the performance of a series of discrete reactions, the conditions and results for which have been compiled in **Table 5**. The reactions were performed through the addition of chloroamine T and, in **Entry 1,** 10 mol% of the complex $Cu(OTf)_2.PhH$, to a solution of benzophenone in anhydrous acetonitrile. After aqueous work-up of the reactions the residues obtained were analysed by ^1H NMR.

Entry	Equivalents of Chloroamine T	$Cu(OTf)_2.PhH$	Temperature	Time	Formation of Amide
1	3	10 mol%	Room temperature	4 days	No
2	3	-	Reflux	24 h	No

Table 5: Reactions of chloroamine T with benzophenone.

Unfortunately, no activity was observed in these reactions; the ^1H NMR spectrum of the crude products obtained from these reaction revealed no evidence of conversion of starting material.[23] The lack of reactivity observed in these reactions prompted us to design and implement a series of screening experiments which would allow an in depth study to be made into the effect that combinations of Lewis acids and bases have on the reaction of **67** with carbonyl compounds. Therefore a screening experiment was planned in which reaction of **67** with cyclobutanone, would be performed in the presence of a wide range of metal complexes in a range of solvents including protic, aprotic and aqueous solvents (**Table 6**). The reactions were performed in parallel according to the procedure used in previous screening experiments (**Table 2**), and were performed both with and without base (diisopropylethylamine or triethylamine).

The reactions were performed in a similar way to those of the previous screening experiment shown in **Table 2**, and the reactions were agitated for 24 hours at room temperature. The reactions were worked-up in parallel by filtration through short plugs of silica (MeCN), evaporated, diluted and analysed by LCMS. Although no evidence was found by LCMS for the desired amide forming reaction taking place in this screening experiment, in some cases there appeared to be low levels of new products formed.

However, these products were only present in very low levels and due to the complexity of the ^{1}H NMR could not be accurately identified.

Entry	Solvent	Complex (100 mol%)	Entry	Solvent	Complex (100 mol%)
1[a]	DCM	AgI	25[b]	DCM	$Pd(0)(PPh_3)_3$
2[a]	MeOH		26[b]	MeOH	
3[a]	MeCN		27[b]	DCM	$Pd(OAc)_2$
4[a]	MeCN:H_2O 1:1		28[b]	MeOH	
5[a]	DCM	Cu(OTf)	29[b]	DCM	$PtBr_2$
6[a]	MeOH		30[b]	MeOH	
7[a]	MeCN		31[b]	DCM	$PtCl_4$[b]
8[a]	MeCN:H_2O 1:1		32[b]	MeOH	
9[a]	DCM	CuBr	33[b]	DCM	$MnBr_2$
10[a]	MeOH		34[b]	MeOH	
11[a]	MeCN		35[b]	DCM	$MnCO_3$
12[a]	MeCN:H_2O 1:1		36[b]	MeOH	
13[a]	DCM	$Cu(OTf)_2$	37[b]	DCM	$Fe(OAc)_2$
14[a]	MeOH		38[b]	MeOH	
15[a]	MeCN		39[b]	DCM	$FeBr_2$
16[a]	MeCN:H_2O 1:1		40[b]	MeOH	
17[a]	DCM	$CuBr_2$	41[b]	DCM	$FeBr_3$
18[a]	MeOH		42[b]	MeOH	
19[a]	MeCN		43[a]	DCM	$BF_3.OEt_2$
20[a]	MeCN:H_2O 1:1		44[a]	MeOH	
21[b]	DCM	$RuCl_2(PPh_3)_3$	45[a]	MeCN	
22[b]	MeOH		46[a]	MeCN:H_2O 1:1	
23[b]	DCM	$RuCl_3$			
24[b]	MeOH				

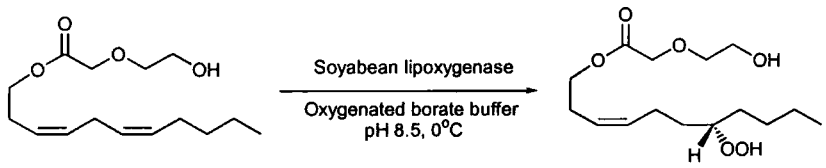
Table 6: Reaction of chloroamine T with cyclobutanone in the presence of a range of metal complexes, both with and without addition of [a] 100 mol% of diisopropylethylamine or [b] 100 mol% of triethylamine.

The failure of the compounds selected and tested so far to undergo the aza-version of the Baeyer-Villiger reaction was disappointing. It was becoming increasingly clear that the development of an aza-Baeyer-Villiger reaction may be not possible. If compounds were capable of behaving as nitrogen containing per-acids equivalents then they were also thermally unstable, whereas if they were stable enough to be handled easily then they would be unreactive. The activation of potential reagents using Lewis acids and bases is the only way in which the desired activity can be encouraged. Although attempts to promote the aza-Baeyer-Villiger reaction through the use of a range of Lewis acids and bases had not been successful so far, the use of a bifunctional catalyst may be more effective. Therefore, it was decided that our investigations would now turn towards the development and testing of bifunctional catalysts.

Chapter 2

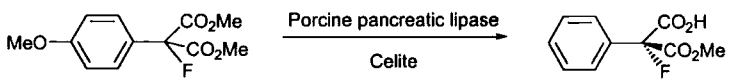
Section 2.1

Many enzymatic reactions are exquisitely enantioselective and diastereoselective, occurring with broad substrate tolerances under aqueous conditions.[42,43] As a result, enzymatic transformations have become powerful synthetic tools. Examples of the application of enzymes to organic synthesis can be seen in **Equations 26** and **27**.[43]



76 **77**, 73% yield, 98% *ee*

Equation 26[44]

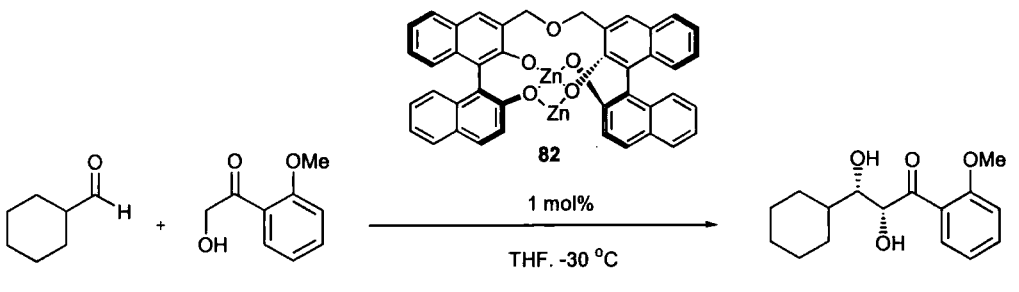


78 **79**, 93% yield, 97% *ee*

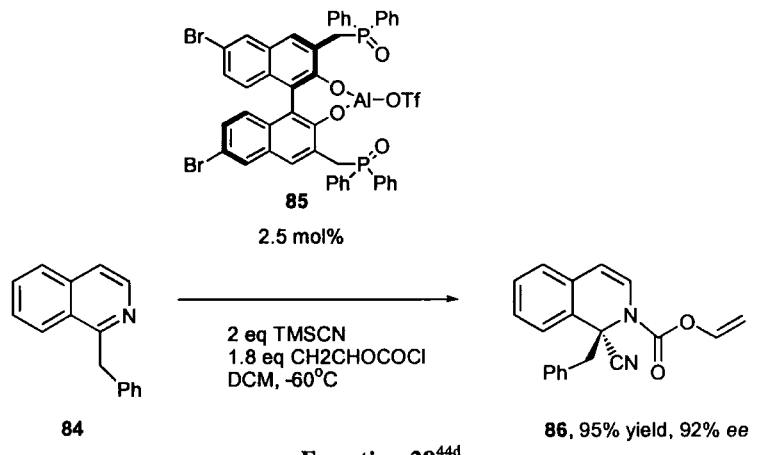
Equation 27[44]

The mechanisms by which enzymes catalyse reactions often involve the interaction of functional groups with the substrate molecules within the active site of the enzyme. These functional groups can include acidic, basic, nucleophilic residues and in some cases even metal ions, for example in serine proteases and carboxy peptidase C.[42] Application of this principle of cooperative interaction, to the design of catalysts has led to the development of a number of synthetic enzymes and novel catalysts.[44] Notable among these are the asymmetric polyfunctional catalysts based on lanthanide metals developed by Shibasaki *et al.*[44d] These polyfunctional molecules have been found to promote a variety of reactions including the nitro-aldol,[45] direct aldol,[46] Michael,[47] nitro-Mannich,[48]

hydrophosphonylation and cyanosilylation.[44d,49,50] Examples of the direct aldol and cyanide addition reactions are shown below in **Equations 28** and **29**.

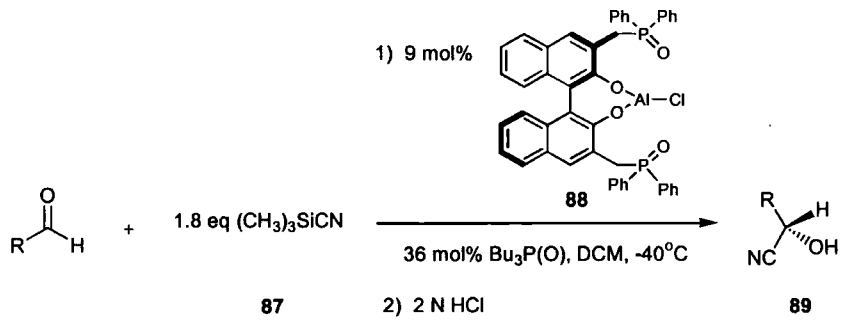


Equation 28[44d]



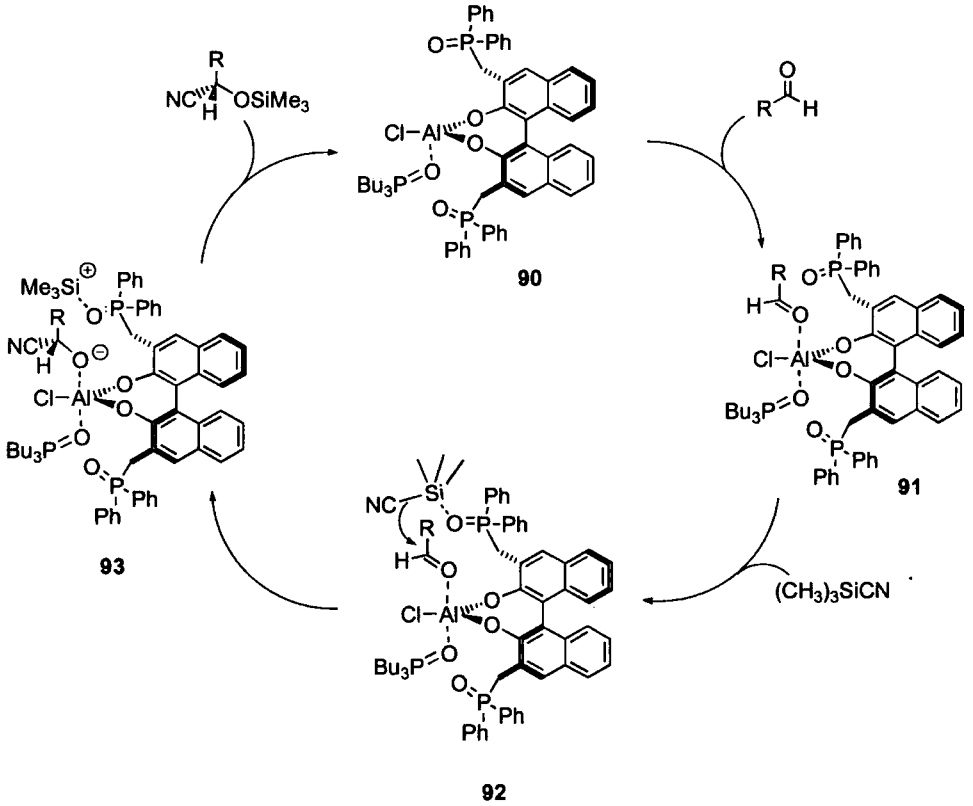
Equation 29[44d]

The polyfunctional catalysts **82** and **85** are expected to catalyse these reactions through polydentate mechanisms.[44d] For example, the mechanism of the cyanosilylation of aldehydes and ketones catalysed by **88** which has been studied in depth, is thought to be promoted by the Lewis acid-Lewis base complex **88** (**Equation 30**) through the joint action of the aluminium centre and the phosphinyl group.[44d,51]



Equation 30[44d,51]

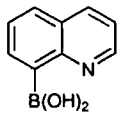
It has been suggested by Shibasaki *et al.* that the complex **88** promotes the cyanosilylation of aldehydes through the complexation of the carbonyl compounds to the aluminium centre to the carbonyl group as shown in the intermediate **91 (Scheme 15)**.[44d,51] This occurs at the same time as the binding of one of the pendent phosphinyl groups to the silyl group of TMSCN, to create a five coordinate silicon, which triggers the loss of cyanide and attack of the ketone as shown in **Scheme 15**.



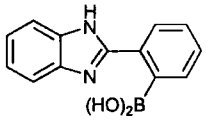
Scheme 15[44d,51]

Polyfuctional catalysts such as the complexes; **82**, **85** and **88** developed by Shibasaki *et al.*, have been shown, in many cases, to be very effective asymmetric catalysts.[44d] Often these complexes were capable of promoting reactions with levels of enantioselectivities to rival those of enzymatic reactions.[44d]

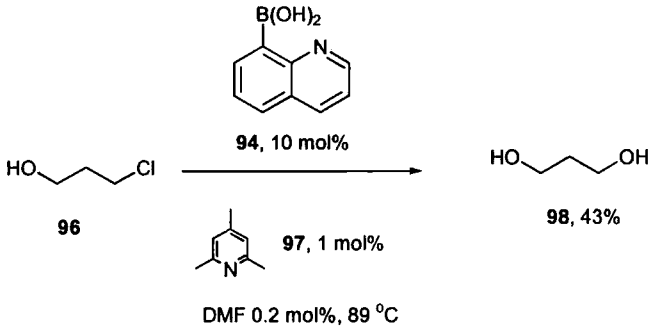
There are also examples of polyfunctional catalysts in the literature which do not contain transition or lanthanide metals.[52] Of these some of the first are the organoboron based bifunctional catalysts reported by Letsinger *et al.* as early as 1950.[53] These bifunctional molecules, for example **94** and **95**, were found to be effective catalysts for the hydrolysis of chloroalcohols such as **96**, which was converted to the diol **98** when in the presence of **94** and **97**, which had been added to these reactions merely to prevent the formation of the ammonium salt of **94 (Equation 31)**.[53c]



94

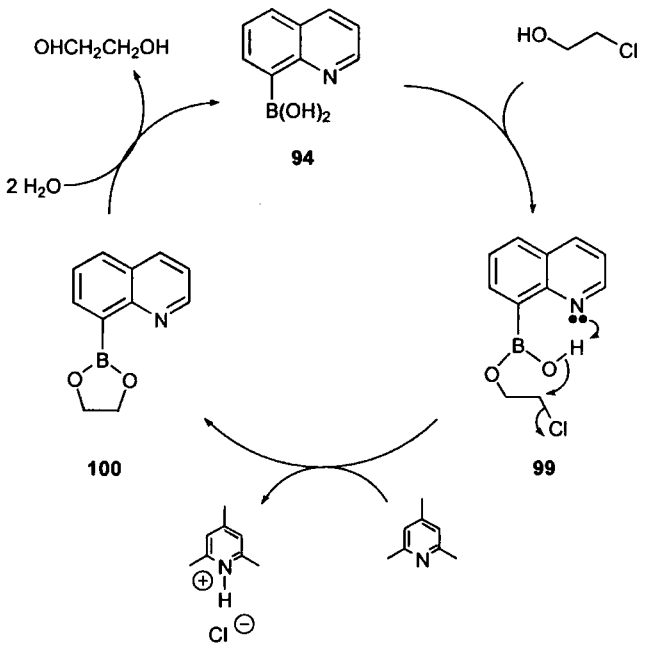


95



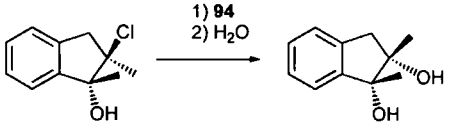
Equation 31[53]

When the hydrolysis of chloroalcohols was attempted using benzene boronic acid and quinoline, the reaction did not proceed to the same extent.[53a] These compounds had been chosen to represent fragments of the catalyst **94**, and the poor reactivity in the presence of these species was thought to indicate the bifunctional activity of the quinoline boronic acid **94**.[53a] It was suggested by Letsinger *et al.* that these catalysts promote the hydrolysis of chloroalcohols through the cooperative interaction of the amine and boronic acid functionalities with the substrate as shown in **Scheme 16**.[53]



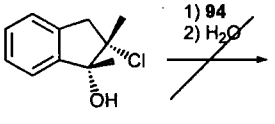
Scheme 16

The proposed mechanism for this reaction involves the complexation of the chloroalcohol to the boronic acid to give the intermediate **99**, which is subsequently attacked by an oxygen nucleophile (**Scheme 16**).[53] It was suggested by Letsinger *et al.* that the oxygen containing nucleophile may be a hydroxyl group bound to the boron atom, or a water molecule suspended between the boron and nitrogen centres. As these reactions occur with an inversion of the stereochemistry, attack of the bound chloroalcohol by the amine of **94** cannot be followed simply by displacement by water.[53c] For example, in the hydrolysis of the indoles **101** and **103** in the presence of **94** (**Equations 32** and **33**), the hydrolysis occurs in a stereoselective manner, rather than with an inversion of configuration, indicating that the oxygen nucleophile attacks from the same face as the hydroxyl group.[53c]



101 **102**, 82 %

Equation 32[53c]

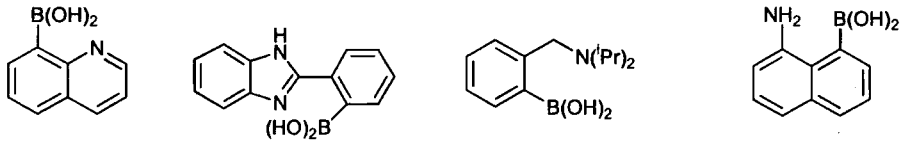


103

Equation 33[53c]

Section 2.2

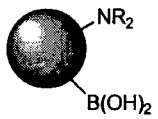
Amino boronate molecules, examples of which are shown below (**Figure 5**), are known to act as bifunctional catalysts.[53,55] For example the catalysts **94** and **95**, discussed above, which were reported by Letsinger *et al.* to be effective catalysts for the hydrolysis of chloroalcohols.[53]



94 **95** **104** **105**

Figure 5

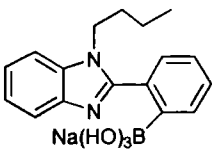
These molecules are based on the model **105**, which contains both boronic acid and amino functional groups separated by a molecular scaffold. In order to behave as effective catalysts, it is understood that the Lewis acid and Lewis basic sites of these molecules must be able to work cooperatively, without suffering de-activation due to intramolecular chelation.[44d] Research within the Whiting group into the development of bifunctional catalysts based on **117**, has led to the synthesis of a number of interesting and potentially effective bifunctional catalysts, including **104** and **105**.[54,55] As these molecules do not contain transition metals, catalysts derived from them have the potential to be readily recyclable, and therefore, environmentally friendly catalysts.



106

Of particular interest to us was the development of amino boronate based bifunctional catalysts which could promote, as well as a number of other organic reactions, an aza-version of the Baeyer-Villiger reaction. If an aza-Baeyer-Villiger reaction could be developed, it should be susceptible to bifunctional catalysis, as other similar reactions are known to be promoted by both acids and bases.[16,19,20,21,23] Preliminary investigations conducted within the Whiting group had indicated that amino boronate based bifunctional compounds similar to the benzimidazole **95** were exciting potential catalysts.[55] ^{1}H NMR evidence had been obtained which indicated that **108** was capable of promoting the aldol

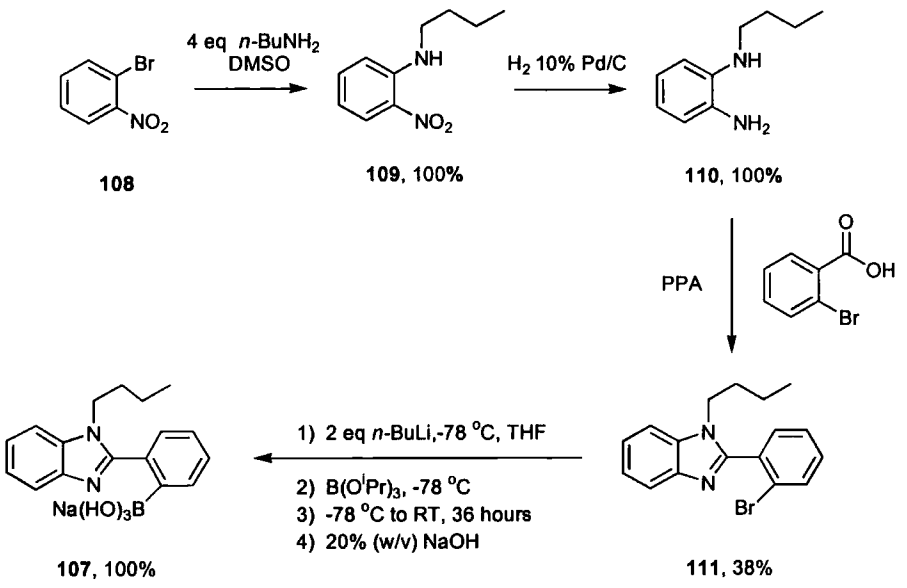
reaction of acetone and aryl aldehydes, as well as the nitroaldol reactions of nitromethane and aryl aldehydes.[55] Although these results had been promising, the synthesis and application of such systems required considerable further development and investigation.[55]



107

Therefore, our investigations into the development of potential bifunctional catalysts for the aza-Baeyer-Villiger reaction, as well as a number of other synthetic reactions, were focused on amino boronate compounds with benzimidazole backbones. Our initial aim was to develop a synthesis which would enable the facile preparation of **107** and a range of analogues, either through the improvement of the synthesis previously employed within the group, or through the development of a new synthetic approach.[55] The ability of these compounds to promote the aza-version of the Baeyer-Villiger reaction was then investigated, as was their effectiveness in a number of other reactions including the aldol reaction.

Previously the approach taken to the preparation of **107** had involved the method outlined in **Scheme 17**.[55] With the exception of the preparation of the benzimidazole **111**, this approach had been very effective. This step had resulted in low yields of **111** and the formation of numerous side products, which had further complicated the isolation of the benzimidazole.[55] The synthesis of **107** in this way had involved the preparation of 2-(N-*n*-butylamine)nitrobenzene **109** from 2-bromonitrobenzene **108**, followed by hydrogenation (10% Pd/C under H_2), to give **110** in quantitative yield (**Scheme 17**).[55]



Scheme 17

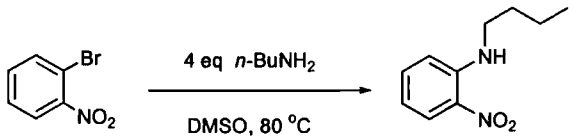
Previously, the preparation of the benzimidazole **111** from **110** had then involved an unpredictable polyphosphoric acid-catalysed reaction between the diamine **110** and 2-bromobenzoic acid as shown in **Scheme 17**.[55] This reaction produced a thick black oil which, although it contained the benzimidazole **111**, also contained a large number of impurities, and typically **111** could only be isolated in low yields.[55] Previously the complex **107** had then been prepared in quantitative yield from the benzimidazole **111** through lithium-halogen exchange, followed by transmetalation as shown in **Scheme 17**.[55]

Section 2.2.1

We therefore embarked on the development of a more efficient and robust synthesis of the boronate **107** and related compounds. The approach previously taken within the group to the synthesis of **107**, with the exception of the benzimidazole forming reaction (**Scheme 17**), had been very effective.[55] Therefore, we decided to utilise this approach but find a more effective method of preparing **111** to be used in place of the polyphosphoric acid-catalysed condensation reaction. As benzimidazoles are observed in many natural products and medically important compounds, including vitamin B_{12}, many novel and interesting

routes to these compounds have been developed.[56,57,58,59] Of the numerous routes to benzimidazole compounds reported in the literature, the simplest approaches were considered first.[56] The procedures chosen were those which involved the reaction of the diamine **110** with 2-bromobenzaldehyde.[56]

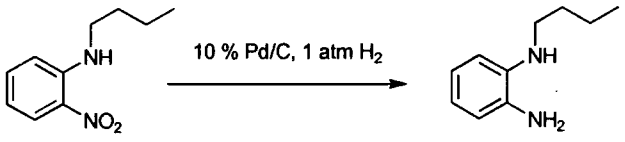
The 2-(N-*n*-butylamine)aniline **110** used in this investigation, was prepared according to the procedure previously used within the group (**Scheme 17**).[55] Hence, 2-bromo nitrobenzene **108** was treated with 4 equivalents of *n*-butylamine as shown in **Equation 34**. The solution was heated for 20 hours after which TLC revealed no remaining starting material.



108 **109**, 100%

Equation 34

The oil obtained after aqueous work-up was identified as **109** by ^{1}H and ^{13}C NMR.[55,61] It was found to have a high level of purity, and was used in subsequent steps without further purification.[60,61] The 2-(N-*n*-butylamine)aniline **110** was then prepared from **109** by hydrogenation over palladium on carbon (10%) as shown in **Equation 35**. This was achieved through the treatment of the hydrogenation catalyst (10 mol%) with a solution of 2-(N-*n*-butylamine)nitrobenzene **109** in methanol. The reaction mixture was then stirred under an atmosphere of hydrogen for 8 hours.

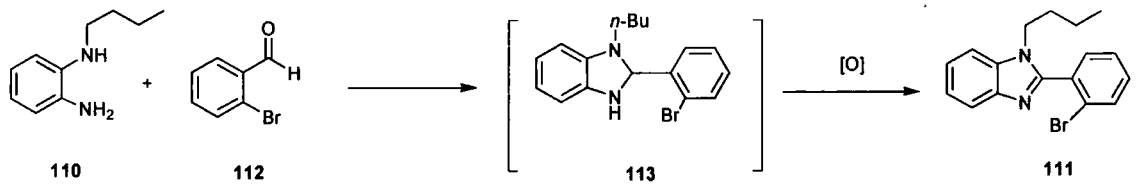


109 **110**, 100%

Equation 35

The 2-(N-*n*-butylamine)aniline **110** was isolated by filtration of the reaction mixture through Celite®, and identified by ^{1}H and ^{13}C NMR. Once again the crude product was found to have a high level of purity and was used in subsequent steps without further purification.[55]

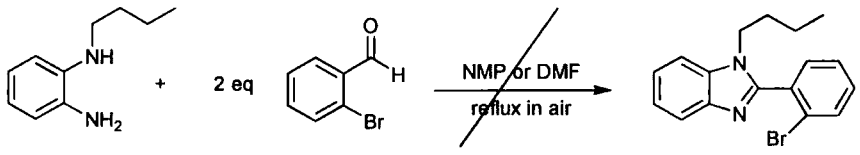
Attempts were then made to find a method of preparing the benzimidazole **111**, to replace the polyphosphoric acid-catalysed condensation reaction used previously in the synthesis of **107**. Although there are many approaches reported in the literature, the simplest are perhaps the coupling of phenylene diamines with aldehydes.[56] It is accepted that the synthesis of benzimidazoles in this way proceeds through the benzimidazoline intermediate **113**, which is oxidised to the benzimidazole **111** (**Scheme 18**).[58] This can either occur through disproportionation or through oxidation by an oxidising agent.[56]



110 **112** **113** **111**

Scheme 18

Initially attempts to prepare **111** focused on the reaction of **110** with 2-bromobenzaldehyde with either NMP or DMF as solvents as shown in **Equation 36**.[57]



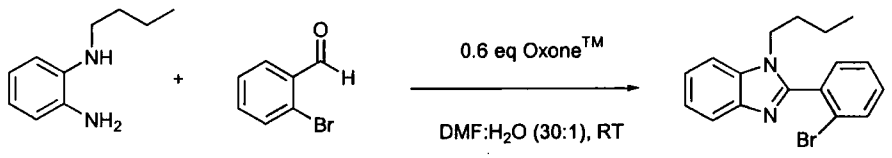
110 **112** **111**

Equation 36

The reaction performed with NMP as the solvent (**Equation 36**), involved the treatment of a solution of **110** in NMP with 2 equivalents of 2-bromobenzaldehyde.[57] The reaction mixture was then refluxed for 3 hours, after which the solution was evaporated to give a black oil. The crude product was not found to contain the desired benzimidazole **111** by ^{1}H NMR, and the major component of the crude material was identified as the 2-bromobenzaldehyde starting material, by peaks at δ_H 7.46-7.41 (m, 2 H, Ar), 7.63 (m, 1 H, Ar), 7.9 (m, 1 H, Ar) and 10.36 ppm (s, 1 H, CHO), and low levels of **110** identified by peaks at 0.98 ppm (t, *J* 7.4 Hz, 3 H, CH_3), 1.50 (hextet, *J* 7 Hz, 2 H, CH_2), 1.67 (quintet, *J* 7.5 Hz, 2 H) and 3.12 ppm (t, *J* 7.1 Hz, CH_2NH).[23,62] The reaction of **110** with 2-bromobenzaldehyde in DMF was performed in a similar way, through the treatment of a

solution of **110** in DMF with 1.5 equivalents of *ortho*-bromobenzaldehyde. After refluxing for 1 week there was no loss of the starting material, or formation of new compounds observed by TLC and the reaction was not investigated further.

Attempts to prepare the benzimidazole **111** from 2-(N-*n*-butylamine)aniline **110** through the treatment with 2-bromobenzaldehyde in the presence of an oxidising agent were more successful. It was reported by Haché *et al.*, that the synthesis of a range of substituted benzimidazoles from diamines and aldehydes was possible in the presence of the oxidising agent Oxone™, which consists of the salts $2KHSO_5.KHSO_4.K_2SO_4$.[58] Hence, the reaction of **110** with 2-bromobenzaldehyde was performed according to the literature procedure, by the addition of Oxone™ to a cooled (0 °C) solution of **110** and benzaldehyde in DMF:water (30:1) as shown in **Equation 37**.[58] The reaction was stirred for 10 hours after which TLC revealed no remaining starting material.



110 **112** **111, 69%**

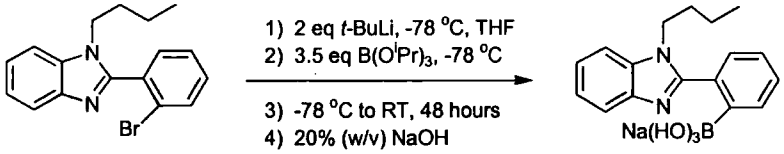
Equation 37

The reaction was quenched, purified by column chromatography and the benzimidazole **111** was obtained as off-white crystals in 69% yield, which were identified by comparison of the characterisation data of **111** with those of the starting materials and **111** prepared previously within the group.[55] Of particular interest were the shifts observed in the ^1H NMR spectrum, corresponding to the *n*-butyl group which were found to have shifted to 0.71 (t, *J* 7.4 Hz, 3 H, CH_3), 1.11 (hextet, *J* 7.5 Hz, 2 H, $CH_3CH_2CH_2$), 1.61 (quintet, *J* 7.5 Hz, 2 H, $CH_2CH_2CH_2$) and 3.98 ppm (t, *J* 7.2 Hz, 2 H, NCH_2CH_2).[55] This assignment was supported by the IR data, which revealed a strong absorption at 747 cm^{-1} due to the bromide of **111**, and was further confirmed by the analytical data.[55] The yield in this reaction is suspected to have been less than quantitative due to the competing oxidation of the diamine **110** by Oxone™.[62] The ^1H NMR of the crude reaction product had been found to contain a number of peaks in the aromatic region which were inconsistent with the starting materials or products, which may have been derived from N-oxidation products of

110.[23,62] Phenylenediamines are known to be susceptible to oxidation, a property which often causes problems in their handling and storage, and although no evidence of the N-oxide was observed during analysis these species may certainly have been present in the reaction.[62]

Section 2.2.2

The successful preparation of the complex **107** was then performed according to the procedure used previously within the group (**Scheme 17**).[55] Lithium-halogen exchange of the bromide **111**, followed by quenching with triisopropyl borate, was achieved as shown in **Equation 38**. This reaction was performed through the treatment of a cooled (-78 °C) solution of benzimidazole **111** with *t*-butyllithium, followed by 3.5 equivalents of triisopropyl borate.

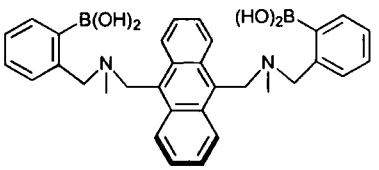


111 **107, 109%**

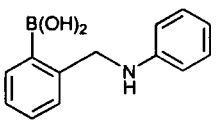
Equation 38

After quenching with aqueous sodium hydroxide (20% w/v), **107** was isolated as a white precipitate, which after washing with further aqueous sodium hydroxide (20% w/v) and diethyl ether, was dried under reduced pressure and obtained in quantitative yield. The white solid was found to retain water and was identified as **107** by comparison of the characterisation data with that of the starting material and with the complex **107** prepared previously within the group.[55] Of the characterisation data obtained the most interesting was the ^{11}B NMR (D_2O) spectrum which revealed peaks at 1.7, 2.9 and 5.6 ppm.[55] The peak at 2.9 ppm is typical of an 'ate'-complex, and strongly indicates the presence of **107**.[55,63] The peak observed at 1.7 ppm is thought to be due to sodium borate, derived from the triisopropyl borate used in the reaction, and precipitated alongside **107**.[63] The peak observed at δ_B 5.6 ppm was identified as the boronic acid **118**, which although boronic acids typically have characteristic shifts in the ^{11}B NMR (D_2O) of between 25-35 ppm,

would be expected to be shifted downfield due to internal donation from nitrogen to boron, resulting in a deviation of the trigonal planar arrangement of the boronic acid to a tetrahedral arrangement.[53c,54,66] Intramolecular nitrogen to boron dative bonds are reported extensively in the literature.[53c,54,66] Research groups such as Shinkai *et al.*, and James *et al.* have pioneered the application of amino boronic acids such as **114** and **115** as saccharide sensors, and have published several articles which describe the effect of nitrogen to boron donation and the behaviour of these compounds.[53c,54,66]



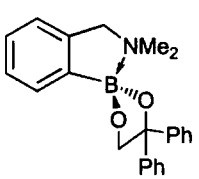
114



115

Although this procedure allowed the facile and effective preparation of **107**, it was found to be somewhat temperamental. Often under these work-up conditions precipitation did not occur, and often could not be encouraged even by the addition of non-polar solvents, excess base and impurities such as sodium chloride to the solution. The boronate complex **107** is highly soluble in water and the concentration of **107** in the reaction mixture plays an important role in precipitation. When the concentration of **107** in the reaction mixtures had not been high enough, or when there had not been adequate mixing of the biphasic mixture, this prevented the precipitation of **107**.

The major component of the material recovered from the reaction shown in **Equation 39** had been the boronate **107**. As the presence of an 'ate'-group in **107**, rather than a boronic acid, may affect the ability of this molecule to behave as a bifunctional catalyst, attempts were made to prepare a quantity of benzimidazole **117** in which the major component was **118**.[53] Although this species contains an internal nitrogen to boron dative bond, it is unlikely that this will affect its ability to behave as a bifunctional catalyst. During research into the hydrolysis of chloroalcohols, Letsinger *et al.* had reported that the benzimidazole **95** was active in these reactions despite possessing nitrogen to boron internal donation.[53] In an investigation into the dissociation of the dative nitrogen to boron bond of the related molecule **116** conducted by Totoyta *et al.*, the energy of this dissociation was calculated to be 63.6(1.3) kJmol^{-1} ($\Delta H^{\neq}$, 233 K).[64,65] When this energy is compared with

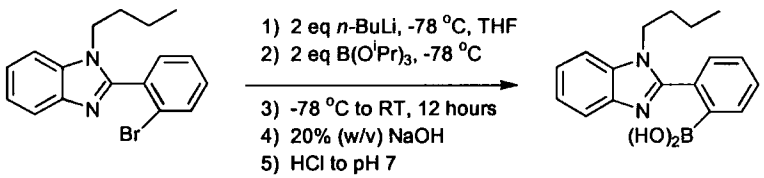


116

the dissociation energy of the O-H bond of acetic acid (reported in the *Handbook of Dissociation Energies of Organic Compounds*) i.e. 442.7(8.4) $kJmol^{-1}$, it can be appreciated how labile the nitrogen to boron bonds in these species are.[67]

Section 2.2.3

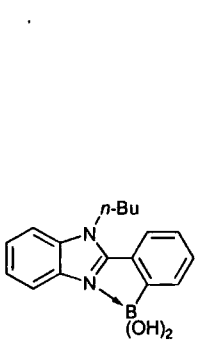
The preparation of **118** was attempted in a similar way to that of the boronate **107**; through lithium-halogen exchange of the bromide **111** followed by transmetalation.[55] As shown in **Equation 39**, a solution of the benzimidazole **111** and triisopropyl borate was treated with *n*-butyllithium at -78 °C. After warming to room temperature and quenching with aqueous sodium hydroxide, a biphasic solution was formed which stirred for 1 hour.



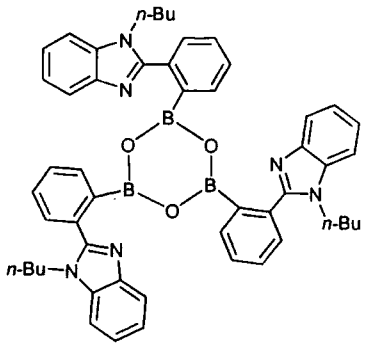
111 **117, 100%**

Equation 39

The solution was neutralised with dilute aqueous HCl, and a white precipitate formed which was collected by filtration, washed (distilled water, diethyl ether) and dried under reduced pressure (100%). Unfortunately, the material recovered was found to be poorly soluble in aqueous solvents as well as organic and mixed solvents making the characterisation difficult. Analysis of the ^{1}H and ^{13}C NMR (CD_3CN:D_2O) spectrum of the crude product revealed shifts in the peaks from those of the starting material **111**. Particularly noticeable were the shifts in the ^{1}H NMR (CD_3CN:D_2O) peaks corresponding to the protons vicinal to the nitrogen of the starting material at 3.98 (t, *J* 7.2 Hz, 2 H) to those of the product **117** at 4.50 ppm (t, *J* 7.5 Hz, 2 H). As with the analysis of the boronate **107**, the ^{11}B NMR of **87** was very interesting. The ^{11}B NMR (CD_3CN:D_2O) spectrum of **117** was found to contain peaks at 12.5, 19.7 and 32.8 ppm. These peaks were due to the internally donated boronic acid **118**, boroxine **119** and a boronic acid, possibly **117**, respectively.[54,63]

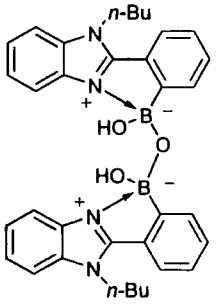


118



119

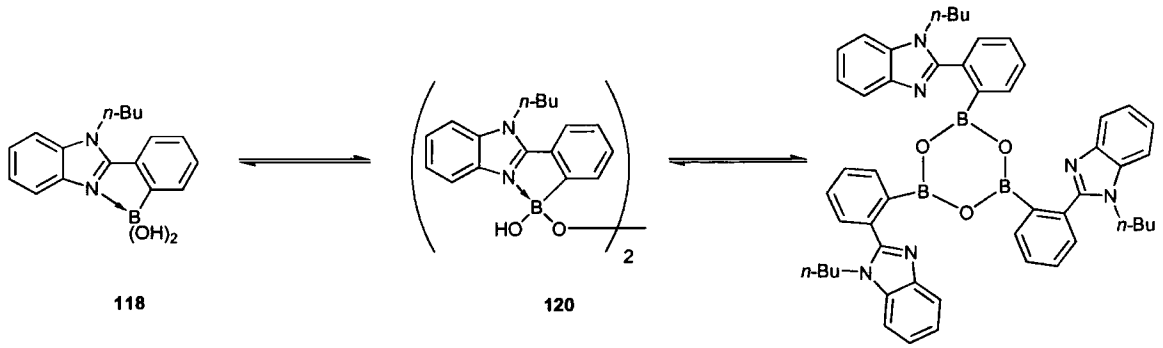
The most intense peak observed in the ^{11}B (CD_3CN:D_2O) spectrum of **117** was the peak at 12.5 ppm, which corresponds to the internally donated boronic acid **118**.[63] The shift in this peak from δ_B 5.6 ppm observed in the ^{11}B NMR (D_2O) spectra of **107**, is due to the different solvents used in these spectra.[63] The mass spectrometry data (ES +) obtained for this material confirmed the presence of the boronic acid **87** due to signals observed at 295.2 (MH^+) and 317.2 (MNa^+), but also revealed a possible dimer complex at 553.4 (2M – 2OH). Although this dimer complex may be due to fragmentation of the boroxine trimer during mass spectrometry, it may also be due to the presence of a dimer of **120** in the material recovered from the reaction shown in **Equation 39**. However, if this is the case then this compound must also contain internal nitrogen to boron donation as there had only been a single peak observed in the ^{11}B NMR (CD_3CN:D_2O) spectrum at 12.5 ppm. This indicated that if the dimer had formed the boron atoms of **118** and the dimer molecule, must be in the same chemical environment. If the dimer had been formed then the assembly of the two molecules of **117** in this species may occur in a number of ways. The structure **120** shown here is thought to be the most plausible arrangement, as the boron atoms would be in the same environment.[53b]



120

The characterisation data obtained so far had suggested that the compound **117** had been successfully prepared (**Equation 39**), and existed mainly in the form **118**. The presence of the boroxine **119** and the possible dimer **120** in the material obtained from the reaction

shown in **Equation 39** indicated that **117** loses water to form these dehydrated compounds as shown in **Scheme 19**.



Scheme 19

Section 2.2.4

The behaviour exhibited by **117** was very interesting; as well as losing water to form a series of dehydrated structures, due to its bifunctionality, it reacted with both acids and bases. This behaviour is consistent with that reported in the literature for other amino boronate complexes, capable of forming internal nitrogen to boron dative bonds.[66] To help to simplify this often complex chemical behaviour, the numerous forms of **117** observed during these investigations have been complied into **Table 7**. Listed alongside the compound numbers and proposed structures are the work-up conditions used in each isolation procedure, details of further manipulations performed and selected evidence for their existence.

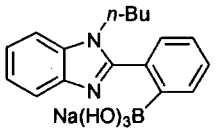
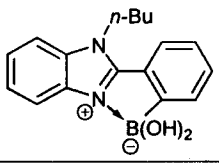
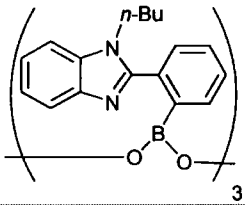
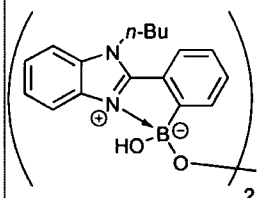
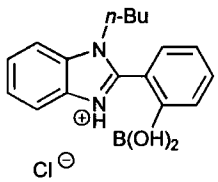
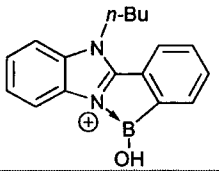
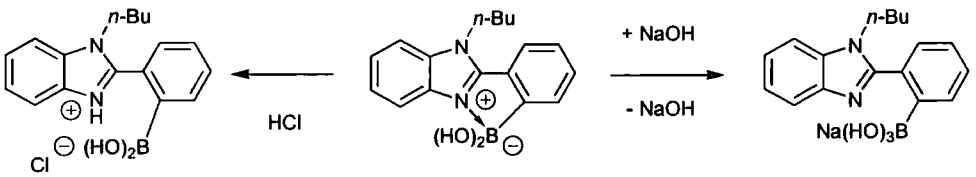
Compound	Proposed structure	Isolation (Equation)	Manipulation[a]	Analytical evidence[b]
107		**38**	-	δ_B (D_2O) 2.9 ppm; m/z ES (-) 309.5 (M – Na).
		39	NaOD in D_2O solution.[c]	δ_B (D_2O: NaOD) 2.4 ppm.
118		**39**	-	δ_B (CD_3CN:D_2O (3:1)) 12.5 ppm; m/z ES (+) 317.2 (M + Na).
		41	-	δ_B (CD_3CN:D_2O (3:1)) 10.4 ppm.
119		**39**	-	δ_B (CD_3CN:D_2O (3:1)) 19 ppm.
			D_3-acetic acid in a solution of D_2O.[c]	δ_B (D_2O: D_3-acetic acid) 23 ppm.
120		**39**	-[d]	m/z ES (+) 553.4 (2M – 2OH).
121		**39**	-	δ_B (CD_3CN:D_2O (3:1)) 32.8 ppm
			D_3-acetic acid in a solution of D_2O.[c]	δ_B (D_2O: D_3-acetic acid) 33 ppm.
		41	-	δ_B (CD_3CN:D_2O (3:1)) 33.4 ppm
122		**41**	-	m/z ES (+) 277.4 (M-OH).

Table 7: Proposed structures of the forms adopted by **117** under a number of conditions.
[a] Not every instance of observation of these species has been included, only those in which the species was present in high levels or where the observation of the species was considered informative; [b] Only selected analytical data has been included here, for example, for full characterisation data see experimental section; [c] Only observed in solution; [d] Only observed in mass spectrometry data.

Although **117** has very poor solubility under neutral conditions in organic solvents, under aqueous conditions and in mixed solvents, it is soluble in acidic aqueous solutions of pH <

5 and basic aqueous solutions of pH > 10. This is due to the formation of the ammonium ion **121** at low pH and the boronate complex, observed previously, at high pH **107** (**Scheme 20**), a characteristic also observed in other amino boronate species.[66] This behaviour was reinforced, and indeed complicated by the examination of the ^{11}B NMR spectra of **118** under acidic and basic conditions.

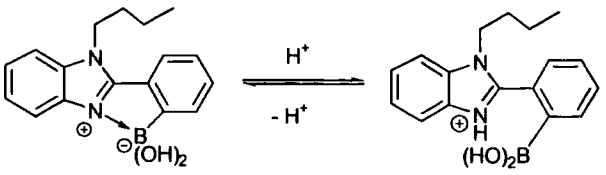


121 **118** **107**

Scheme 20

When the ^{11}B NMR spectrum of **118** in a solution of D_2O and NaOD was obtained, it was found to contain peaks at 1.5 ppm and at 2.4 ppm, very similar to the ^{11}B NMR (D_2O) spectrum of **107** which had contained peaks at 1.7, 2.9 ppm as well as a peak at 5.6 ppm due to the internally donated boronic acid **118**. In these spectra the peaks observed at δ_B 1.5 (**117**, D_2O:NaOD) and 1.7 ppm (**107**, D_2O) were attributed to sodium borate, present due to residual boric acid carried through from the preparation of these compounds, or due to cleavage of the boronic acids of **117**. This suggested that the boronate salt **107** could be formed from the boronic acid **117** on treatment with base.[66]

When a solution containing **117** in D_2O and D_3-acetic acid was analysed by ^{11}B NMR the spectrum obtained was found to contain peaks at δ_B 23 ppm and 33 ppm, consistent with shifts of the boroxine **119** and the ammonium salt **121** respectively.[63] This behaviour is consistent with that reported in the literature for other molecules containing internal nitrogen to boron dative bonds by a number of research groups including James *et al.*, and Shinkai *et al.*[66] The formation of **121** from **118** was clearly a reversible process (**Equation 40**), as when solutions of **117** in strongly acidic conditions were neutralised re-precipitation of **118** was observed.

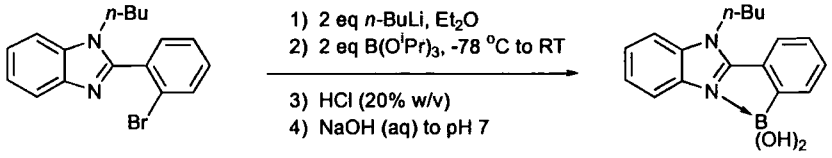


118 **121**

Equation 40

As the signal at δ_B 33 ppm due to the boronic acid can be observed only when the **121** complex is formed, the presence of the complex **121** in neutral solutions, as seen in the ^{11}B NMR (CD_3CN:D_2O) of **117** in which peaks were observed at 12.5, 19.7 and 32.8 ppm, indicates that the pH is slightly below the isoelectric point of this material.[68] The determination of the isoelectric point could, in theory, be achieved by observing the ^{11}B NMR of **117** at a range of pH's. However, as this would be difficult due to the insolubility of **117** in the crucial pH range, it would be more appropriate to use another form of analysis. For example, in research reported by James *et al.*, the pKa's of the individual forms taken by compound **115** were determined by acid-base titration.[66a] Potentially this method could be used to determine the pKa's and isoelectric points of the various forms taken by **117**. However, as the material obtained from neutral pH solutions only contained low levels of the ammonium salt **121**, this should have very little impact on the potential of **117** to behave as a bifunctional catalyst, and so instead attempts were made to test the activity of this compound in a number of reactions.

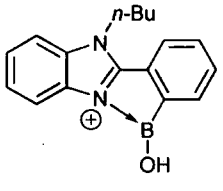
The results obtained so far had indicated that under neutral conditions the material exists mainly as the internally donated form **118**, with the boroxine **119**, ammonium salt **121** and dimer **120** forms present in low levels. These forms of **117** were observed in varying proportions depending on the conditions such as solvent, concentration and pH used. Indeed, even the work-up procedures used in the preparation of **117** were found to alter the proportions in which these forms were recovered. For example, when the reaction was worked-up as shown in **Equation 39**, the internally coordinated compound **118**, boroxine **119** and ammonium salt **121** were all found to be present. However, when the reaction was worked-up through acidification of the reaction mixture, followed by neutralisation as shown in **Equation 41**, peaks were observed in the ^{11}B NMR (CD_3CN:D_2O) spectrum at 10.4 and 33.4 ppm, which were due to the internally donated complex **118** and the ammonium salt **121** respectively.[63]



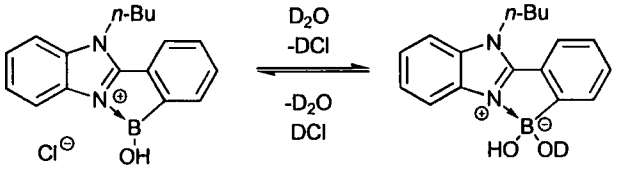
111 **118**, 56%

Equation 41

A cooled (-78 °C) solution of the benzimidazole **111** was treated with 2 equivalents of *n*-butyllithium, triisopropyl borate and was warmed slowly to room temperature. The reaction was quenched with aqueous HCl and the pH was adjusted to 7 using aqueous sodium hydroxide. The light brown precipitate which formed was collected, washed (diethyl ether, distilled water) and dried in air (56%). The material obtained from this reaction (**Equation 41**) was found to have very similar characterisation data to that recovered previously, however, subtle differences were observed. These work-up conditions had been expected to lead to increased levels of the dehydrated compounds; boroxine **119** and dimer **120**. However, the mass spectrometry data (ES +) for this compound revealed that there were only low levels of the dimer species present, and the majority of the material was a monomer. The monomer observed was found to have a mass of 277.4 (M-OH), as this had not been observed previously it is unlikely to be due to the fragmentation of **117** or **118** during mass spectrometry, but instead due to the presence of a dehydrated form of the monomer, possibly with the structure **122**. It would not be possible to observe **122** by NMR spectroscopy, due to hydrolysis under the NMR conditions for example by water as shown in **Equation 42**.



122



121 **123**

Equation 42

Section 2.2.5

The complex behaviour displayed by this material, and our intention to use **118** as a bifunctional catalyst, had made the need for firm evidence vital. Attempts were therefore made to obtain decisive evidence for the structure of **117** though single crystal X-ray diffraction analysis. There were a number of difficulties associated with the analysis of **117** (**Equation 39**) in this way. Not only did this material exist in a number of different forms, but the physical behaviour of this material is not conducive to crystallisation. It is virtually insoluble in a large range of solvents, including organic, aqueous and mixed systems. Also, it had been thought that this material may be amorphous as no tendency towards crystallisation had been observed and it had appeared to be hydrophobic: forming a layer around water droplets or on top of a larger amount of water. Indeed, when the material can be induced to mix with solvents, the mixtures formed often appear to be a suspension of micelles. Despite these problems, after a great deal of effort, our attempts to prepare a crystal of **117** suitable for single crystal X-ray crystallography were successful.[69] Of the numerous solvent systems tested, the most successful was found to be a mixture of DMF and chloroform, recrystallisation from which was encouraged by temperature cycling.[69] However, this crystallisation could only be performed when the material used had first been acidified (pH<5 (HCl)) and then re-precipitated from neutral solution. Four very different shaped crystals were obtained using this method; the presence of these four morphologies may be due to the co-crystallisation of a number of the different **117** substructures. Unfortunately, only one of these crystals was of a high enough quality for single crystal X-ray diffraction analysis.[69] Structural determination confirmed the chemical connectivity of **117** and also revealed that the molecules of **117** existed as a boroxine trimer, represented in **Figure 6 (Appendix 4)**.[28,69]

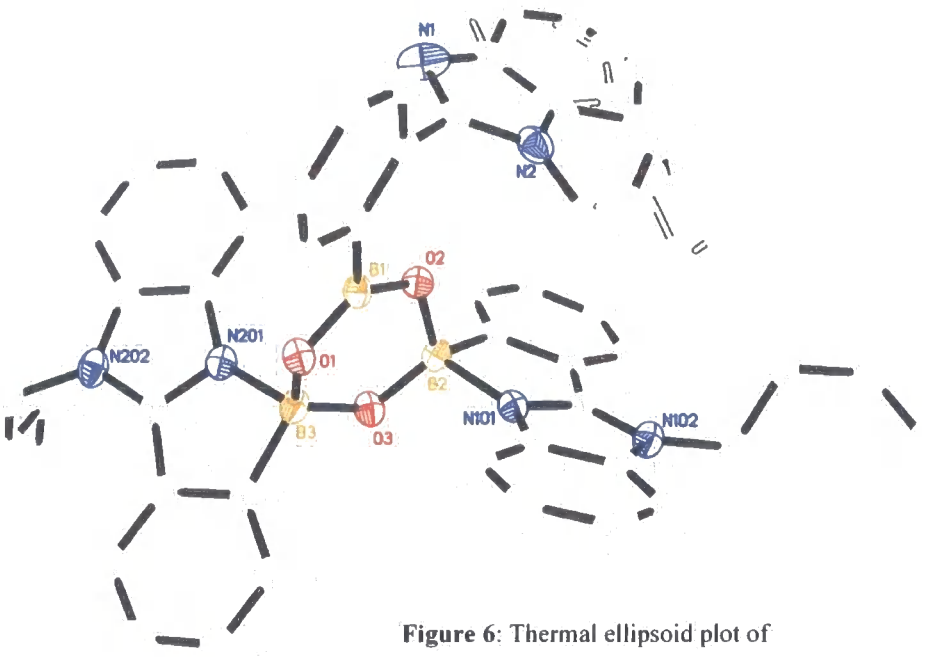
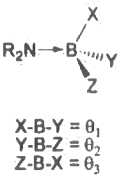


Figure 6: Thermal ellipsoid plot of **119** at 50% probability.[419]

Finally, this had brought conclusive proof that **117** had been formed (**Equation 39**), and went someway towards proving the proposed behaviour of these species. Unfortunately, it still cannot be categorically stated that all of the product obtained from this reaction was **117** or a substructure thereof, only that the crystal analysed was this material.

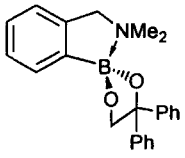
From this structure, the internal donation from nitrogen to boron can be seen (**Figure 6**). This can be seen in two of the benzimidazoles units, and results in a planar arrangement in which the boron atoms appeared to posses some tetrahedral character. Although a large number of boroxine rings are reported in the literature in which one of the boron atoms is known to possess some tetrahedral character, there are considerably less in which two of the boron atoms have tetrahedral character.[64] Attempts to quantify this character were made using the percentage 'tetrahedral character' calculation described by Toyota *et al.* (**Equation 43**).[64c]

$$THC(\%) = 120^{\circ} - \frac{\left(\left(\theta_1 - \theta_2 - \theta_3\right)/3\right)}{120^{\circ} - 109.5^{\circ}} \times 100$$

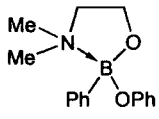


X-B-Y = θ_1
Y-B-Z = θ_2
Z-B-X = θ_3

Equation 43[64c]



116, 51%



124, 54 % THC[426]

Using this equation it was calculated that the boron atoms B2 and B3 possessed 48% and 53% tetrahedral character respectively. This is similar to those of the molecules **116** and **124** calculated by Toyota *et al.* from the crystal structures of these compounds which were reported to be 51% and 54% (THC) respectively.[64c] However, these values must be treated with some care as the temperature at which the X-ray diffraction analysis of these structures was performed was not reported.[64c]

The lengths of the dative nitrogen to boron bonds observed in the internally donated benzimidazoles units of the crystal structure shown in **Figure 6** were 1.665(4) Å and 1.641(4) Å for N101-B2 and N201-B3 respectively. These bond lengths are similar to those observed in other internally donated boron to nitrogen, for instance in the species **116** and **124**; the bond lengths are reported to be 1.754(4) Å and 1.682 Å respectively.[64c] However, the comparison of these values to our own must be treated with caution, as again the temperature at which the X-ray diffraction analysis of these compounds was performed was not reported.[64c] These, and other selected bond lengths and angles have been compiled in **Table 8**, and a more complete list can be found in **Appendix 4**.

Atoms (X-X)	Bond length (Å)	Atoms (X-X-X)	Bond angle (°)
N101-B2	1.665(4)	C1-C12-C17	121.9(3)
N201-B3	1.641(4)	C101-C112-C117	107.4(2)
C1-C12	1.483(4)	C201-C212-C217	107.4(3)
C101-C112	1.470(4)	O1-B1-O2	122.1(3)
C201-C212	1.474(4)	O2-B2-O3	115.1(2)
C12-C17	1.396(4)	O3-B3-O1	114.4(2)
C112-C117	1.400(4)	N101-B2-O2	105.0(2)
C212-C217	1.400(4)	N201-B3-O1	105.0(2)
C17-B1	1.585(4)	N101-B2-O3	110.1(3)
C117-B2	1.634(4)	N201-B3-O3	111.6(3)
C217-B3	1.631(5)	C117-B2-O2	113.8(3)
B1-O2	1.359(4)	C217-B3-O1	112.7(3)
B2-O2	1.458(4)	C117-B2-O3	115.9(3)
B2-O3	1.418(4)	C217-B3-O3	116.2(3)
B3-O3	1.416(4)	N101-B2-C117	94.1(2)

B3-O1	1.479(4)	N201-B3-C217	94.6(2)
B1-O1	1.359(4)		

Table 8: Selected bond lengths and angles from X-ray crystallography 120(2) K.

The lack of nitrogen to boron donation observed in the third benzimidazole unit of the X-ray crystal structure may be due to steric congestion in the molecule. It appears that the third benzimidazole is forced to adopt an unfavourable arrangement to allow it to 'fit' into the boroxine molecule. This peculiar arrangement can be seen in the representation of the chemical connectivity (**Figure 7**), in which evidence of steric constraint can be observed in the unusual conformation of the *n*-butyl group of the third benzimidazole unit (C8, C9, C10 and C11). The uniformity of the two internally donated benzimidazoles and the constraint of the third, supports the possibility that the dehydration of **117** proceeds through the initial formation of the dimer **120**, and that the final benzimidazole unit slots into place after its formation. This results in the third benzimidazole unit adopting an unusual arrangement to allow it to 'fit' around the other benzimidazole units.

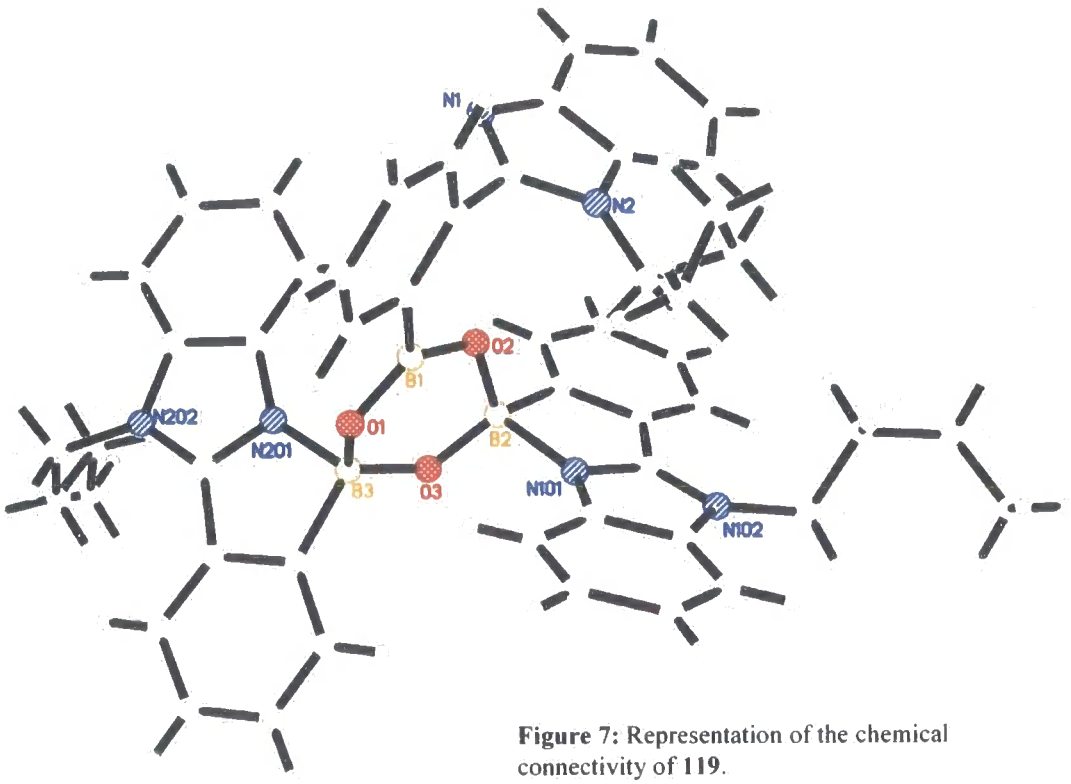
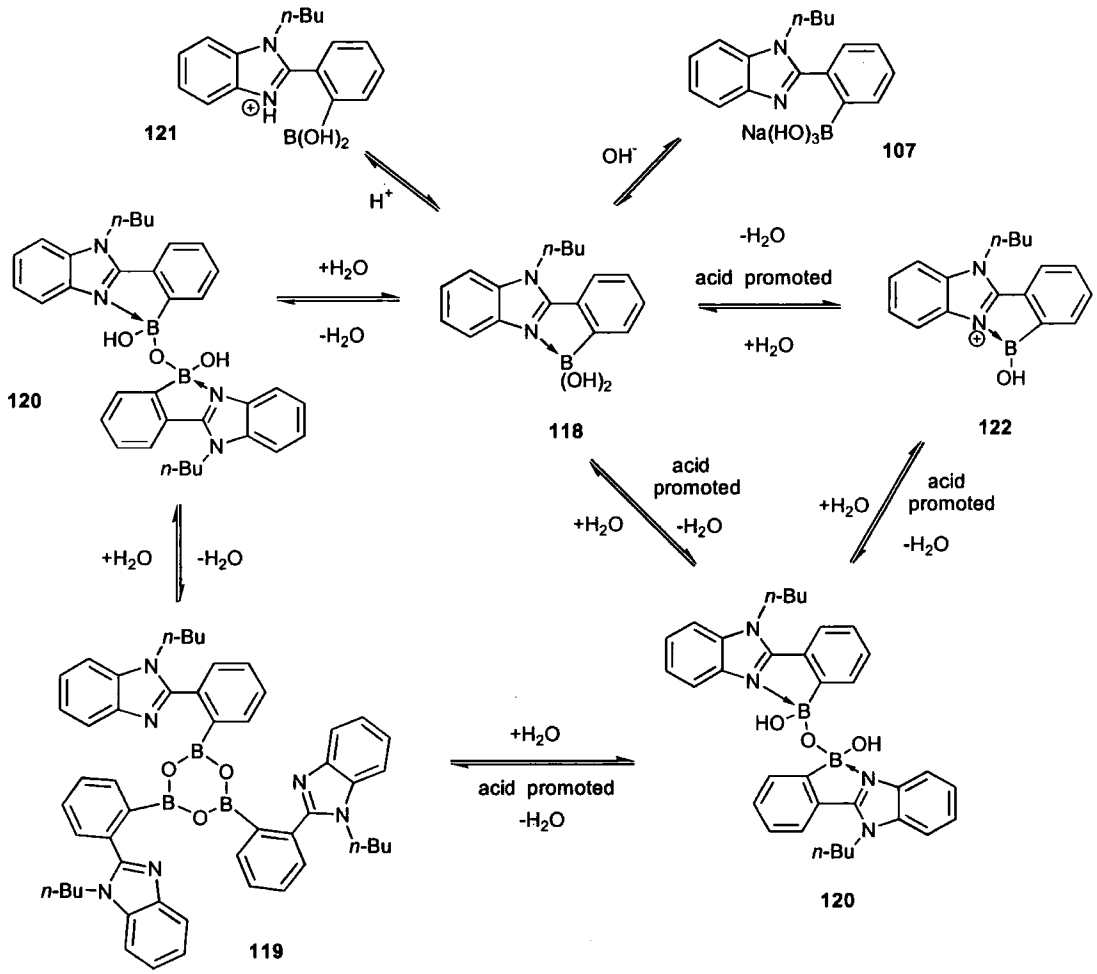


Figure 7: Representation of the chemical connectivity of **119**.

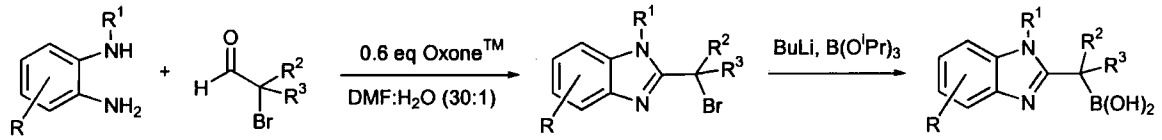
The relationships between the structures suggested for the benzimidazole **117** listed in **Table 7**, are summarised below (**Scheme 21**). This includes the dehydrated forms of **117** as well as those which exist at low and high pH. Identification of these species was in many cases difficult and not entirely conclusive, as often only limited evidence for the formation of these species could be obtained. However, by taking all of the various pieces of evidence into account, and by comparing the activity observed with that of similar molecules reported in the literature, an accurate picture can be built up of the behaviour and structures adopted by **117** which can be used to predict the behaviour of this material.[66]



Scheme 21

Section 2.3

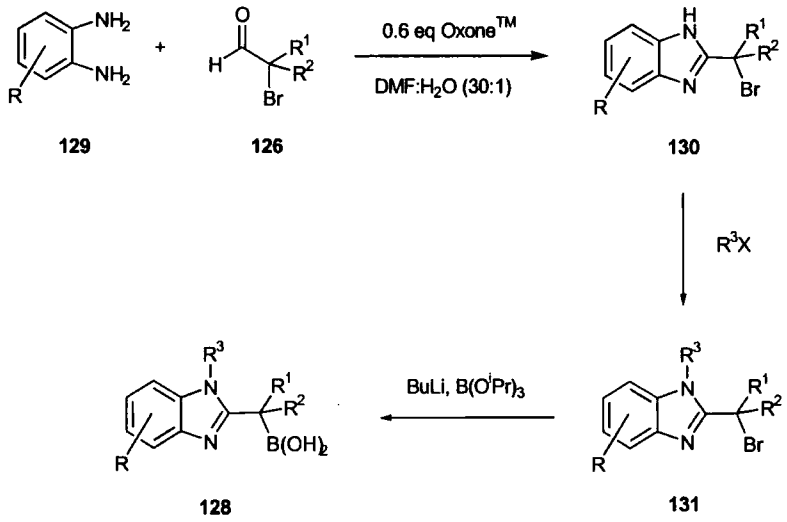
The approach taken in the synthesis of **117** (**Section 2.2**) had been very successful. Using this chemistry, it should also be possible to prepare a number of interesting analogues of **117**, through the coupling of various diamines and aldehydes, followed by the conversion of the benzimidazoles produced to the corresponding boronic acids as shown in **Scheme 22**. It was hoped that the investigation of analogues of **107** and **117** may lead to the discovery of species with improved activity, solubility and alternative applications.



125 **126** **127** **128**

Scheme 22

However, if benzimidazoles such as **130** could be prepared, these may offer a more efficient route to analogues of **117**. Structures such as **130** should provide a flexible route to a range of compounds based on **117** through the attachment of a variety of side chains (**Scheme 23**).



129 **126** **130** **131** **128**

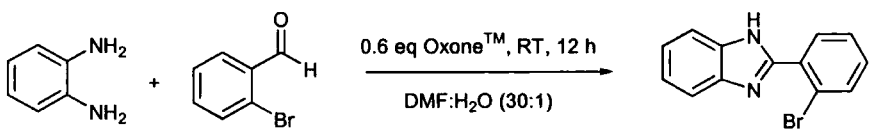
Scheme 23

The synthesis of boronic acids based on the structure **120** using this approach (**Scheme 23**), would involve three steps from commercially available starting materials to boronic acids. This represents an improvement on the approach previously taken in which four steps were required from the starting materials to the desired products (**Section 2.2**). However, the main advantage of this route is the ability to add the side chain after the benzimidazole scaffold has been created. Although, a range of analogues which differed in the benzimidazole scaffold are accessible using our previous route (**Scheme 22**), to add different side chains the synthesis would have to be repeated, as the installation of the side chain occurs at the very first step. Therefore, the synthetic approach shown in **Scheme 23** should compliment our previous strategy, and allow a wide range of analogues to prepared quickly.

Section 2.3.1

Hence, attempts were made to synthesise more soluble analogues of **117** from the 2-(2-bromobenzene)benzimidazole **133**. During the preparation and analysis of **107** and **117**, problems had been encountered due to the poor solubility of **117**. The synthesis of a soluble analogue of **117** would allow investigations into the activity of these compounds to be carried out untainted by solubility problems.

The 2-(2-bromobenzene)benzimidazole **133**, was successfully prepared through the coupling of phenylenediamine with 2-bromobenzaldehyde in the presence of Oxone™ as shown in **Equation 44**.[61]



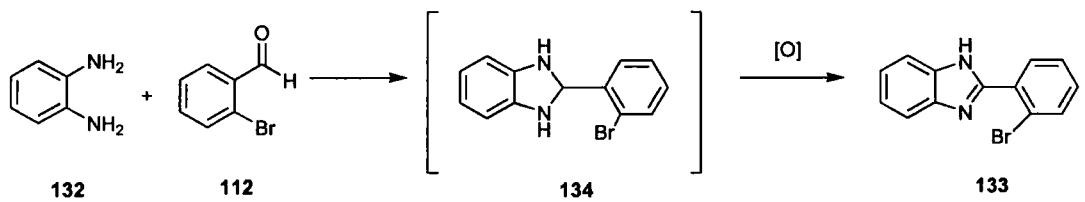
132 **112** **133, 30%**

Equation 44

The reaction was performed by treatment of phenylenediamine and 2-bromobenzaldehyde at 0 °C with 0.6 equivalents of Oxone™. After 12 hours, the reaction was quenched with

an aqueous solution of sodium hydroxide and the precipitate, was collected and purified by recrystallisation (hexane:ethyl acetate) to give pale yellow crystals (26% yield).[61] As well as a loss of the peak from the aldehyde, there was also an increased number signals observed in the aromatic region of the ^{1}H NMR spectrum of the purified **133**, as well as a shifting of those present from the starting materials. This confirmed by the ^{13}C NMR ($CDCl_3$) spectrum which revealed peaks at 115.5 (ArBr), 120.4 (*Ar*C), 127.2 (ArH), 128.0 (ArN), 130.5 (ArH), 131.2 (ArH), 132.8 (ArH), 134.0 (ArH), 138.1 (ArH) and 149.8 ppm (*C*Ph). The identification of this material as **133** was supported by the mass spectrometry (EI +) which revealed ions at, amongst others, *m/z* 271.94 (M^+) and 273.95 (M^+). The detailed characterisation of this compound can be found in the experimental section (**Experiment 2.1**).

The low yield obtained in this reaction (**Equation 44**), compared to that of the *n*-butyl-substituted diamine **110** with 2-bromobenzaldehyde (**Equation 37, Section 2.1**), reflects the increased propensity of phenylenediamine towards oxidation.[62] The susceptibility of phenylenediamine to oxidation, even by air, is well known and is a common problem associated with the handling and storage of this compound.[62] As the formation of **133** is accepted to occur through the pathway shown in **Scheme 24**, the oxidation of phenylene diamine could prevent the formation of the benzimidazoline **134** and therefore compete with the desired reaction.

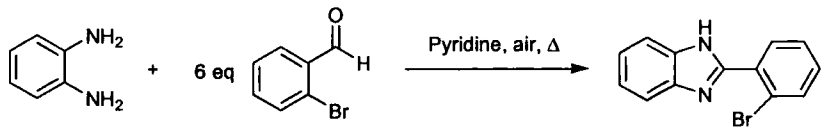


132 **112** **134** **133**

Scheme 24

Hence, attempts were made to prepare the benzimidazole **133** without an oxidising agent. This approach had been considered previously during the synthesis of the *n*-butylbenzimidazole **111,** but had been unsuccessful. The increased reactivity of phenylenediamine, indicated by the ease of oxidation, should allow the synthesis of **133** in this way. Therefore, phenylenediamine was reacted with 2-bromobenzaldehyde in a

solution of pyridine as shown in **Equation 45**.[56] The reaction was refluxed for 72 hours, after which there appeared to be remaining starting material by TLC.



132 **112** **133**, 33%

Equation 45

When the crude material was isolated, it was found to contain residual pyridine by ^1H NMR, as well as unreacted 2-bromobenzaldehyde and phenylenediamine, and low levels of impurities derived from phenylenediamine.[23,62] Purification by crystallisation of **133** from the crude oil (chloroform:toluene), gave **133** as colourless crystals (33%), which were identified by comparison of the characterisation data with that prepared previously (**Equation 44**). The low yield achieved in this reaction is due to a combination of incomplete reaction of **132** and competing oxidation, as was suspected in the reaction performed in the presence of Oxone™ (**Equation 44**). As there are numerous approaches to the synthesis of benzimidazoles, we remain hopeful that a more effective approach to the synthesis of **133** can be achieved. Perhaps the most effective methods would be those which avoid the use of phenylenediamine, for instance the one-step reductive cyclisation of 2-nitroanilines with aldehydes.[57e]

Section 2.3.2

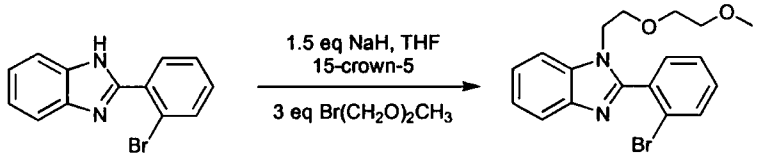
Attempts were then made to determine if the benzimidazole **133** could be successfully coupled with alkyl halides. Attempts were made to couple the commercially available alkyl bromide **135,** which contained a short polyethylene glycol (PEG) chain, to the benzimidazole **133**.[55] If this side chain could be installed, this should improve the solubility of the corresponding boronic acids. Therefore, this was first attempted through the reaction of 1-bromo-3,6-dioxaheptane **135** with **133** in the presence of K_2CO_3 as shown in **Equation 46**.

133 **136**, 94%

Equation 46

This reaction was performed through the addition of **135** and excess K_2CO_3 to a mixture of 2-(2-bromobenzene)benzimidazole **133** in anhydrous DMF. The reaction mixture was heated to reflux for 5 hours, after which the reaction appeared to be complete by TLC. After work-up, the crude product obtained was subjected to silica gel chromatography and **136** was obtained as a pale brown oil (94%). The shifts in the ^{1}H NMR spectrum due to the alkyl protons of the PEG chain of **136** were very informative, these had shifted from those of the starting material **135** to 3.28 (s, 3 H), 3.37-3.42 (m, 4 H), 3.69 (t, *J* 6.0 Hz, 2 H) and 4.26 ppm (t, *J* 6.0 Hz, 2 H).[23]

When the coupling of **133** with **135** was performed in the presence of sodium hydride, the reaction was found to be even more effective. This involved the addition of an excess of the alkyl halide **135** to a mixture of the benzimidazole **133,** sodium hydride (THF) and 15-crown-5 as shown in **Equation 47**.



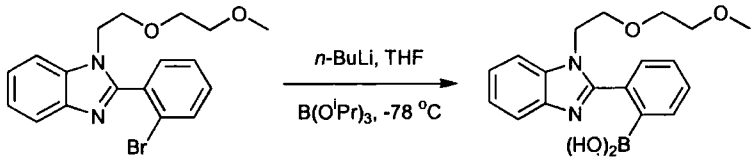
133 **136**, 100%

Equation 47

After work-up, the crude product was purified by column chromatography, and **136** was recovered in quantitative yield as a pale brown oil. This was identified by comparison of the characterisation data with previously isolated **136** (**Equation 46**).

Unfortunately, our attempts to prepare the corresponding boronic acid **137** from the bromide **136** were unsuccessful. The synthesis of **137** was attempted according to the procedure used in the preparation of the boronic acid **117** and boronate **107**, through

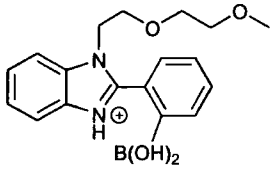
lithium-halogen exchange of the bromide **135**, followed by trapping the aryl-lithium formed with triisopropyl borate (**Equation 48**). This reaction was performed through the treatment of a cooled (-78 °C) solution of **136** with 2 equivalents of *n*-butyllithium, and the resulting pink solution was treated with triisopropyl borate, and allowed to warm to room temperature.



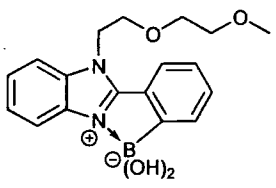
136 **137**

Equation 48

After work-up and neutralisation with dilute aqueous HCl, a small amount of white precipitate was observed, which on standing re-dissolved to give a homogeneous solution. As the expected solubility of **137** may mean that it is not be possible to precipitate this species from solution, attempts were made to isolate the reaction products through extraction of the biphasic mixture into diethyl ether. After evaporation of the diethyl ether extracts and the aqueous layer the crude products obtained (77%) and (100%) respectively, were found to contain peaks in the ^{11}B NMR ($CDCl_3$) spectrum at 33 and 5 ppm. This was encouraging, as it is similar to the spectrum observed in the ^{11}B NMR (D_2O:CD_3CN) of the *n*-butylbenzimidazole **117**, and it indicates that the species **138** and **139** were formed.



138



139

Unfortunately, attempts to purify and isolate the benzimidazole **137** were unsuccessful. As the precipitation of **137** from the aqueous solution could not be achieved (pH from 1 to 14), an alternative approach to the isolation of **137** was considered. The isolation of **137** was attempted using Amberlite® resin.[70,71] Such resins can be used to isolate various compounds, including metal salts and amino acids.[70] Amberlite® [IR 120(+)] resin was chosen for this isolation of **137**, as it has acidic residues on its surface, which it was hoped would interact with **137** to form ion pairs, and retain this species until cleavage. An acidic resin was chosen for this isolation rather than a basic resin, as a basic resin could bind to

boric acid impurities present in the crude product as well as to **137**, which would be more difficult to remove than basic impurities.

Hence, attempts were made to isolate **137** through the adsorption of the crude product (**Equation 48**) onto Amberlite® [IR 120(+)] resin, through swirling an aqueous solution of the crude product at pH 2.5 (HCl) over the resin.[71] After 30 minutes the resin was collected and was washed thoroughly with aqueous acid (HCl, pH 2) to remove species not bound to the resin. Attempts were then made to displace the adsorbed material by washing with ammonium methoxide (pH 10), followed by an aqueous solution of ammonium hydroxide (pH 10).[71] Unfortunately, the desired benzimidazole **137** was not observed by NMR (^{11}B, ^{1}H) or TLC in any of the fractions obtained from these washes. After evaporation of all of the fractions collected, the ^{11}B NMR of these residues contained no signals indicating that no boron containing compounds were present. This was surprising, as when the same process had been performed with **118**, 57% recovery had been achieved. This recovery was not as high as would be expected in soluble analogues of **117**, as **107** was only partially soluble at pH 2.5 and therefore, not all of this material could have been adsorbed onto the surface of the Amberlite® resin.

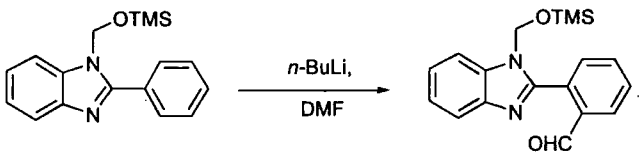
It is likely that the reaction shown in **Equation 48** had produced **137**, but only in low levels. The only evidence for the formation of the boronic acid **137** that could be obtained had been the ^{11}B NMR spectrum. However, this merely revealed that there were boron containing species with similar ^{11}B NMR shifts to those expected for **137** present in the crude products, and gave no indication of the relative quantities of these compounds. When compared to the quantitative yields obtained in the synthesis of **117** (**Section 2.1.5**) the apparent failure of the synthesis and isolation of **137** (**Equation 48**) was surprising. The difference between these reactions may be due to the polyethylene glycol chain of **136**. The oxygen atoms in the side chain could certainly have become complexed to *n*-butyllithium and may even have competed in directing lithiation. Alternatively, the boronic acid **137** may have been formed, but may have been more susceptible to protodeboronation due to its improved solubility.

It may be possible to avoid the problems encountered in the preparation of **137** through the use of higher quantities of *n*-butyllithium or *t*-butyllithium, or alternatively, by installing

the boronic acid first, before the polyethylene glycol side chain. If the loss of **137** was found to have occurred during isolation, this could also be solved by preparing the pinacol ester of **137** which should make this species more soluble in organic solvents.

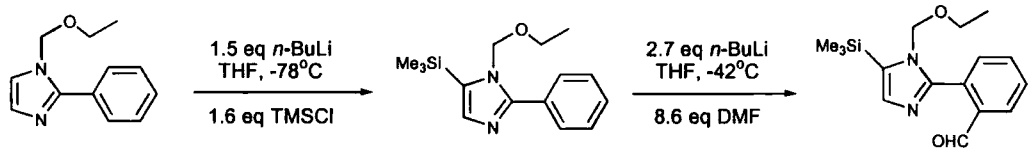
Section 2.3.3

During the synthesis of the benzimidazole **117** and the attempted synthesis of the analogue **137**, we became aware that there may be a simpler route to these types of compounds. It had been reported in the literature that 2-(2-phenyl)benzimidazoles could be prepared using directed metalation. Examples of these reactions are shown in **Equations 49** and **50**.[72] This indicated that potentially, compounds of the type **117** could be prepared in a two step process, possibly even in a one pot reaction. However, it is unclear in the literature reports of these reactions whether the metalation is directed by the nitrogen atoms of the benzimidazole, or by the oxygen atoms of the N-alkyl side chains (**Equations 49** and **50**).[72,73] Indeed no literature reports could be found in which directed metalation of these systems was attempted without the presence of oxygen atoms in the side chain.



140 **141, 53%**

Equation 49[72a]

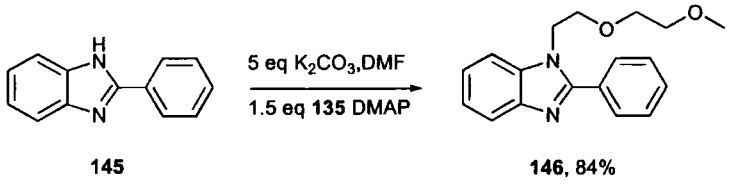


142 **143, 52%** **144, 73%**

Equation 50[72b]

Attempts were made to prepare the benzimidazole **137** from the benzimidazole **146** using this approach, through directed metalation followed by quenching with triisopropyl borate.

The benzimidazole **146** was prepared through the reaction of **135** with the commercially available 2-phenylbenzimidazole **145** as shown in **Equation 51**. This involved the treatment of a solution of 2-phenylbenzimidazole **145** with K_2CO_3, DMAP and **135** at room temperature.



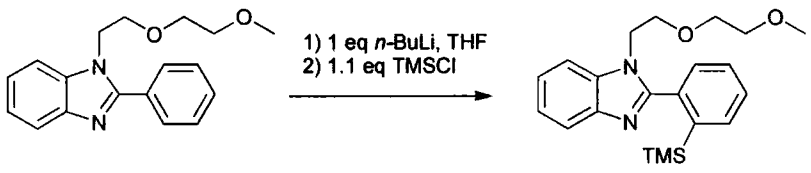
145 **146, 84%**

Equation 51

The solution was refluxed for 5 hours, after which no remaining starting material was observed by TLC. After aqueous work-up, the crude product was purified by column chromatography to yield a pale yellow waxy solid (84%). This product was identified as the desired benzimidazole **146** by comparison of the characterisation data with that of the starting materials.[23] Of these comparisons, the shift in the ^{1}H NMR of the peak due to the methylene of **135** next to the bromine atom was the most extreme. In the ^{1}H NMR spectrum of the starting material this peak had appeared at 3.47 ppm (t, *J* 6.4 Hz, 2 H) but was shifted to 3.88 ppm (t, *J* 5.8 Hz, 2 H, NCH_2CH_2OR) in the product.[23] The identification of this compound was confirmed by the mass spectrometry (EI +) which was found to contain ions at *m/z* 296.1638 (MH^+) and 207.0968 (M - C_7H_9) due to the protonated molecular ion and the ion formed on loss of the phenyl group and methyl. For a detailed characterisation of this compound please refer to the experimental section.

Attempts were then made to study the directed metalation of **146**, which may enable the preparation of the boronic acid **137**. However, neither the regioselectivity of the possible directed metalation, or which group or groups may direct it were known. Due to the difficulties encountered during our attempted synthesis of **137** using lithium-halogen exchange, it was decided that quenching the reaction using triisopropyl borate may be impractical. Therefore, to determine the regioselectivity of this reaction, and perhaps identify the directing group, after lithiation the reaction was quenched with trimethylsilyl chloride. It was hoped that the distinctive ^{1}H shifts of the trimethylsilyl groups would allow the position of the substitution to be determined. Hence, the directed metalation of

146 was attempted using *n*-butyllithium, followed by trapping of the lithiated species with trimethylsilyl chloride. This was performed as shown in **Equation 52**, through the drop-wise treatment of a cooled (-78 °C) solution of **146** in anhydrous THF with *n*-butyllithium. After stirring at -78 °C for 1 hour, trimethylsilyl chloride was added to the reaction and the solution was warmed to room temperature.



146 **147,24%**

Equation 52

The reaction was quenched by the addition of distilled water and extracted into ethyl acetate. The crude material obtained on evaporation was found by ^{1}H NMR to contain a number of products, the major of which was identified as the starting material **146**. The crude product was purified by column chromatography to give a yellow crystalline solid in 24% yield. Although this was found to contain a trimethylsilyl group by ^{1}H and ^{13}C NMR, the complexity of the aromatic regions of these spectra made the precise structure difficult to assign. Mass spectrometry (EI +) of this compound also confirmed the presence of a species containing a trimethylsilyl group due to the presence of ions at *m/z* 353.1539 ($M-CH_3$) and 207.1366 ($M - C_6H_6SiMe_3$). Fortunately, on standing a number of crystals were formed one of which was found to be suitable for single crystal X-ray diffraction analysis.[74] As well confirming the chemical connectivity of **147**, this analysis also provided proof for the regioselectivity of the directed metalation reaction (**Figure 8,**

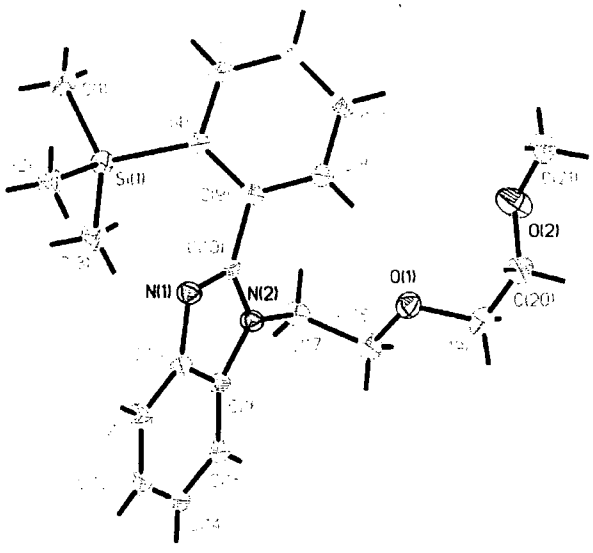
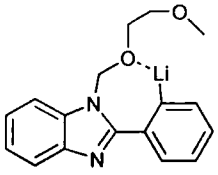
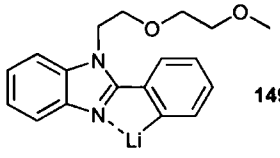


Figure 8: Thermal ellipsoid plot of **147** at 50 % probablilty[27,74]

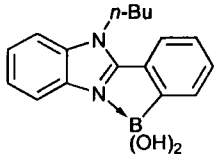
Appendix 5).[28,74] The crystal analysed was found to contain 105 in which the trimethylsilyl group was in the *ortho*-position of the phenyl ring as can be seen in the thermal ellipsoid plot shown in **Figure 8**.[28,74] This was interesting as it revealed the possibility of a two step route to these boronic acids, possibly through a one-pot reaction.



148



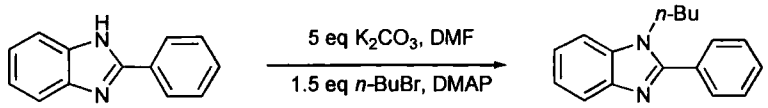
149



118

Although the regioselectivity of the directed metalation was clear from the crystal structure, what was not clear was which group had directed the lithiation. If an oxygen atom of the polyethylene glycol side chain was directing the lithiation, then this would involve the formation of either seven or ten-membered chelation ring systems. However, if the nitrogen of the benzimidazole was the directing group, then a five-membered ring would be formed, possibly with the structure **148**.[73] Formation of a similar five-membered ring through the internal bonding of nitrogen and boron had already been observed in the benzimidazole **118** (**Section 2.1**). Due to this, the delivery of the lithium cation by nitrogen through the formation of a five-membered ring such as **149** is certainly plausible.

Attempts were made to determine if, as suspected, the nitrogen atoms of the benzimidazole were directing the lithiation in the reaction of **146** shown in **Equation 52**. This was achieved by examining the lithiation of the N-*n*-butylbenzimidazole **109**. As this compound did not contain heteroatoms in the side chain, if the lithiation of **109** occurred with the same regioselectivity then this would suggest that it was the nitrogen atoms of the benzimidazole that were directing lithiation. The N-*n*-butylbenzimidazole **109** was prepared using the conditions reported above in the preparation of the N-PEG-benzimidazole **146** (**Equation 52**). This reaction was carried out through the addition of *n*-butyl bromide to a mixture of **145**, K_2CO_3 and DMAP in anhydrous DMF as shown in **Equation 53**.

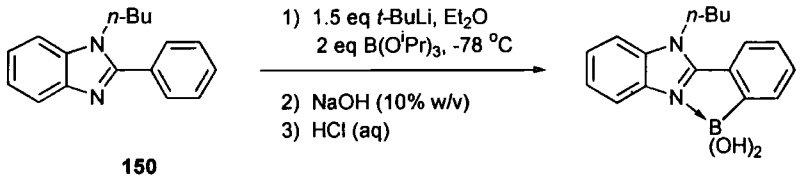


145 **150**, 85%

Equation 53

The reaction mixture was refluxed for two hours after which TLC revealed no remaining starting material. After aqueous work-up, crude product was purified by silica gel chromatography to give a waxy solid in 85% yield which was identified as **150** by comparison with literature data.[61]

Lithiation of the benzimidazole **150** was then attempted. It was decided that the lithiated complex possibly formed during this reaction would be quenched with triisopropyl borate, as the compound **117** which would be the major product if this reaction was successful, had been prepared previously this would allow direct comparison. The directed lithiation of **150** was performed in a similar way to that of **146 (Equation 52)**. Hence, a solution of the benzimidazole **150** (diethyl ether) was cooled to -78 °C, treated *t*-butyllithium and stirred for 2 hours as shown in **Equation 54**. Triisopropyl borate was added, and the solution allowed to warm to room temperature.



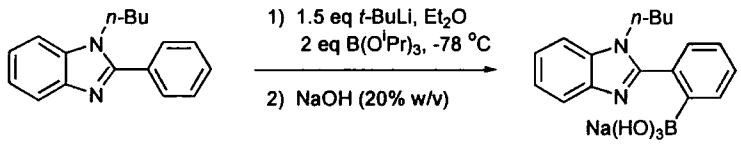
150 **118**, 100%

Equation 54

The reaction was quenched by addition of aqueous sodium hydroxide, followed by neutralisation by aqueous HCl. At pH 7 precipitation occurred the resulting precipitate was collected by filtration, washed (diethyl ether and distilled water) and dried in air. The resulting powder was identified as the boronic acid **117** by comparison of the characterisation data obtained with that of the **117** previously prepared by lithium-halogen exchange. The synthesis of **117** in this way (**Equation 54**) gave a yield of 100%,

substantially higher than that observed in the directed lithiation, and silylation of **146** shown in **Equation 52**

It was found that the boronate complex **107** could also be prepared from **104** by directed metalation. This was successfully achieved through the treatment of a solution of the benzimidazole **150** in diethyl ether (-78 °C) with *t*-butyllithium. After addition, the solution was treated with triisopropyl borate (**Equation 55**).



150 **107**, 100%

Equation 55

The reaction was quenched with aqueous sodium hydroxide and the precipitate formed was collected by filtration, washed with diethyl ether and dried in air. This material was found to be identical to **107** previously prepared (**Section 2.2.2**).

Due to the successful preparation of the **117** and **107** through directed metalation, it had been shown that the nitrogen atoms in the benzimidazole backbone were directing the lithiation, and that rather than aiding the reaction by directing lithiation, the oxygens of the polyethylene glycol side chain of **146** may have been hindering it. It was now thought that the polyethylene side chain may also have been the cause of the low yields that had been achieved in the directed metalation and silylation of **146** (**Equation 52**). Not only would the formation of a complex between the lithium cations and the oxygen atoms in the side chain reduce the concentration of lithium cations in the reaction mixture but may also lead to a scrambling of the positions to which the butyllithium was delivered.[73]

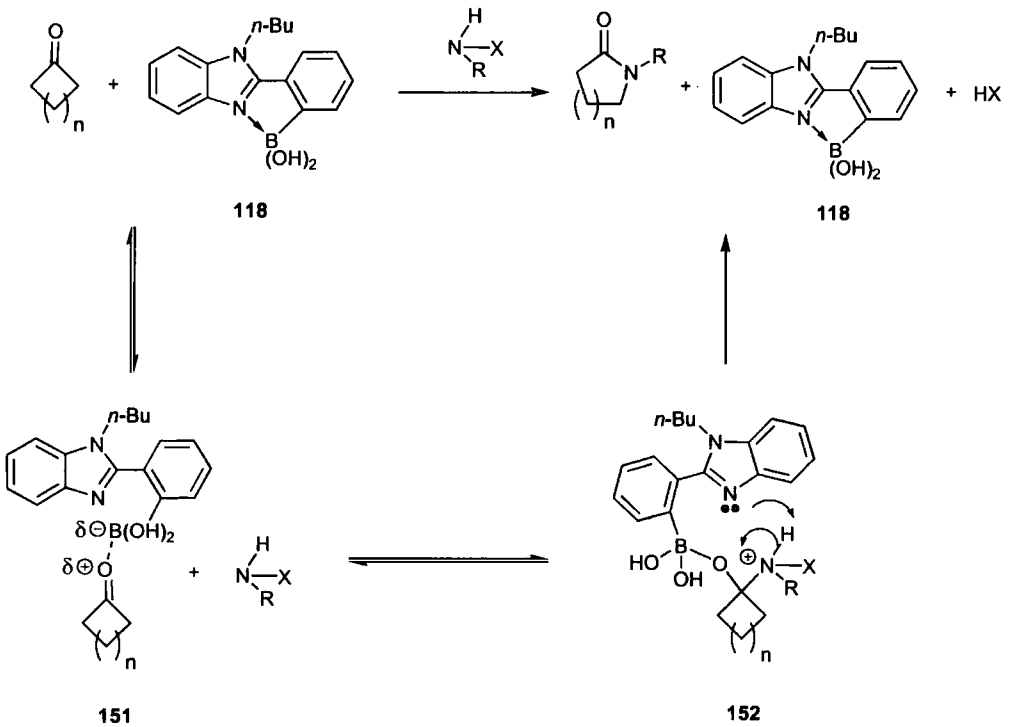
These results provided evidence that in the lithiation of the N-substituted 2-phenylbenzimidazoles **146** and **150** it is the nitrogen atoms of the benzimidazole backbone that are mainly responsible for directing the metalation. In these species the lithiation is vaulted across from the nitrogen atom of the benzimidazole to the *ortho*-position of the phenyl ring. They had also indicated that an effective one-pot synthesis of a range of

bifunctional benzimidazoles may be possible. Even the preparation of N-PEG-(2-boronophenyl)-2-benzimidazole **137** should be possible, shown by the successful synthesis of **147**. However, it is expected that the preparation of analogues containing other directing groups by this route would be inappropriate.

Chapter 3

Section 3.1

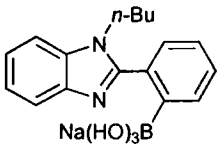
Attempts were made to assess the potential of the bifunctional molecule **117** as a catalyst for an aza-version of the Baeyer-Villiger reaction. If such a reaction could be developed, it should be susceptible to catalysis by bifunctional molecules.[16,19,20] Despite the problems encountered in the development of an aza-Baeyer-Villiger reaction, it was hoped that by applying the potential bifunctional catalyst **117**, activity could be induced in previously unreactive systems. Potentially, the bifunctional molecule **117** could promote an aza-version of the Baeyer-Villiger reaction through the activation of the carbonyl compound, as well as by deprotonation of the tetrahedral intermediate, as shown in **Scheme 25**.



Scheme 25

Section 3.1.1

Our investigation into the use of bifunctional molecules as catalysts for the aza-Baeyer-Villiger reaction initially focused on the two most stable reagents prepared previously. The N-Boc-O-(diphenylphosphoryl)hydroxylamine **65**, known to be stable at low temperatures even in large quantities, and the commercially available nitrene equivalent precursor chloroamine T **67** (**Chapter 1**). Due to the solubility problems associated with the benzimidazole **117**, the investigation was conducted using the boronate complex **107**. This material contains both the internally coordinated boronic acid **118** and the boronate salt **107** (**Section 2.1.5**), and should therefore, provide an effective way of delivering **117** to the reaction mixture, which avoids the solubility problems associated with **118**.



107

The investigation into the effect that **107** has on the reactions of **65** and **67** with carbonyl compounds was carried out through a series of screening experiments, in which the nitrene equivalent precursor **65** and hydroxylamine **67** were reacted with cyclobutanone in the presence of the bifunctional molecule **107** (**Table 9**). Triethylamine was added to these reactions as an attempt to prevent the possible formation of the ammonium salt **121**, and to make these reactions consistent with the screening experiments performed previously with these compounds.[53]

Entry	Reagent	Solvent	Additive (10 mol%)	Reaction
1	65	DCM	-	No
2			NEt_3	No
3		MeOH	-	No
4			NEt_3	No
5	67	DCM	-	No
6			NEt_3	No
7		MeOH	-	No
8			NEt_3	No

Table 9: Reactions of **65** and **67** with cyclobutanone in the presence of 8.8 mol% of the bifunctional molecule **107** and triethylamine.

This experiment was performed using a Robbins block™, the wells of which were first charged with mixtures of **65** or **67** in dichloromethane or methanol, and treated with cyclobutanone. The resultant solutions were treated with a solution of 10 mol% of the bifunctional complex **107**, followed by triethylamine. The Robbins block™ was sealed and shaken for 1 day at room temperature, after which the reactions were worked-up in parallel by filtration through short plugs of silica, followed by evaporation of the solvents. The residues obtained were analysed by LCMS and all, unfortunately, were found to have been inactive.

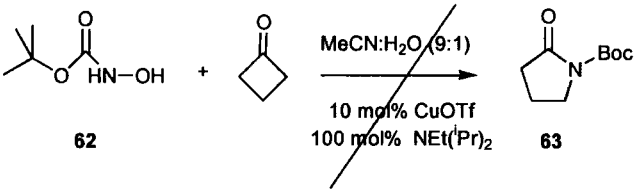
The lack of reactivity of **65** and **67** with carbonyl compounds in the presence of **107** was very disappointing. It had been hoped that the bifunctional molecule **107** would activate **65** and **67** and encourage the desired reactivity. From the screening experiment described above, it was not clear if the bifunctional molecule **107** was capable of promoting the aza-Baeyer-Villiger reaction or not. The absence of the desired compounds in the crude products may instead be an indication of the unsuitability of **65** and **67** as reagents for this reaction. This problem had been encountered throughout our investigations into the development of an aza-Baeyer-Villiger reaction; in many cases it had not been possible to determine whether the potential nitrogen containing per-acid and nitrene equivalents were unsuitable or were not being activated by the Lewis acids and bases (**Chapter 1**).

Section 3.1.2

Rather than continue the investigation into the effect of **107** on the activity of the nitrogen containing per-acid equivalents previously selected, our focus now turned towards the investigation of the hydroxylamine **62**. This move was triggered by the lack of activity observed in the screening experiments of these reagents, and the possibility that the complexation of hydroxylamines to **118** could lead to the formation of leaving groups *in situ*.

An early investigation had been made into the potential of the hydroxylamine **62** to undergo the aza-Baeyer-Villiger reaction with carbonyl compounds in the presence of

Lewis acids and bases. This had been achieved through the reaction of **62** with cyclobutanone, benzophenone and chalcone, in parallel, in the presence of copper(I) triflate, both with and without diisopropylethylamine as shown in **Equation 56** and **Table 10**. Copper salts were chosen as the Lewis acids as there are many examples in the literature of copper nitrenoids.[37,38]



Equation 56

This experiment was performed through the addition of solutions of the carbonyl compounds (MeCN:H_2O) to small screw-top vials (1.5 ml) which contained solutions of the hydroxylamine **62** (MeCN:H_2O). The solutions were subsequently treated with CuOTf (10 mol%) and diisopropylethylamine (100 mol%), and stirred at room temperature for 4 days during which they were analysed by TLC.

Entry	Reagent	CuOTf	EtN(^{i}Pr)	Reaction
1	Cyclobutanone	-	-	-
2		10 mol%	-	-
3		10 mol%	100 mol%	-
4	Benzophenone	-	-	-
5		10 mol%	-	-
6		10 mol%	100 mol%	-
7	Chalcone	-	-	-
8		10 mol%	-	-
9		10 mol%	100 mol%	-

Table 10: Reaction of hydroxylamine **62** with cyclobutanone, benzophenone and chalcone in the presence of CuOTf and diisopropylethylamine.

Unfortunately, during this time there was no evidence of reaction observed by TLC. Despite this lack of activity, it was still hoped that **62** could be activated using the bifunctional molecule **107**. This activation could occur through complexation of **62** with the boronate **107** to form the leaving group *in situ* or through the activation of the carbonyl compound. To investigate the potential of the bifunctional complex **107** to promote the

aza-Baeyer-Villiger of hydroxylamine **62**, a screening experiment was conducted in which **62** was reacted with cyclobutanone, benzophenone and *trans*-chalcone in the presence of **107** (**Table 11**).

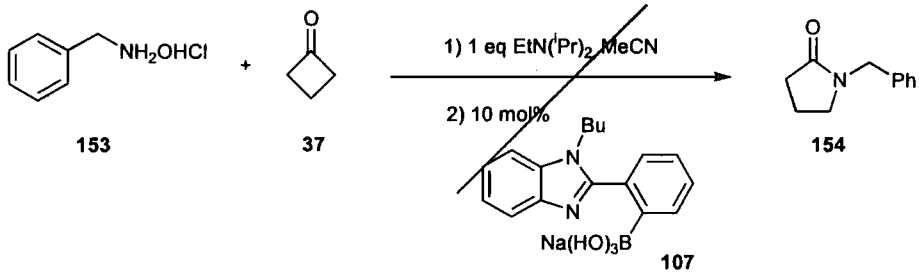
Entry	Substrate	Solvent	**107**	$EtN(^iPr)_2$	**83**
1	Cyclobutanone	MeCN	-	-	No
2		MeCN:H_2O 9:1	-	-	No
3		MeCN	8.9 mol%	-	No
4		MeCN:H_2O 9:1	8.9 mol%	-	No
5		MeCN	8.9 mol%	100 mol%	No
6		MeCN:H_2O 9:1	8.9 mol%	100 mol%	No
7	Benzophenone	MeCN	-	-	No
8		MeCN:H_2O 9:1	-	-	No
9		MeCN	8.9 mol%	-	No
10		MeCN:H_2O 9:1	8.9 mol%	-	No
11		MeCN	8.9 mol%	100 mol%	No
12		MeCN:H_2O 9:1	8.9 mol%	100 mol%	No
13	Chalcone	MeCN	-	-	No
14		MeCN:H_2O 9:1	-	-	No
15		MeCN	8.9 mol%	-	No
16		MeCN:H_2O 9:1	8.9 mol%	-	No
17		MeCN	8.9 mol%	100 mol%	No
18		MeCN:H_2O 9:1	8.9 mol%	100 mol%	No

Table 11: Reaction of **62** with cyclobutanone, benzophenone and *trans*-chalcone in the presence of **107** and diisopropylethylamine. [a] Slight loss of starting material; formation of low levels of unidentified products.

The reactions were performed through the addition of a solution of the hydroxylamine **62** (MeCN) to solutions of cyclobutanone, benzophenone and chalcone in screw-top vials (1.5 ml). The subsequent solutions were then treated with 8.9 mol% of the bifunctional molecule **107**, as a solid, followed by diisopropylethylamine. The reactions were stirred at room temperature for 5 days, during which they were followed by TLC. Unfortunately, the reactions performed in this experiment were not found to undergo significant levels of reaction, and in the few cases where low levels of reaction were observed, ^1H NMR revealed the presence of low levels of multiple products. Due to the low levels of reaction and the multiple products observed these reactions were not worked-up or analysed further.

Section 3.1.3

Although the desired reactivity had not been observed, the screening experiment shown in **Table 11** had displayed the highest level of activity seen so far during our investigations into the aza-Baeyer-Villiger reaction. The possibility that the desired reactivity could be encouraged if a hydroxylamine without a Boc group was used was considered. Such a hydroxylamine should be more nucleophilic than **62**, and more susceptible to promotion by **117**. Investigation of the unstabilised hydroxylamine **153** as a reagent for the aza-Baeyer-Villiger reaction when in the presence of **107** was conducted through the reaction shown in **Equation 57**.



Equation 57

The reaction was performed through the treatment of a solution of **153** and diisopropylethylamine with cyclobutanone, and the boronate **107**. The addition of base to this reaction was intended to prevent the formation of the ammonium salt **121** which could potentially prevent **117** promoting the reaction. The cloudy solution which was formed on addition of **107** was stirred for 19 hours at room temperature. The reaction was worked-up through evaporation, dissolution of the residue obtained in diethyl ether and removal of the precipitate formed by filtration. The precipitate consisted of diisopropylethylamine hydrochloride, and benzimidazole **107**, and after its removal the solution was evaporated and the residue obtained was subjected to column chromatography. Unfortunately, the fractions collected were found to contain multiple products by ^{1}H, ^{13}C and TLC. Of these products the deprotonated hydroxylamine starting material was identified by ^{1}H, ^{13}C NMR and mass spectrometry.[23] In the second column fraction collected, ^{1}H and ^{13}C NMR indicated the presence of the desired nitrogen inserted product **154**. This could only be tentatively identified as **154**, due to the low levels observed and the presence of many other

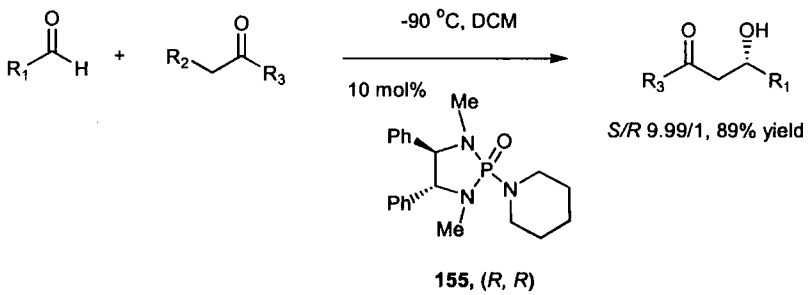
products, due to the observation of peaks in the ^{1}H NMR similar to that expected for the desired product. This identification was strengthened by the observation of a peak at δ_C 180 ppm in the ^{13}C NMR. However, when this material was analysed by mass spectrometry (EI +) the molecular ion for the desired compound was not observed, only those derived from the starting material alone, for example the ion at *m/z* 105 ($M-H_2O$, 100%). Therefore, it was unlikely that the unstabilised hydroxylamine **153** had undergone the desired reaction, and the presence of peaks in the NMR spectra which had appeared to indicate the presence of **154** could have been attributable to a number of compounds

There are a number of possible explanations for the lack of activity observed in the reaction of **153** and cyclobutanone in the presence of **117**. If the formation of the boronate ester of **153** and **117** occurred before the nucleophilic attack of the cyclobutanone, this could reduce the nucleophility of **153** and render it inactive. Alternatively, the boronate complex could undergo rearrangement reactions to form imines, in a similar way to the rearrangements of the N-alkyl-O-(4-nitrobenzenesulfonyloxy)hydroxylamines and N-alkyl-O-(diphenylphosphinyl)hydroxylamines (**Section 1.2**). It is also possible that the tetrahedral intermediate if formed, was not capable of rearranging to give the pyrrolidinone as shown in **Scheme 25**.

The inability of **107** to promote the aza-Baeyer-Villiger reactions of the compounds **65**, **67** and **62** with carbonyl compounds, led us to consider the possibility that these reagents were unsuitable for the aza-Baeyer-Villiger reaction. It is very unlikely that if these compounds were capable of undergoing an aza-Baeyer-Villiger reaction, no evidence of this would have been seen during our investigations. The development of reagents for the aza-Baeyer-Villiger had been difficult; a fine balance is required between the lability of the leaving group and the nucleophilicity of the nitrogen centre, but this balance results in the reagent being thermally unstable. Although it was possible that a stable compound could be found which could be activated to the desired reactivity, without a starting point for this investigation it would require the screening a large number of nitrogen-containing compounds against Lewis acid, base and combinations of the two. Even with the performance of such a large, virtually random investigation, the discovery of a suitable set of reagents may still be unsuccessful, and unwillingly we had to admit that screening on such a scale was not possible with the equipment at our disposal.

Section 3.2

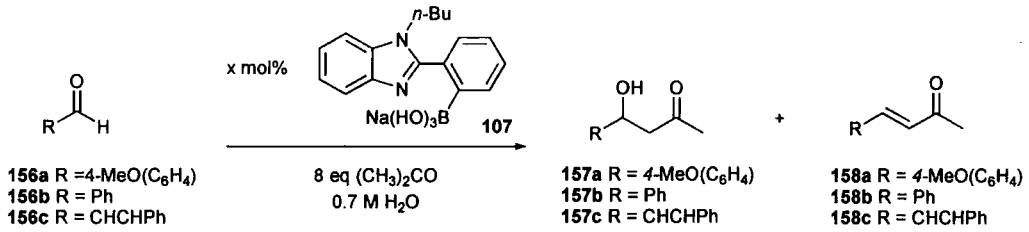
Despite the inability of **107** to promote the aza-Baeyer-Villiger reactions of **62**, **65** and **67** with carbonyl compounds (**Section 3.1.3**), we continued our investigation into the ability of benzimidazoles based on **117** to behave as bifunctional catalysts, focusing on other organic reactions. In research conducted previously within the Whiting group, it had been found that the complex **107** promoted the self-condensation reaction of acetone, and tentative steps had been made towards the investigation of its ability to promote the aldol reaction of acetone with aryl and conjugated aldehydes.[55] Therefore, this presented a natural starting point for our investigations into the use of **117** and its related structures as bifunctional catalysts. The aldol reaction is accepted to be one of the most important reactions in organic synthesis, as it allows the formation of carbon-carbon bonds, as well as the simultaneous generation of two chiral centres.[75] This has lead to the development of many catalytic systems for this reaction, including highly stereoselective and environmentally friendly catalysts an example of which is shown in **Equation 58**.[76]



Equation 58[79a]

Section 3.2.1

To determine the ability of bifunctional benzimidazoles to promote the aldol reaction, the reactions of acetone with a range of aldehydes were performed in the presence of **107**. Hence, the reactions of 4-anisaldehyde **156a**, benzaldehyde **156b**, and *trans*-cinnamaldehyde **156c** with acetone, were performed through the addition of the complex **107** to a biphasic solution containing the aldehyde in distilled water and acetone as shown in **Equation 59** and **Table 12**.



Equation 59

Entry	156	Acetone Eq.	107	Time (h)	157	158
1	4-anisaldehyde **156a**	8	9 mol%	22	-	**158a**, 38%
2	benzaldehyde **156b**	8	15 mol%	72	-	**158b**, 17%[a]
3	*trans*-cinnamaldehyde **156c**	8	9 mol%	22	-	-

Table 12: Reaction of aldehydes with acetone in the presence of the boronate **107**.

[a] Reaction performed on an NMR scale (0.7 ml), and the yield calculated from the ratio of the products observed by ^{1}H NMR.

When the reaction was performed with the aromatic aldehyde 4-anisaldehyde **156a**, after stirring for 22 hours the biphasic reaction mixture contained a small amount of precipitate. By ^{1}H NMR and TLC the reaction was found to have reached equilibrium between the aldehyde, hydrate, and aldol condensation product.[23,77,78] When the reaction was performed on an NMR scale (~0.7 ml) the ratio between these species at equilibrium appeared, by ^{1}H NMR, to be 1:3.1:1.7 respectively.[23,77,78] The aldehyde starting material **156a** was identified by, amongst others, the peak characteristic of the aldehyde proton at 9.58 ppm in the ^{1}H NMR spectrum.[23,77,78] The hydrate of 4-anisaldehyde was identified by peaks in the aromatic region of the ^{1}H NMR at 7.19 (d, *J* 8.7 Hz, 2 H) and 6.78 ppm (d, *J* 8.7 Hz, 2 H),

and the aldol condensation product **158a** was identified by, amongst other signals, the ^{1}H NMR peak characteristic of an alkene proton at 6.46 ppm (d, *J* 16.2 Hz, 1 H).[23,78] After aqueous work-up, the crude residue obtained was subjected to column chromatography and the purified ketone **158a** was obtained as yellow crystals in 38% yield, the characterisation data of which was found to be identical to literature values.[77]

The reaction of acetone with benzaldehyde in the presence of 15 mol% of the complex **107** (**Entry 2, Table 12**), was performed on an NMR scale (~0.7 ml) in a similar way to that of 4-anisaldehyde as described above. This involved the addition of the complex **107** to a solution of benzaldehyde **156b** in a solution of acetone and D_2O. After 72 hours, ^{1}H NMR of the reaction mixture revealed only a small amount of benzaldehyde **156b**.[23] As in the reaction of **156a** (**Entry 1, Table 12**), there appeared to be an equilibrium between the aldehyde, the hydrate and the aldol condensation product **158b**, which was calculated from the ^{1}H NMR spectrum to be 1:11.2:2.5 respectively.[23,78,79] The aldol condensation product **158b** was identified by the peaks at 6.72 (d, *J* 16 Hz, 1 H) and 2.32 ppm (s, 3 H), and was observed alongside a number of low level peaks due to impurities, such as acetone self-condensation products identified by peaks between 2 and 3 ppm.[79,80] The yield of the aldol condensation product **158b** was calculated from the ^{1}H NMR spectrum to be 17%.[79]

When the reaction was performed with the unsaturated aldehyde, *trans*-cinnamaldehyde **156c**, the aldol condensation product **158c** was not formed (**Entry 3, Table 12**). The reaction was performed under similar conditions to those of 4-anisaldehyde and benzaldehyde (**Entries 1 and 2, Table 12**), and was monitored by ^{1}H NMR. Although it appeared that there were formation of new alkene containing compounds, these were not the aldol or aldol condensation products **157c** and **158c** due to the discrepancies between the ^{1}H NMR spectra observed and those reported in the literature.[23,81,82] Column chromatography failed to adequately separate these compounds, and with the exception of the aldehyde starting material **156c**, these species could not be identified accurately. Amongst the compounds observed, acetone self-aldol products were identified by a complex pattern of ^{1}H NMR peaks between 2 and 4 ppm, noticeably the doublets at 3.79 (d, *J* 8.4 Hz, 1 H) 3.75 (d, *J* 8 Hz, 1 H), 3.48 (d, *J* 5.6 Hz, 1 H) and 3.44 ppm (d, *J* 6 Hz, 1 H).[80]

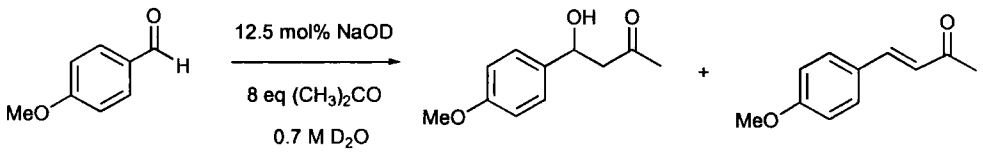
The absence of the aldol addition products **157a** and **157b** (**Entries 1** and **2**, **Table 12**) in the crude products obtained from the reactions of 4-anisaldehyde and benzaldehyde with acetone performed in the presence of **107**, suggests that the aldol products **157a** and **157b** are completely converted to the aldol condensation products.[79,83] Alternatively, it may indicate that the boronate **107** promotes the formation of the aldol condensation products directly from the aldehydes, through the formation of a transition state which, after converting the substrates to the aldol products, instead of eliminating the products, forms a complex with them and promotes their dehydration. This could be promoted in a number of ways, for instance an E_2 mechanism in which the aldol product is deprotonated by the amino group of **107** or by a hydroxide ion eliminated from **107**. To determine the mechanism, further investigations into these reactions were planned.

Section 3.2.2

The discovery that the aldol reactions of 4-anisaldehyde and benzaldehyde were promoted by the complex **107** was exciting; however, it did raise several important questions; the most important being the identity of the active species. Although the reactions appeared to be promoted by the bifunctional compound **107**, a different species may have been responsible for the activity observed. The parent structure **117** is known to exist in a number of forms (**Section 2.2**), any of which could be active. It was also possible that the aldol reactions of 4-anisaldehyde and benzaldehyde had been promoted due to the complex **107** acting as a source of hydroxide ion, rather than as a bifunctional catalyst.

The possibility that sodium hydroxide was the active species in the aldol reactions, and that **107** was active because it is in someway contaminated with it, was investigated. In the reactions which had been performed in the presence of 9-15 mol% of **107** (**Entries 1 and 2**, **Table 12**), if hydroxide had been present it must either be as an impurity of **107**, or be generated *in situ,* and therefore must be present in concentrations up to 9-15 mol%. Therefore, to test the activity of sodium hydroxide under these conditions the reaction of 4-anisaldehyde with acetone was performed in the presence of 12.5 mol% of sodium hydroxide as shown in **Equation 60**. This involved the addition of 4-anisaldehyde to an

aqueous solution (D_2O) containing 12.5 mol% of NaOD and 8 equivalents of acetone. The resulting solution was stirred at room temperature for 1.5 hours, during which the reaction was monitored by ^1H NMR.

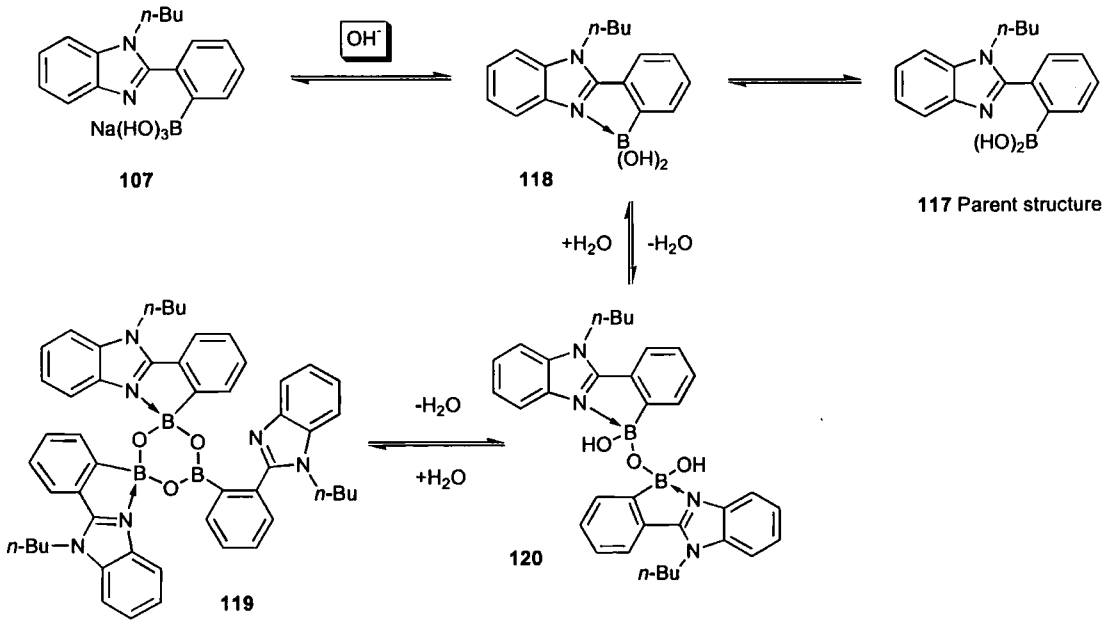


Equation 60

After 1.5 hours, ^1H NMR revealed that all of the starting material had been consumed.[23] The major product formed was identified as the aldol condensation product **158a** due to the presence of peaks in the ^1H NMR spectrum at 7.44-7.40 (m, 3 H), 6.86 (d, *J* 8.8 Hz, 2 H), 6.54 (d, *J* 16.4 Hz, 1 H) 3.86 (s, 3 H) and 2.29 ppm (s, 3 H).[77] A number of other products were also observed in the crude material which were attributed to acetone self-condensation products, due to the observation of a complex pattern of ^1H NMR peaks at 2.28-2.25 (m) and 2.11-2.06 (m), and a number of side products derived from 4-anisaldehyde which could not be identified due to the low levels formed.[80] After aqueous work-up, the aldol condensation product was obtained as a pale yellow crystalline solid in 63% yield.[77] As in the reaction of **156a** with acetone in the presence of **107**, there had been no aldol product **157a** isolated from this reaction. The similarity between the reaction of 4-anisaldehyde and acetone promoted by sodium hydroxide (**Equation 60**) with that performed in the presence of **107** (**Entry 1, Table 12**) was remarkable, and we began to consider that the possibility that **107** was acting merely as a source of hydroxide.

Section 3.2.3

Despite our suspicions that hydroxide was responsible for the promotion of the aldol reactions of 4-anisaldehyde and benzaldehyde with acetone performed in the presence of **107**, this was by no means conclusive and the possibility that other species may also be active was explored. The benzimidazole **117** is known to exist in solution in a number of forms as shown in **Scheme 26**.



Scheme 26

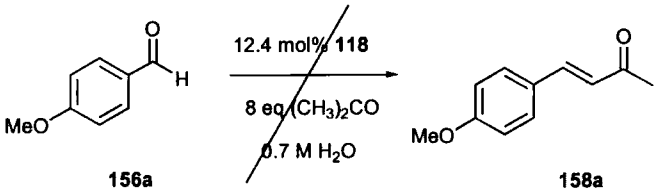
All of these species are expected to have been present in the aldol reactions promoted by **107** in varying quantities, and therefore their catalytic activity was explored. This investigation involved the reaction of 4-anisaldehyde with acetone in the presence of material which contained the various forms of **117** shown above (**Scheme 26**) as identified by ^{1}H, ^{11}B NMR and mass spectrometry data. The results obtained from these investigations, and details of the benzimidazole compounds tested have been compiled in **Table 13**.

Entry	'Catalyst' structure	Preparation	Loading	Equivalents of Acetone	Time	Activity
1	**118**	**Equation 39**	10 mol%	8	4 days	No
2	**118**	**Equation 39**	12.5 mol%	5	25 hours	No
3	**118**	**Equation 62**	12.5 mol%	13	24 hours	No
4	**118**	**Equation 62**	20 mol%	10	2 weeks	No
5	**122**	**Equation 41**	10 mol%	8	24 hours	No

Table 13; Reactions of **156b** with acetone in the presence of a range of forms taken by **117**.

The first structure to be studied was the internally donated monomer **118** (**Entry 1, Table 13**). The material used was isolated from the reaction mixture during preparation

(**Equation 39, Section 2.1.5**) through treatment with sodium hydroxide (20% w/v) followed by neutralisation with dilute aqueous HCl. The aldol condensation reaction was performed in the same way as the experiments described previously (**Entry 1** and **2, Table 12**; and **Equation 58**) through the addition of 10 mol% of the benzimidazole **118** to a 1 M aqueous solution containing 4-anisaldehyde and 8 equivalents of acetone (**Equation 61**). Unfortunately, benzimidazole **118** was not soluble in the reaction solution, and even after sonication the material did not dissolve; instead, a biphasic mixture was formed in which the aqueous phase appeared to be a suspension of **118**.

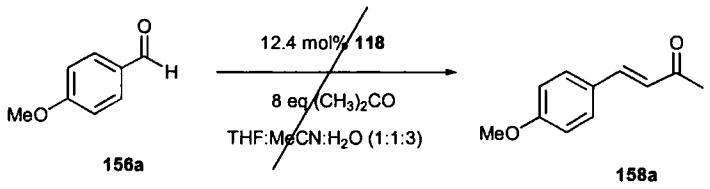


156a **158a**

Equation 61

After 4 days, there were no aldol or aldol condensation products **157a** or **158a** observed by ^{1}H NMR in samples taken from the reaction mixture, and there was no loss of starting material observed; the peak corresponding to the aldehyde proton at 9.80 ppm in the ^{1}H NMR spectra did not diminish.[23,77,83] There was also no evidence of any acetone self-condensation products, which had been observed in the reactions performed in the presence of **107** (**Entries 1** and **2, Table 12**).[80] Although the lack of activity observed in this reaction (**Equation 61**) indicates that the internally donated complex **118** is not active in the aldol condensation reaction, there were a number of factors that could have affected the ability of **118** to promote the reaction. These included the problematic solubility, and also the presence of the dimer and trimer forms.

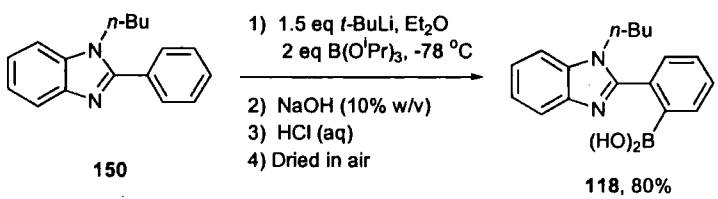
To encourage the solubility of **118**, the reaction was repeated in a combination of THF, MeCN and water (**Entry 2, Table 13, Equation 62**). It was possible that the reactions performed in the presence of **107** were promoted by **118**, as this species was present in low levels in the material characterised as **107**, but that when **118** was added to the reaction mixture as described above (**Entry 1, Table 13**), its poor solubility prevented it from being active.



Equation 62

The reaction of **156a** and acetone in the presence of 12.5 mol% of **118** in THF, MeCN, water and 5 equivalents of acetone, as shown in **Entry 2 Table 13**. After addition of the aldehyde a solution was formed which, although contained some particles, was thought to be homogenous. Despite this, there was no activity observed under these conditions. After aqueous work-up, ^{1}H NMR of the crude product revealed none of the aldol addition or condensation products **157a** and **158a**; and only peaks attributable to the starting material **156a** were observed.[23,77,83]

The lack of reactivity observed in the reactions performed in the presence of **118** (**Entries 1** and **2, Table 13**), indicated that the internally donated benzimidazole **118** is inactive in the aldol condensation reaction. This may have been due to the presence of the dimer **120** and boroxine trimer complexes **119** (**Scheme 26**) in this material as well as **118**. The presence of these species could reduce the concentration of **118** in the reactions of **156a** with acetone (**Entries 1** and **2, Table 13**) to such low levels that it was rendered inactive. Therefore, the reaction of 4-anisaldehyde with acetone was performed in the presence of a quantity of **118** that had been specially prepared to contain as little of the dimer **120**, trimer **119** and boronic acid **121** as possible, as shown in **Equation 63**. The larger proportion of **118** present in this material allowed the activity of **118** to be tested more effectively.



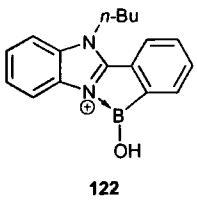
Equation 63

This was achieved according to the procedure previously described (**Equation 39, Section 2.2.3**); but with dilute sodium hydroxide (10% w/v) and HCl (10% w/v), and the precipitate isolated was dried in air rather than under reduced pressure. The material prepared in this way was found to contain a single ^{11}B NMR peak, due to the monomer with internal nitrogen to boron chelation at 12.2 ppm. However, despite the observation of a single species by ^{11}B NMR ($CD_3CN:D_2O$), mass spectrometry (ES +) revealed there to be some of the dimer **120** present, and therefore possibly also the boroxine, identified by an ion at *m/z* 553.34 (2M – 2OH) as well as the protonated molecular ion at *m/z* 295.20 (MH^+).

The reaction of 4-anisaldehyde with acetone was performed in the presence of **118** prepared in this way (**Equation 63**), as shown in **Entry 3 Table 13**. The benzimidazole was added in 12.5 mol% loading, to a 0.7 M aqueous solution which contained 4-anisaldehyde and 13 equivalents of acetone. As in the reactions performed previously (**Equation 39, Section 2.2.3**), the reaction mixture produced was not homogeneous. Even after 24 hours there was no reaction observed; the peaks characteristic of the aldol and aldol condensation products **157a** and **158a** were absent, and there was also no evidence of loss of the aldehyde starting material **156a**, and no peaks were observed due to acetone self-condensation peaks.[23,77,80,83] Even when the reaction was repeated in the presence of 20 mol% of **118**, there was still no activity observed (**Entry 4, Table 13**).

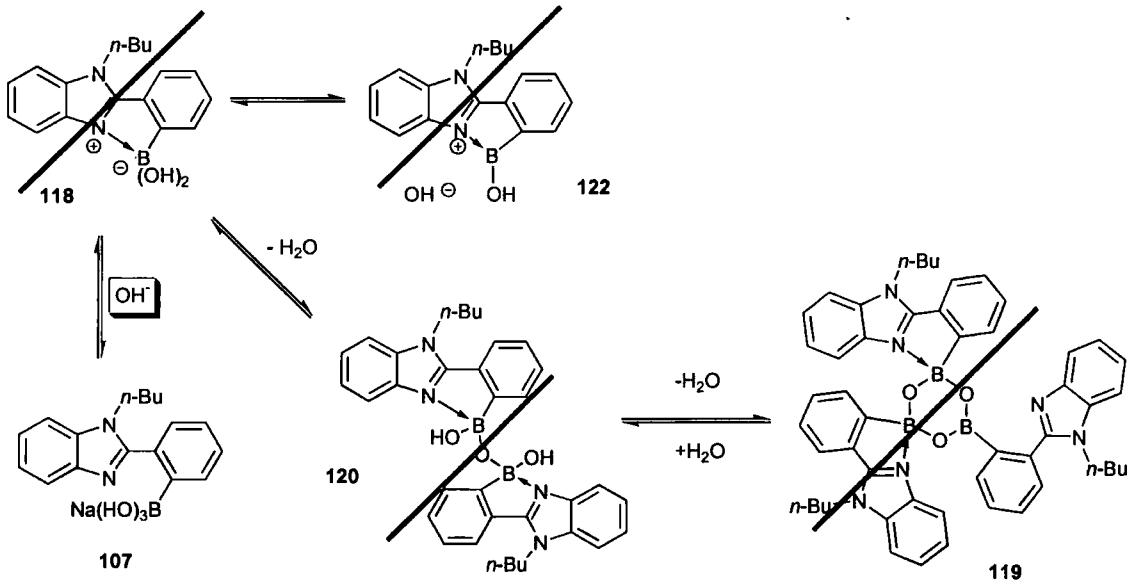
The lack of reaction observed when the **156a** and acetone were reacted in the presence of the benzimidazole **118** (**Equation 63**) confirmed our suspicions that this species was inactive. However, it was still unknown whether other forms taken by **117** were active in these reactions. Therefore, attempts were made to discover if the dehydrated forms of **117** were active in the aldol reactions. It had already been observed that acidic conditions and drying the material under reduced pressure caused dehydration of **117**, and the observation of dehydrated forms of **117** in the material prepared as shown in **Equation 63**, indicated that basic conditions might also promote dehydration of **118**, or at the very least fail to prevent it. Therefore, it was possible that boroxine and dimer complexes could be present in solutions of **107** under the reaction conditions.

To test the activity of dehydrated forms of **117** the reaction of **156a** and acetone was carried out in the presence of the dehydrated benzimidazole **122** (**Entry 5, Table 13**). This material had been prepared as shown in **Equation 41** (**Section 2.2.4**) through the work-up of the reaction mixture by direct neutralisation with HCl. The reaction of **156a** and acetone in the presence of 10 mol% of this species was performed in the same way as the reactions performed previously (**Entries 1, 2, 3 and 4, Table 13**), and after addition of 4-anisaldehyde was found to form an entirely homogeneous, pale brown biphasic solution. Even after 24 hours there was still no evidence of activity observed; the ^{1}H NMR spectrum only revealed peaks characteristic of the starting material.[23,77]



122

It had become clear that the forms **118**, **119**, **120** and **122**, taken by the benzimidazole **117** (**Scheme 27**), are inactive in the aldol condensation reaction of 4-anisaldehyde with acetone. It therefore appeared that these reactions might simply be promoted by hydroxide alone, or possibly by both hydroxide and the boronate **107**.

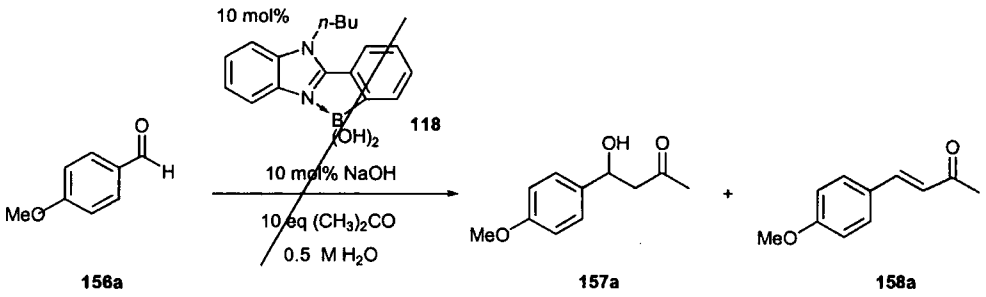


Scheme 27

Section 3.2.4

To determine if **107** was active in the aldol condensation reaction, and did not merely act as a source of sodium hydroxide, attempts were made to prepare the complex **107** *in situ* from **118**. When **118** in D_2O was treated with NaOD the ^{11}B NMR (D_2O) spectrum revealed peaks at 1.5 ppm and at 2.4 ppm, due to the boronate **107** and sodium borate respectively. This suggests that, not only is it possible to form the salt **107** from the boronic acid **118**, it is also possible to prepare a solution richer in the boronate complex than solutions of authentic **107**, which are known to contain **118**. If the boronate complex is the active species in the aldol condensation reactions, then solutions of **107** generated in this way should display the same, or even higher activity than solutions of authentic **107**.

Attempts to test this hypothesis were made through the reaction of **156a** and acetone in the presence of sodium hydroxide and the benzimidazole **118** (**Equation 64**). This reaction was performed by the addition of the aldehyde to a solution containing 10 equivalents of acetone, 10 mol% of sodium hydroxide and 10 mol% of **118**, prepared as shown in **Equation 41** (**Section 2.1.5**). Prior to addition of the aldehyde, the benzimidazole **118** and sodium hydroxide were stirred together at room temperature for two hours, during which **118** dissolved slowly.



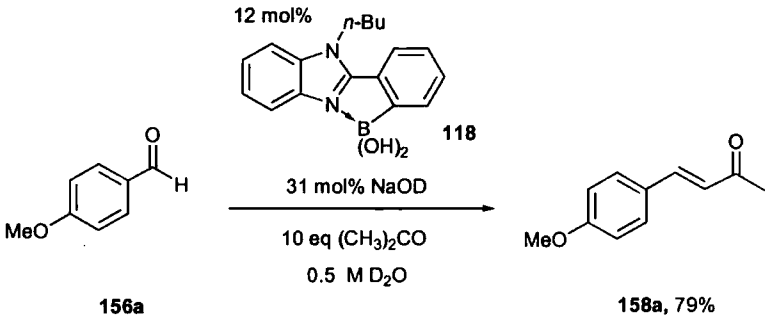
Equation 64

After addition of 4-anisaldehyde the reaction was stirred at room temperature for 24 hours. After aqueous work-up, ^1H NMR of the crude product revealed that no reaction had occurred.[23,77] The ^1H NMR spectrum of this material revealed only peaks attributable to

the starting material **156a**, and none due to the aldol addition or condensation products **157a** and **158a**, or those characteristic of acetone self-condensation products.[23,77,80,83]

The lack of reactivity in the reaction shown in **Equation 64** was very surprising. It had been thought that a solution of **118** and sodium hydroxide would have the same, or even higher, activity than the reaction performed in the presence of **107**. Such a solution should be a richer source of **107**, and due to the reversible formation of the boronate complex should also be a richer source of hydroxide ions. The lack of reactivity observed under these conditions (**Equation 64**) could indicate that the complex **107** is formed irreversibly from **118** under the reaction conditions, and is inactive in the aldol condensation reaction. This would account for the lack of activity, as it would effectively remove hydroxide from the reaction mixture.

To determine if the lack of activity observed in **Equation 64** was caused by the reaction between sodium hydroxide and the benzimidazole **118**, the reaction was repeated with an excess of hydroxide. If the reaction was found to be similar to those carried out in the presence of sodium hydroxide alone, then this would prove that the presence of benzimidazole **118** had caused the inactivity. Hence, the reaction of 4-anisaldehyde with acetone was performed in the presence of 12 mol% of **118** and 31 mol% of NaOD as shown in **Equation 65**. This involved the addition of 4-anisaldehyde to an aqueous solution containing acetone, and NaOD.



156a **158a**, 79%

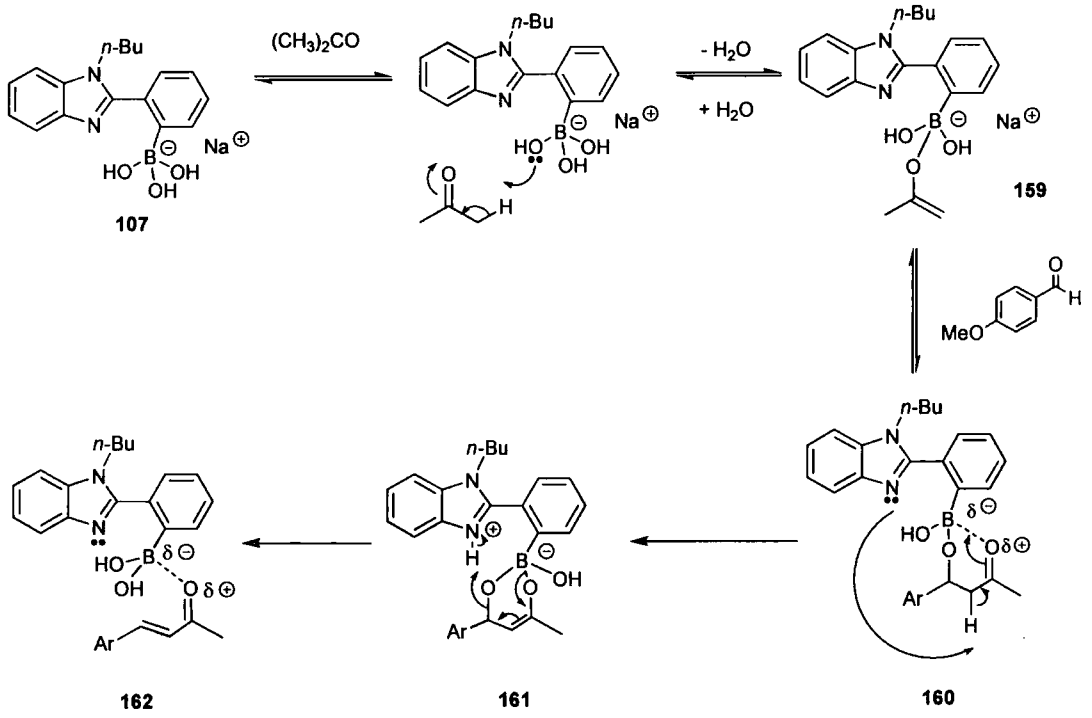
Equation 65

The reaction was carried out on an NMR scale (~ 0.7 ml) and the progress of the reaction was followed by ^{1}H NMR. After 25 hours, the reaction was found to have reached completion due to the loss of the aldehyde **156a**, and the formation of the aldol

condensation product **158a**, identified by peaks at δ_H 7.42-7.37 (m, 3 H), 6.82 (d, *J* 8.8 Hz, 2 H), 6.50 (d, *J* 16.4 Hz, 1 H) 3.74 (s, 3 H) and 2.06 ppm (s, 3 H).[23,77] After aqueous work-up, the condensation product **158a** was obtained as the major product (79%), with only low levels of side products, which included acetone self-condensation products.[77,80] This result indicated that the reaction of 4-anisaldehyde with acetone carried out in the presence of **118** and NaOH in equal quantities (**Equation 65**) had been unreactive due to the presence of the benzimidazole **118**.

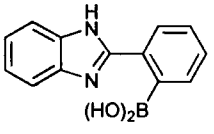
The results obtained from the reactions shown in **Equations 64** and **65** were unexpected. They indicated that not only was the complex **107** inactive, but that it was not in equilibrium with **118** in solution, and did not eliminate hydroxide. When solutions of **107** were analysed by ^{11}B NMR, they had been found to contain **118** as well as **107**, indicating a deficit of hydroxide. Therefore, hydroxide ions could not have been the active species in the aldol condensation reactions performed in the presence of **107**; if hydroxide ions had been present they would have been 'scavenged' by **118**. However, if **107** is inactive and hydroxide was not present, then there should no activity in the reactions performed in the presence of **107**. Instead, these results suggested that **107** had not been formed *in situ* in the reaction shown in **Equation 64**, when solutions of **118** and NaOD had been analysed by ^{11}B NMR (D_2O), it had been necessary to sonicate and severely heat the mixtures to dissolve the benzimidazole. However, when the equimolar solution of **118** and sodium hydroxide had been prepared for the reaction of 4-anisaldehyde and acetone shown in **Equation 64**, they had been dissolved at room temperature by stirring for two hours. Instead of reacting to form the boronate complex **107** under these conditions, **118** could have reacted with sodium hydroxide to form inactive species such as the dehydrated forms **119** and **120**, rather than **107**. This was supported by the failure of our attempts to isolate **107** generated *in situ*. When **118** was dissolved in sodium hydroxide (20% w/v) and treated with diethyl ether no precipitate was formed, however, after addition of excess solid sodium hydroxide a small amount of white precipitate was observed. After filtration and washing with diethyl ether, the ^{11}B NMR of this precipitate revealed a small peak at 10.5 ppm and a hump beneath the base line at 2.5 ppm, indicating only a small amount of the 'ate'-complex had been formed.

The results obtained from this investigation indicate that both the complex **107** and sodium hydroxide promote the aldol condensation reaction of **156a** and acetone. Furthermore, **107** promotes the reaction as the boronate complex and not as a source of hydroxide or of **118**. This promotion could occur in a number of ways, such as through the deprotonation of acetone by a pendant hydroxide followed by complexation of the aldehyde to the boronic acid formed as shown in **Scheme 28**.

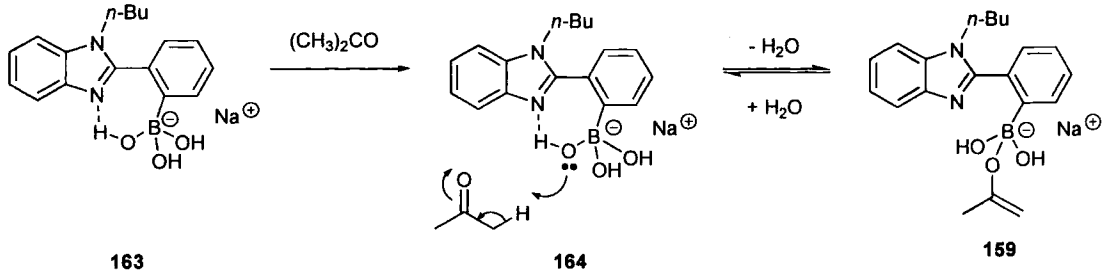


Scheme 28

However, it is also possible that the reaction is promoted by the activation of the hydroxide by **107**, rather than the substrate. In the hydrolysis reactions of chloroalcohols reported by Letsinger *et al.* it was suggested that the attacking oxygen originated from a water atom or hydroxide ion held between the boronic acid and amino functionalities of **95**.[53b] Therefore, the aldol condensation reaction is expected to be promoted in a similar way, by a hydroxide ion held within **107** (**Scheme 29**).[53b] It would be possible to test this hypothesis further by performing the aldol condensation reaction of **156a** or **156b** with acetone in the presence of a trialkoxyboronate, as in these compounds the 'suspended' hydroxide ion could not be formed.



95



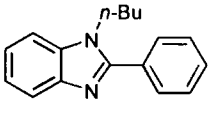
Scheme 29

The results obtained from these experiments had raised more questions than they had answered. To provide a clearer picture of the mechanism of these reactions to be built up, it was necessary to conduct an in-depth study of the aldol condensation reactions promoted by **107**, which would allow us to determine the identity of the active species, if not the mechanism.

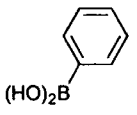
Section 3.3

In order to gain a better understanding of the aldol condensation reactions of **156a** and **156b** with acetone promoted by **107** (**Section 3.2.1**), these reactions were studied in greater depth. By performing the aldol condensation reactions in the presence of a number of potentially active species including **107**, and following them over time, it was possible to learn more about these reactions.

Hence, the aldol condensation reaction was carried out in the presence of sodium hydroxide and **107**, as well as phenylboronic acid **165** and N-*n*-butyl-2-phenylbenzimidazole **150**, which were chosen to represent fragments of **117**, both with and without sodium hydroxide. Performing the reaction in the presence of **150** and **165**, should allow the effect that having amino and boronic acid groups on the same molecule to be determined. By following the progress of the reactions performed under these conditions, the differences between them were observed and a clearer picture of the mechanism by which these reactions were promoted was obtained.

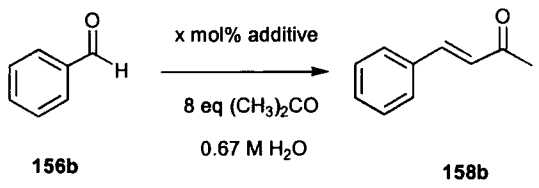


150



165

To enable an accurate investigation, these reactions were made as simple as possible. This was important as the behaviour of **117** observed so far had been complicated and often difficult to understand. With this in mind, the reaction between benzaldehyde and acetone was chosen as a model system (**Equation 66**). This reaction had been found to proceed with less side products than the corresponding reaction of 4-anisaldehyde, and the product **156b** was not as prone to precipitation under the reaction conditions, as had been observed in the reactions of the equivalent **156a**.



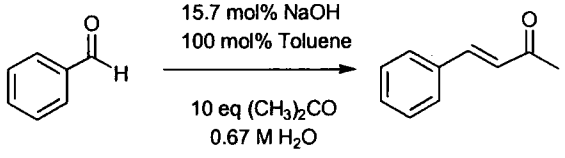
156b **158b**

Equation 66

To effectively follow the reactions over time, a way of sampling the reactions without altering the reaction conditions was needed. To achieve this, a large number of reactions were run in parallel, each of which could be stopped and analysed individually without the risk of changing the reaction conditions by repeated sampling. The reactions were carried out on a small scale (0.5 ml) and were worked up in groups of up to eight, to ensure a high level of accuracy. The reactions were followed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30), and the components of the reaction were detected by UV (254 nm). To allow the measurement of the amounts of each of the reaction components the analysis was carried out in the presence of a known quantity of standard. Toluene was chosen as the standard as it was known to have an appropriate retention time under the chromatography conditions (10 minutes, MeCN:H_2O, 70:30), and was known to give a well defined peak. In order to calculate the amount of starting material and products present in the reaction, the UV absorption at 254 nm of known quantities of these compounds were measured in the presence of 1 equivalent of toluene and the ratios calculated. Comparison of these ratios with those observed in the reactions allowed the calculation of the relative amounts of each of the components present.

Section 3.3.1

Initially, our investigations focused on the effect of 16 mol% of sodium hydroxide on the aldol condensation reaction of benzaldehyde and acetone (**Equation 67**). This investigation was performed in a screening experiment as described above, in which 112 reactions were performed in parallel, each of which was carried out on a 0.5 ml scale and contained one equivalent of toluene as the standard. The reactions in this experiment were performed through the addition of an aqueous solution of sodium hydroxide to solutions of benzaldehyde in acetone, followed by a solution of toluene and acetone.

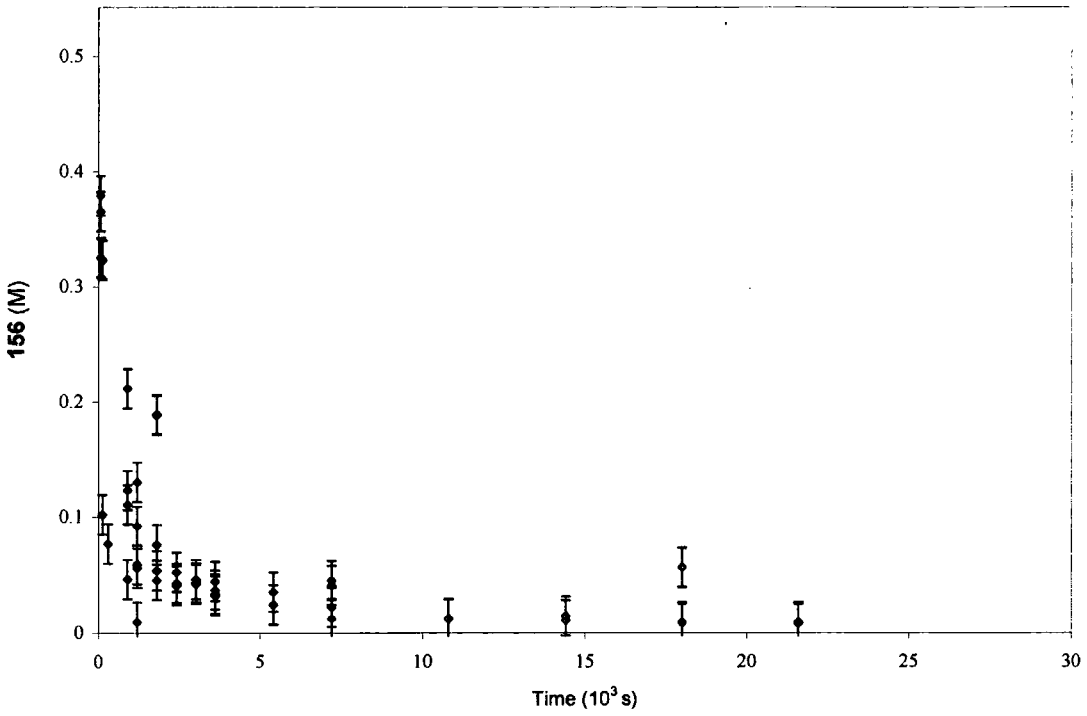


156b **158b**

Equation 67

The reactions were stirred at room temperature for a period of 24 hours, during which groups of reactions were analysed by HPLC. The reactions were sampled by the addition of diethyl ether (0.5 ml), followed by shaking, and the removal of a small portion of the organic layer (15 µl). This sample was diluted by the addition of MeCN:H_2O (70:30) to a concentration of 0.002 M before being analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30).

Comparison of the peaks observed for the benzaldehyde and aldol condensation product **158b** with that of the toluene standard allowed the concentration of benzaldehyde and **158b** to be calculated. In this way, the concentration of benzaldehyde was calculated with an average deviation of 0.017 M. In **Graph 1** the calculated concentration of **156b** is plotted against time (10^3 s), and the deviation represented by error bars.



Graph 1: Concentration of **156b** (M, error 0.0017 M) against time (10^3 s)

As can be seen from **Graph 1** the values obtained were often found to have a high degree of variance. It was felt that despite these fluctuations, enough data points had been collected to allow an accurate investigation to be made, however, they were still a matter of some concern. From **Graph 1** it can be seen that there is a low level of variance associated with the data points sitting roughly on the trend line, as well as larger fluctuations leading to some data points appearing up to 86% above or below the average value at that point. These variations indicate that there are two main causes for deviation in this experiment; the accumulated error of measurements and instrumentation, and the unreliability of the reactions themselves which cause the severe departures from the average values observed in **Graph 1**. Although a clear pattern of behaviour had been observed in the aldol condensation reactions previously performed, there had been a number of anomalous results obtained. In a few cases, when reactions which had previously displayed activity were repeated, they were found to be inactive. An example of this is the reaction of 4-anisaldehyde with acetone performed in the presence of sodium hydroxide (**Section 3.1.2**) which, despite having previously been found to give the aldol condensation product **158a**,

when it was repeated was often found to be inactive. These inconsistencies are thought to be due to differences in the mixing of these reactions. The formation of a biphasic mixture in these reactions could effectively separate the catalytic species from the substrates, and it is the mixing of the reactions that brings them together and allows them to react. If different reactions were stirred to different extents, then varying levels of reactivity would be expected.

In subsequent screening experiments efforts were made to reduce these inconsistencies by trying to ensure that all reactions were stirred to the same extent. This included positioning the reaction vials as close together as possible, and the use of similar shaped reaction vials and stirrer beads. Although the error resulting from measurements and instruments used is important, quoting this value as the overall error in the concentrations of **156b** and **158b** is misleading. The larger fluctuations observed mean that the smaller errors are less significant, and therefore the most appropriate way of representing the error associated with the concentrations calculated is as the deviation from the average values, represented as a percentage of these values.

To learn more about this reaction, attempts were made to determine the order of the reaction with respect to benzaldehyde. This was achieved through least squares fitting of mathematical models for first and second order reactions to the experimental data. The rate equations for first order and second order reactions are shown in **Equation 68 and 69 respectively**,.[85,86]

$$\frac{d[A]}{dt} = -k[A] \quad \textbf{Equation 68}$$

$$\frac{d[A]}{dt} = -k[A]^2 \quad \textbf{Equation 69}$$

Using the mathematical software program Scientist® the best fit to the experimental data was found to a first order rate equation. The model used in this calculation is shown in **Equation 70**.[84,85]

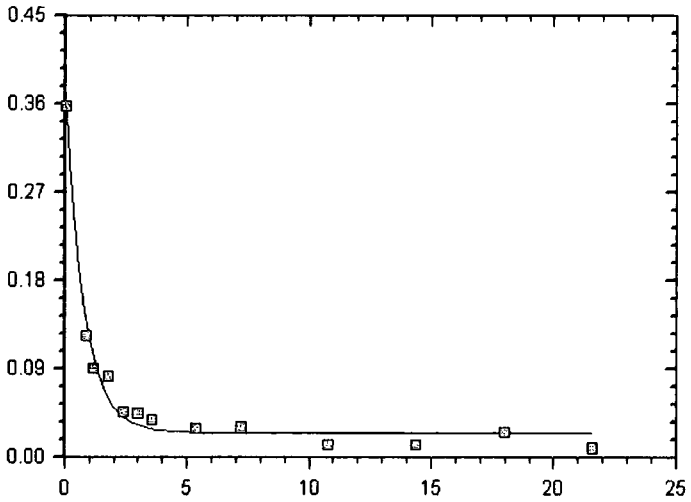
$$[A] = [A]_0 e^{-kt} + C_1 \quad \textbf{Equation 70}$$

In this Equation the term [A] represents the concentration of **156b**, $[A]_0$ represents the initial concentration, t represents time and k_1 and C_1 are the rate constant for the reaction and a numerical constant respectively. This relationship can also be represented by the integrated rate equation shown in **Equation 71**.

$$\ln[A] = \ln[A]_0 - kt \quad \textbf{Equation 71}$$

In the analysis of this data we were making a number of assumptions. Firstly as the aldol addition product had not been observed in the products of the reactions performed previously, we were assuming that the formation of the aldol product **157b** was rate determining, and that its subsequent conversion to the condensation product **158b** was fast and did not affect the rate. We were also assuming that the reverse reaction had no impact on the rate. In a similar way, it was assumed, that the formation of the hydrate, which had been observed previously under similar conditions and was thought to be in equilibrium with the aldehyde **156b** (**Section 3.2.1**), was insignificant when compared to the rate and amounts of **158b** formed and would have no impact on the reaction rate. Finally, although only 10 equivalents of acetone were present in these reactions, it was assumed that acetone was present in excess.

After plotting the average values of the concentration of **156b** observed, and the removal of a number of anomalous results, least squares fitting of **Equation 70** resulted in a calculated curve which followed the experimental data well (**Graph 2**), indicating that the reaction was pseudo-first order with respect to **156b**, and therefore followed the rate equation shown in **Equation 72**.[85,86] Least square fitting gave values for the constants $[A]_0$, $k_1$and C_1 of 0.294 M, 1.10 x 10^{-3} s^{-1} and 0.0202, quoted

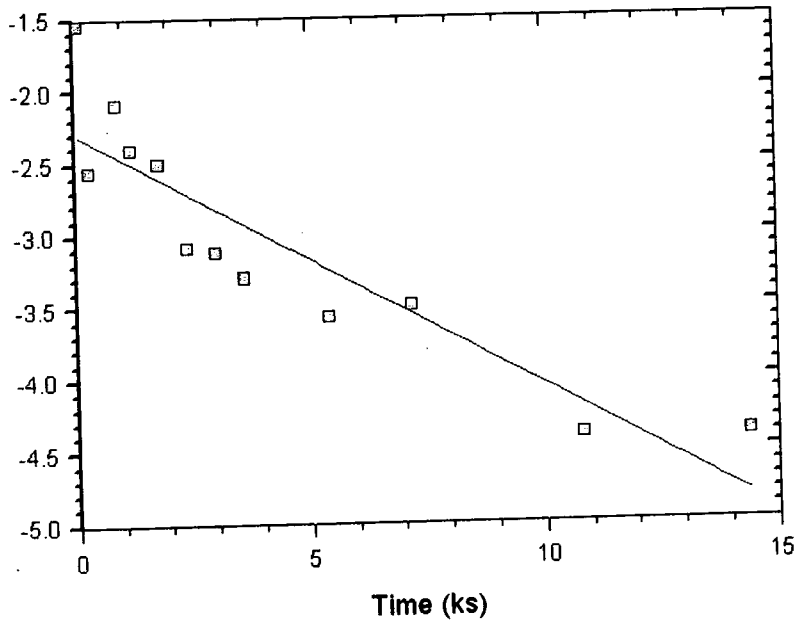


Graph 2: Average concentration of **156b** (M, error 0.0017 M) against time (10^3 s).

$$\frac{d[A]}{dt} = -1.1\times10^{-3}\,[A] \quad \textbf{Equation 72}$$

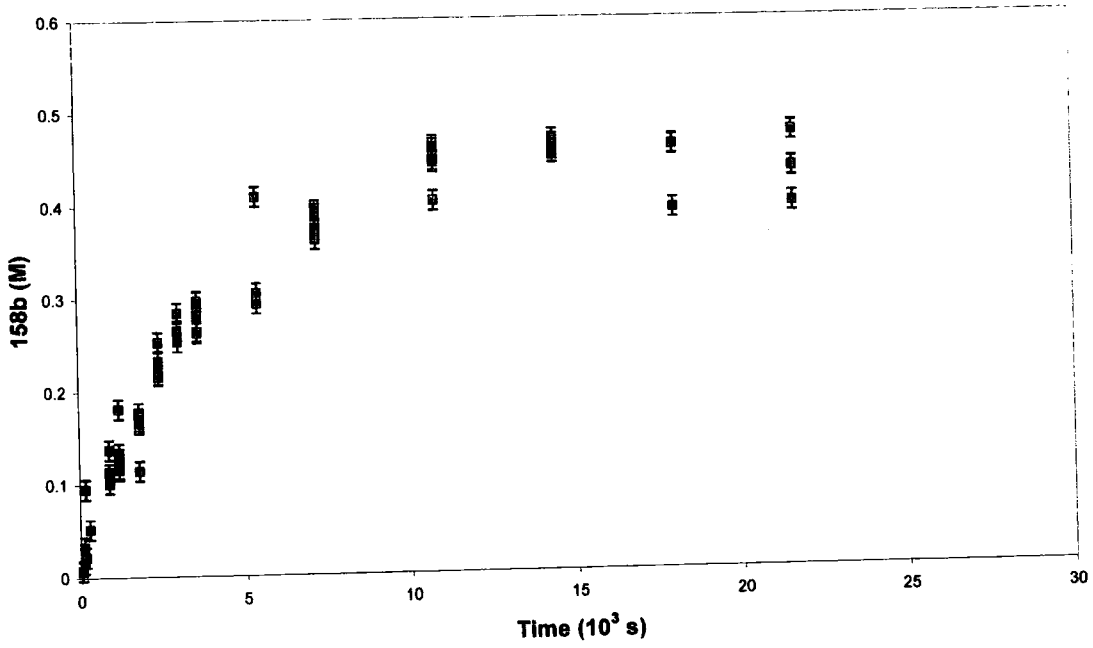
to within 3 significant figures, with standard deviations of 0.0273 M, 2.51 x 10^{-4} s^{-1} and 0.0122 respectively.[84,85,86]

To support this interpretation the natural log of the concentration of **156b** against time is shown in **Graph 3**. For first order reactions this plot gives a straight line i.e. the reaction follows the integrated rate equation shown in **Equation 71**. In **Graph 3** the first fifteen minutes of the reaction are shown, and the trend line which follows **Equation 71** gives $[A]_0$ and k_1 values of 0.136 M and 0.249 x 10^{-3} s^{-1} for this period.[85,86]



Graph 3: Average of ln[**156b**] against time (10^{-3} s).

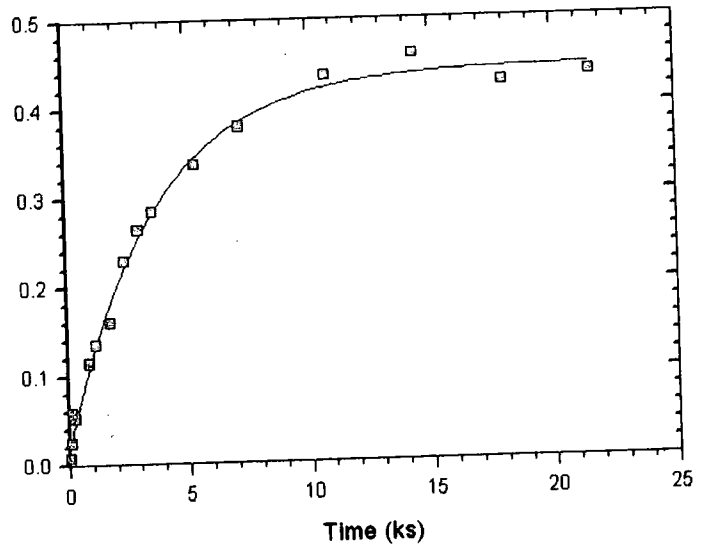
The concentration of condensation product **158b**, calculated from the HPLC data with an average deviation of 0.017 M, was plotted against time (**Graph 4**). This appears to be an inverted version of the curve obtained for benzaldehyde concentration over time (**Graph 1**).



Graph 4: Concentration of **158b** against time (10^3 s)

Using Scientist®, it was also possible to fit this data to the mathematical model shown in **Equation 73**, where [B] and $[B]_\infty$ are the concentration and the final concentration values of **158b** observed, and k_2 and C_1 are the rate constant for the reaction and a numerical constant respectively.[85]

$$[B] = C_1 - [B]_\infty e^{-kt} \quad \textbf{Equation 73}$$



Graph 5: Average concentration of **158b** (M, error 0.017 M) against time (10^3 s).

Least squares fitting of the average concentration of **158b** over time (**Graph 5**) gave the values for $[B]_\infty$, k_2 and C_1 of 0.425 M, 2.77 x 10^{-4} s^{-1} and 0.441 with standard deviances of 0.00929 M, 1.65 x 10^{-5} s^{-1} and 0.00700 respectively, quoted to within 3 significant figures. This indicates that the formation of the aldol condensation product **158b** is pseudo-first order, following the rate equation shown in **Equation 74**.

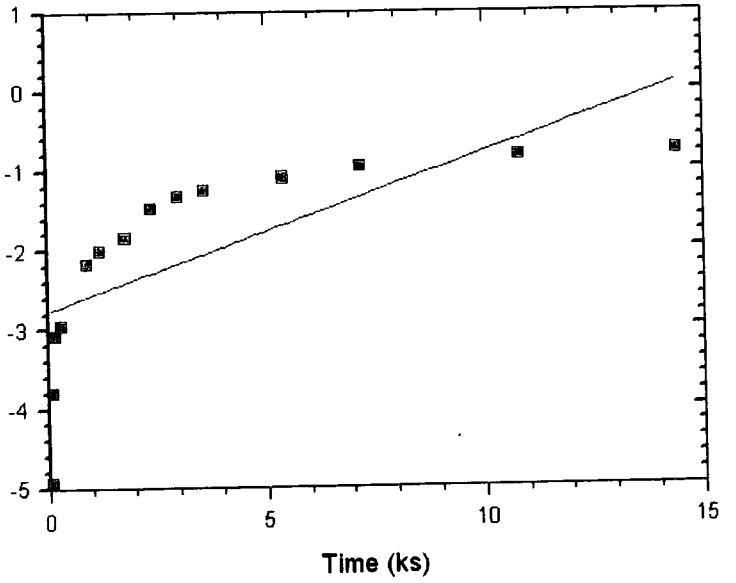
$$\frac{d[B]}{dt} = 2.77 \times 10^{-4}([B]_\infty - [B])$$ **Equation 74**

The results obtained from this screening experiment revealed that under the reaction conditions the conversion of **156b** to **158b** did not occur in one step. The rate constant k_2 for the second step was nearly four times less than the rate constant for the loss of benzaldehyde k_1. Although no evidence had been observed directly by HPLC; the aldol product must have been formed during the reaction. Presumably, either the work-up used in this experiment (**Equation 67**), had failed to separate both the aldol and aldol condensation products from the reaction mixture, leaving the aldol product in the aqueous layer, or the aldol product had a low uv absorbance at 254 nm. These problems could be resolved in future experiments by analysing both the aqueous and organic layers at a range of wavelengths.

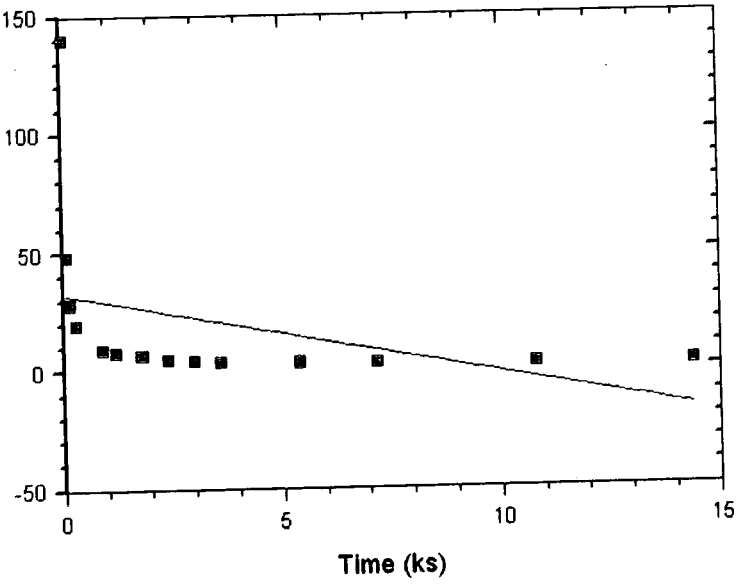
The conversion of **156b** to **158b** through an intermediate was supported by the plots of the integrated rate equations for first and second order reactions: **Graphs 6** and **7**. Neither of these plots gave a linear relationship, indicating that the reaction did not through a simple first or second order mechanism.

The integrated rate equation for a second order reaction is shown in **Equation 75**, and is plotted as the reciprocal of the concentration of **158b** against time.

$$\frac{1}{[B]} = -\frac{1}{[B]_\infty} - k_2 t$$ **Equation 75**



Graph 6: Average ln[**158b**] against time (10^{-3} s)

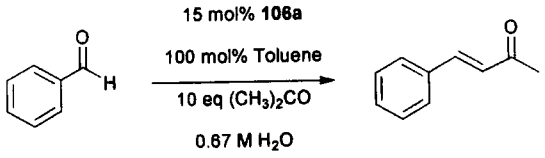


Graph 7: Average 1/[**158b**] against time (10^{-3} s)

Section 3.3.2

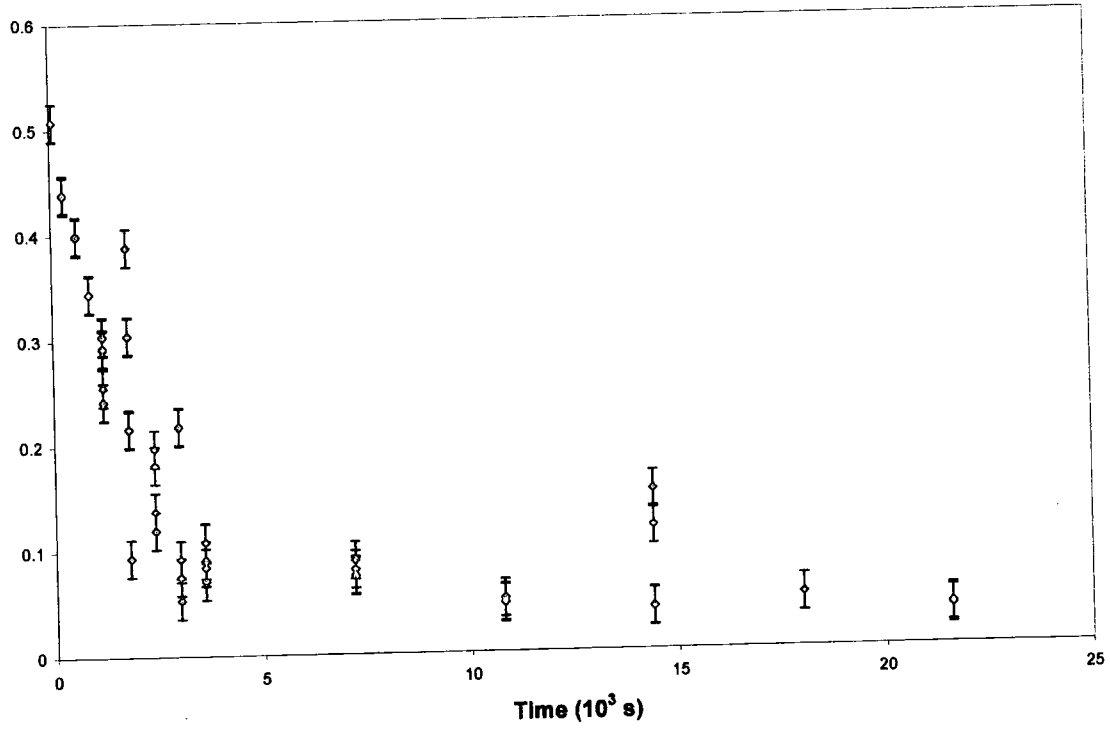
To determine if the aldol condensation reactions promoted by **107** were indeed promoted by hydroxide impurities present in the reaction mixtures, a screening experiment was planned and implemented (**Equation 76**). This screening experiment was performed in a

similar way to that described above (**Equation 67**), through the reaction of benzaldehyde and acetone in the presence of 15 mol% of the boronate complex **107** and a toluene standard in a series of 74 reactions which were analysed over a period of 72 hours.



Equation 76

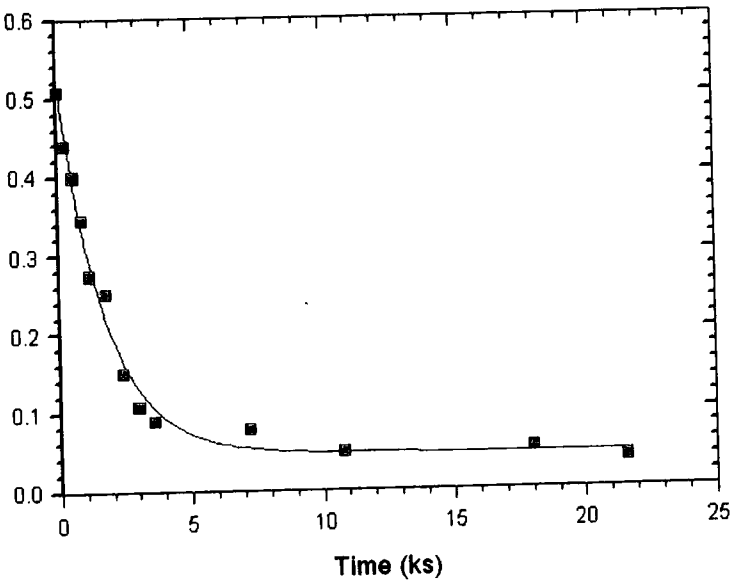
The reactions were stirred at room temperature over a period of 72 hours during which they were analysed through the addition of diethyl ether (0.5 ml), shaking, and sampling from the organic layer (15 µl). This was diluted (0.002 M) with MeCN and H_2O (70:30) and then analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30). The concentration of benzaldehyde was calculated by comparison with the toluene standard, with an average deviation of 0.018 M. When the concentration of **156b** was plotted against time (**Graph 5**), the curve obtained was found to be a similar shape to that observed in the screening experiment performed in the presence of sodium hydroxide (**Graph 1**).



Graph 8: **156b** (M, 0.018 M error) against time (10^3 s), in the presence of **107**.

As with the screen of the reaction of benzaldehyde with acetone in the presence of sodium hydroxide, the reactions carried out in the presence of **107** were also found to occur with a degree of variation. This was thought to be due to errors in measurements and the differences in the stirring of these reactions. Although the reactions had been carried out using the same equipment, and efforts were taken to ensure all of the reactions had been stirred to the same extent, often small differences in the positioning of reaction vials on stirrers and the movement of the stirrer beads within the reaction vials could not be prevented, or in many cases observed.

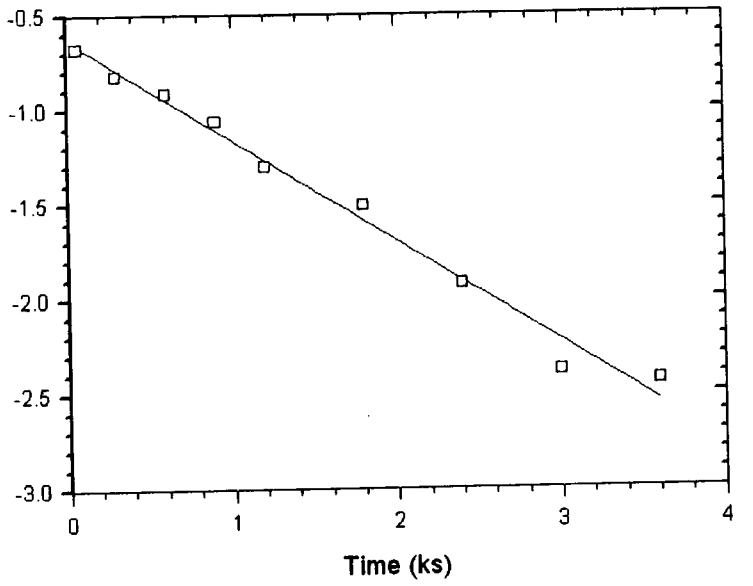
When the average concentration of benzaldehyde over time was plotted in Scientist®, least squares fitting of the mathematical model for a first order reaction shown in **Equation 70** followed this data very well.[85,86] From this, the constants $[A]_0$, k_1 and C_1 were calculated to be 0.490 M, 5.58 x 10^{-4} s^{-1} and 0.0356 with standard deviations of 0.0186 M, 4.90 x 10^{-5} s^{-1} and 0.0110 respectively, quoted to within 3 significant figures. Therefore, this reaction follows the rate equation shown **Equation 77**.[85]



Graph 9: Average concentration of **156b** (M) against time (10^3 s).[88]

$$\frac{d[A]}{dt} = -5.58 \times 10^{-4}[A]_0 \quad \textbf{Equation 77}$$

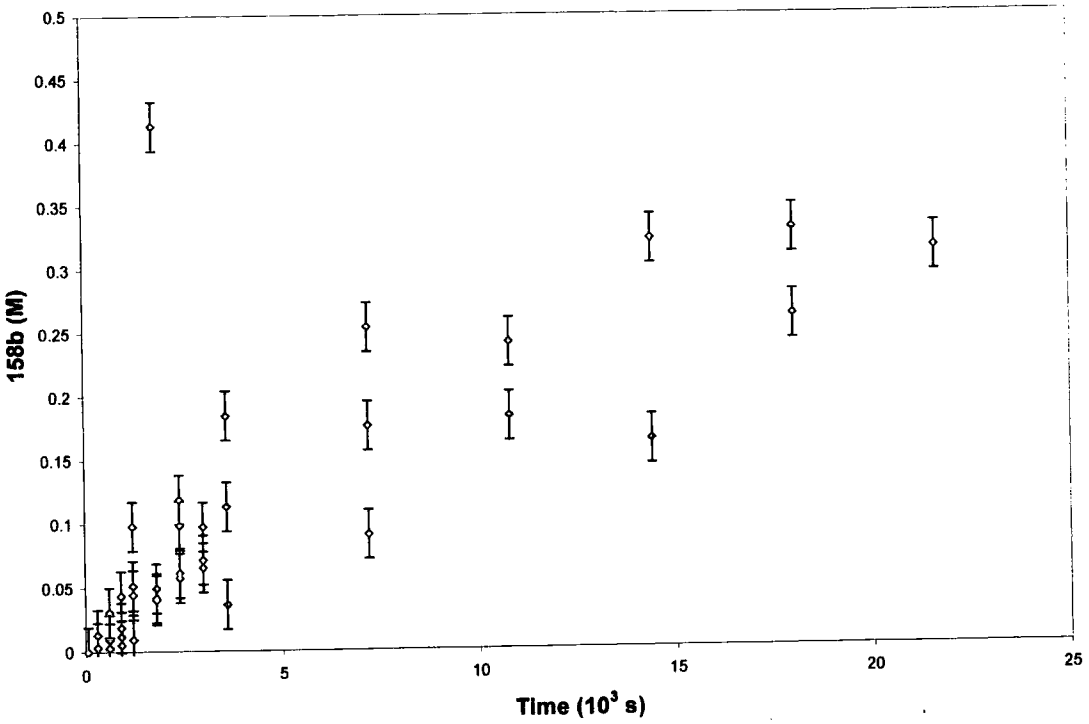
The first order nature of the reaction was again further confirmed by the plot of ln[156b] against time, which gave a linear graph (**Graph 10**). From this plot the $\ln[A]_0$ and k_1 values for the initial period of the reaction were calculated to be -0.632 and -0.531 x 10^{-3} s^{-1} with standard deviations of 0.046 and 0.0238 x 10^{-3} s^{-1}.[85,86]



Graph 10: Average ln[**156b**] against time (10^3 s).

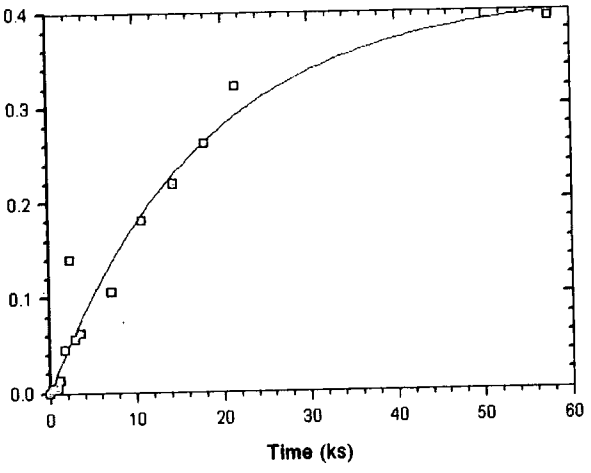
Comparison of the k_1 values in this screening experiment with that observed in the experiment performed in the presence of sodium hydroxide revealed that the reactions in the screening experiment performed previously were almost twice as fast. Therefore, it is unlikely that the reactions performed in the presence of **107** were promoted by hydroxide.[85,86]

The concentration of the aldol condensation product **158b** observed in this screening experiment was also plotted against time (**Graph 11**) to give a curve which resembled an inverted plot of that of the benzaldehyde concentration over time (**Graph 8**). The concentration of **158b** had been calculated by comparison of the peaks observed by HPLC with an average deviance of 0.019 M from the average values.



Graph 11: 158b (M, 0.019 M error) against time (10^3 s).

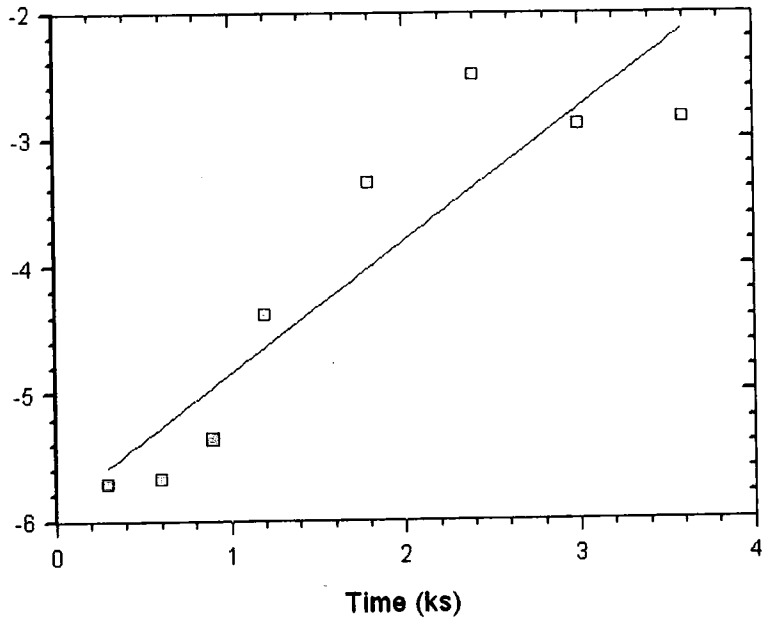
The data obtained from this screening experiment was also found to conform to that of a first order reaction. Using Scientist®, the average concentration of **158b** was plotted against time and was found to approximate to the mathematical model for a first order reaction (**Equation 73**).[85,86] Least squares fitting of this model to the experimental data gave $[B]_\infty$, k_2 and C_1 values were found to be 0.416 M, 5.59 x 10^{-5} s^{-1} and 0.415 with standard deviations of 0.0381 M, 1.14 x 10^{-5} s^{-1} and 0.0391, quoted to 3 significant figures, respectively. This indicates that the rate equation for this reaction is first order as shown in **Equation 78**.



Graph 12: Average concentration of **158b** (M, 0.019 M error) against time (10^3 s).[88]

$$\frac{d[B]}{dt} = 5.59 \times 10^{-5}([B]_\infty - [B]) \quad \textbf{Equation 78}$$

Again this could be confirmed by plotting the integrated rate equation for a first order reaction (**Graph 9**). From this plot the values for $\ln[A]_0$ and k_1 were calculated to be -5.88 and 1.04 x 10^{-3} with standard deviations of 0.392 and 0.191 x 10^{-3} s^{-1} respectively.



Graph 13: Average ln**[158b]** against time (10^3 s)

As with the k_1 values for benzaldehyde concentration, the formation of **158b** when the reactions were performed in the presence of the complex **107** was very different to that observed when the reactions were performed in the presence of hydroxide. Indeed, in the reactions performed in the presence of sodium hydroxide the k_1 value was almost 5 times that observed in the presence of **107**.[85]

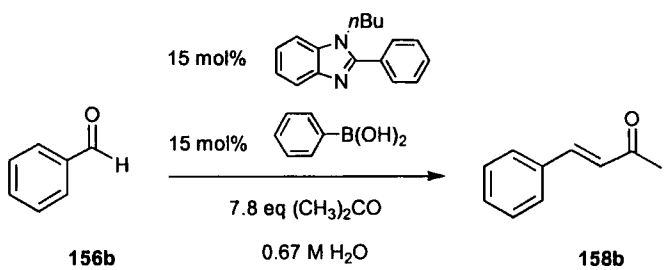
The results obtained from the screening experiment performed in the presence of **107** and that performed in the presence of sodium hydroxide were exciting. They had confirmed that the aldol condensation reactions performed in the presence of **107** were not active merely due to the presence of hydroxide impurities. Comparison of the rate constants calculated for the reaction promoted by **107** and those calculated for the reaction promoted by sodium hydroxide, also revealed that these reactions were not as similar as they had first appeared. In the reaction performed in the presence of **107**, the calculated k_1 value was almost ten times the k_2 value, much bigger than the equivalent difference between the k_1 and k_2 values calculated for the reaction promoted by sodium hydroxide which was only a

factor of four. This indicates that not only is the conversion of **157b** to **158b** slower than the loss of **156b**, but the mechanism of this conversion is significantly different to that in the reactions promoted by sodium hydroxide. This may be due to the need to regenerate the boronate complex **163** after the deprotonation of acetone, or alternatively could indicate that the aldol product **157b** becomes complexed to the boronate before deprotonation to give the condensation product **158b** occurs.

Section 3.3.3

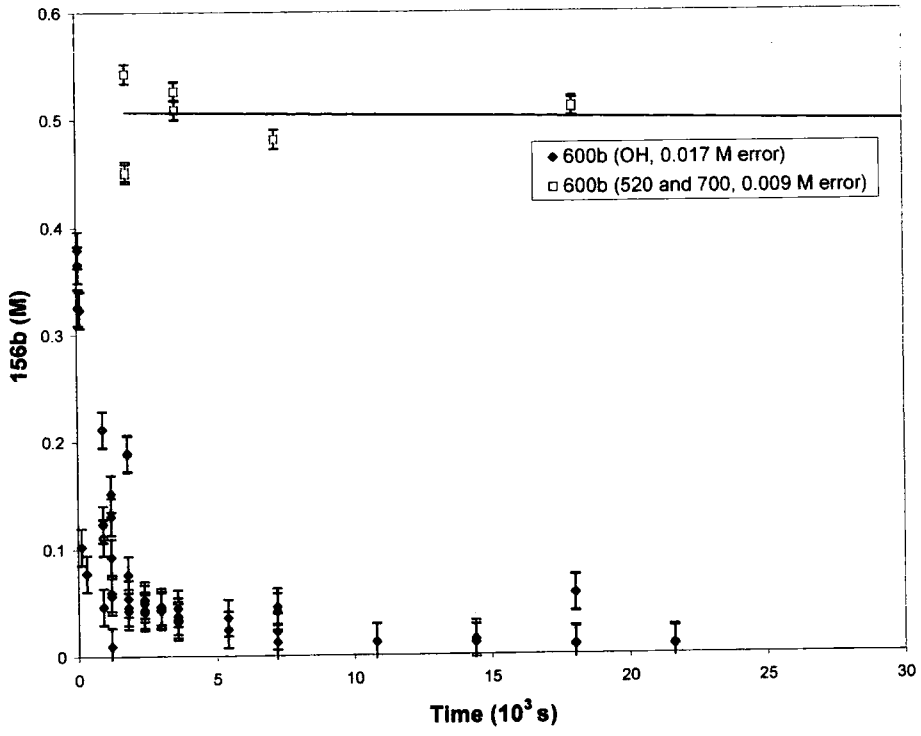
Although a number of mechanisms for the aldol condensation reaction promoted by **107** had been considered, further investigations were needed. Therefore, a screening experiment in which the reaction of benzaldehyde and acetone in the presence of the benzimidazole **150** and phenylboronic acid **165** was performed, which was intended to allow the role that intramolecularity of the two functional groups played in the behaviour of **117**. A similar examination was performed by Letsinger *et al.* during the investigation of 8-quinoline boronic acid **94** as a catalyst for the hydrolysis of chloroalcohols. It had been shown by Letsinger *et al.* that when the hydrolysis of 2-chloroethanol was performed in the presence of quinoline and phenylboronic acid, rather than 8-quinoline boronic acid **94**, the conversion after 24 hours was approximately 13 times less, proving that the bifunctionalilty of **94** was necessary for the high levels of activity.

Hence, a series of 21 reactions were performed, on a 0.5 ml scale, in which benzaldehyde and acetone were reacted together in the presence of phenylboronic acid **165**, **150** and a toluene standard (**Equation 79**).



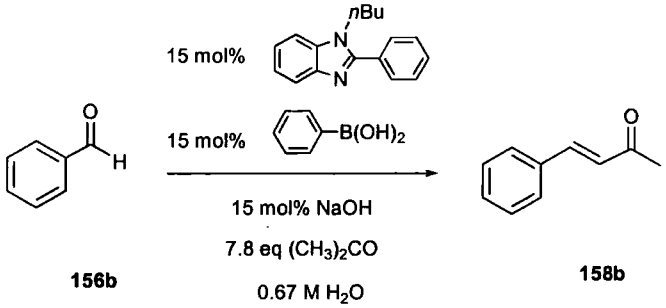
Equation 79

The reactions were performed through the addition of a solution of phenylboronic acid and **150** in acetone to a solution containing benzaldehyde, acetone and toluene. The reactions were stirred over a period of 4 days, during which they were sampled and analysed. This was performed through the addition of diethyl ether (0.5 ml) to the reaction mixtures, shaking and sampling the organic layer (15 µl). The samples were then diluted (0.002 M) with MeCN and H_2O (70:30, 3.5 ml) and analysed by HPLC (Phemonomex 18 C Luna, MeCN:H_2O, 70:30). After 4 days, HPLC revealed that only a small amount of benzaldehyde had been lost and there had been no observable formation of products. The concentration of benzaldehyde was calculated from the HPLC data with 0.009 M deviation from the average values, and is plotted against time alongside the concentration of **156b** observed in the reactions performed in the presence of sodium hydroxide (**Graph 14**), so that the lack of activity observed can be fully appreciated.



Graph 14: Concentration of **156b** (M) against time (10^3 s).

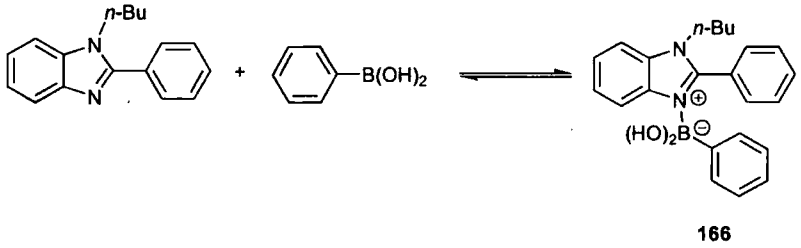
This result was not surprising, as the reactions of 4-anisaldehyde with acetone which had previously been performed in the presence of **118** had also been found to be inactive. In these reactions the lack of reactivity might be to be due to the formation of an internal dative bond, however, it is also likely that even without internal donation, the benzimidazole would still be inactive. In this screening experiment the fragments might simply have been inactive, or could have formed an adduct such as **166** (**Equation 80**) which caused them to be inactive.



Equation 80

Section 3.3.4

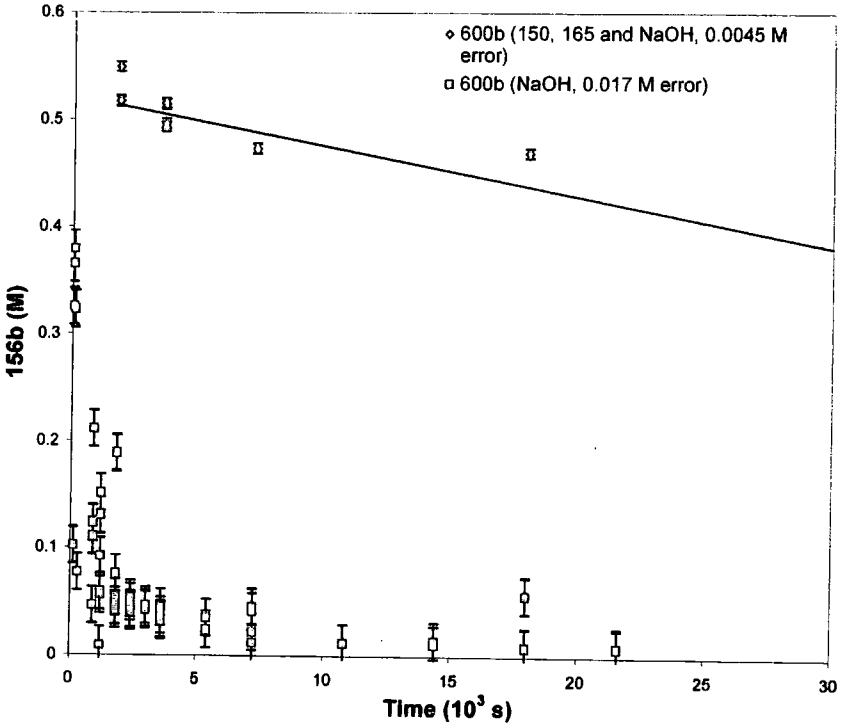
A further screening experiment was planned to asses the activity of a mixture of phenylboronic acid **165** benzimidazole **150** and sodium hydroxide on the aldol condensation reaction of **156b** (**Equation 81**). Therefore, a screening experiment was planned in which the reaction of **156b** and acetone was performed in the presence of the two fragments **150** and **165**, and sodium hydroxide as shown in **Equation 81**.



166

Equation 81

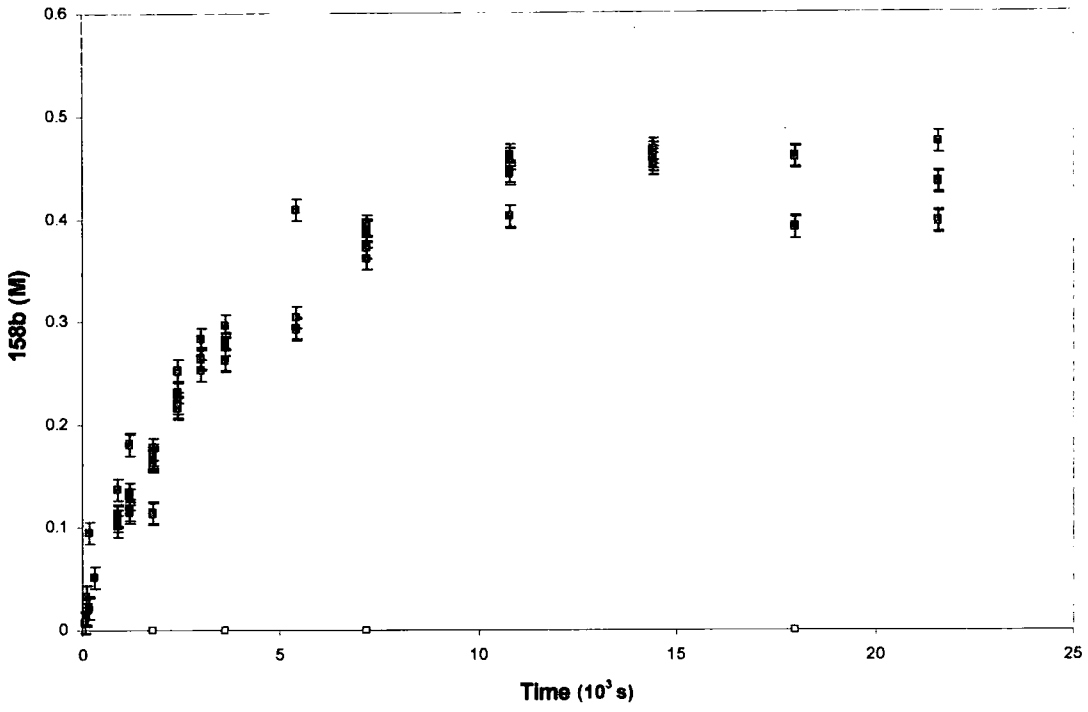
The reactions in this experiment were performed in a similar way to those in the screening experiments performed previously, through the addition of phenylboronic acid **165**, and **150** as a solution in acetone to solutions of benzaldehyde in acetone and toluene followed by an aqueous solution of sodium hydroxide. Hence, 27 such reactions were performed on a 0.5 ml scale and were stirred at room temperature and sampled over a 72 hour period. The reactions carried out under these conditions were found by HPLC (Phemonomex 18 C Luna, MeCN:H_2O, 70:30) to display only low levels of activity. This can be best appreciated when the concentration of benzaldehyde, calculated from the HPLC data with a average deviation of 0.0045 M from the average values, is plotted alongside that observed in the reactions promoted by sodium hydroxide (**Graph 15**).



Graph 15: Concentration of **156b** (M) against time (10^3s).

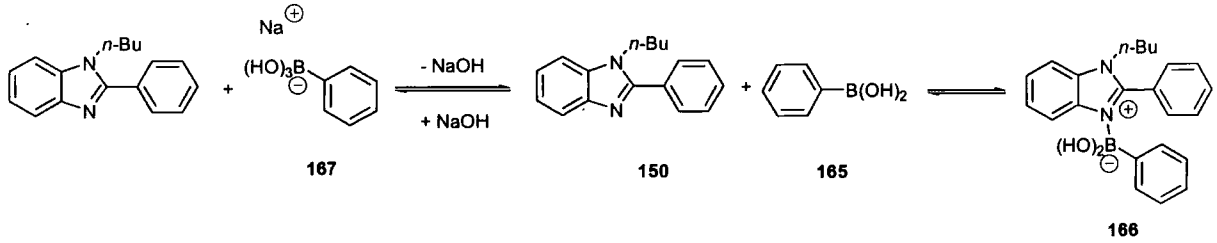
Formation of the aldol condensation product **158b** was also seen in low levels, during this screening experiment. To demonstrate the levels of **158b** formed in this reaction, the concentration of **158b**, which was calculated with an average deviation of 6.67 x 10^{-6} M from the HPLC data by comparison of the peaks for **158b** and the toluene standard, was plotted alongside the concentration of **158b** observed in the reactions carried out in the presence of sodium hydroxide (**Graph 16**). Although loss of benzaldehyde had occurred in

this experiment, only low levels of the aldol condensation product **158b** had been observed and, as in the previous screening experiments, there had been no direct evidence for the formation of the aldol product **157b**. Presumably, as the loss of benzaldehyde occurs to a far greater extent than the formation of product, a species is formed during the reaction which could not be observed by HPLC, possibly the hydrate of **156b**, which had been observed previously under similar reaction conditions (**Section 3.1.1**).



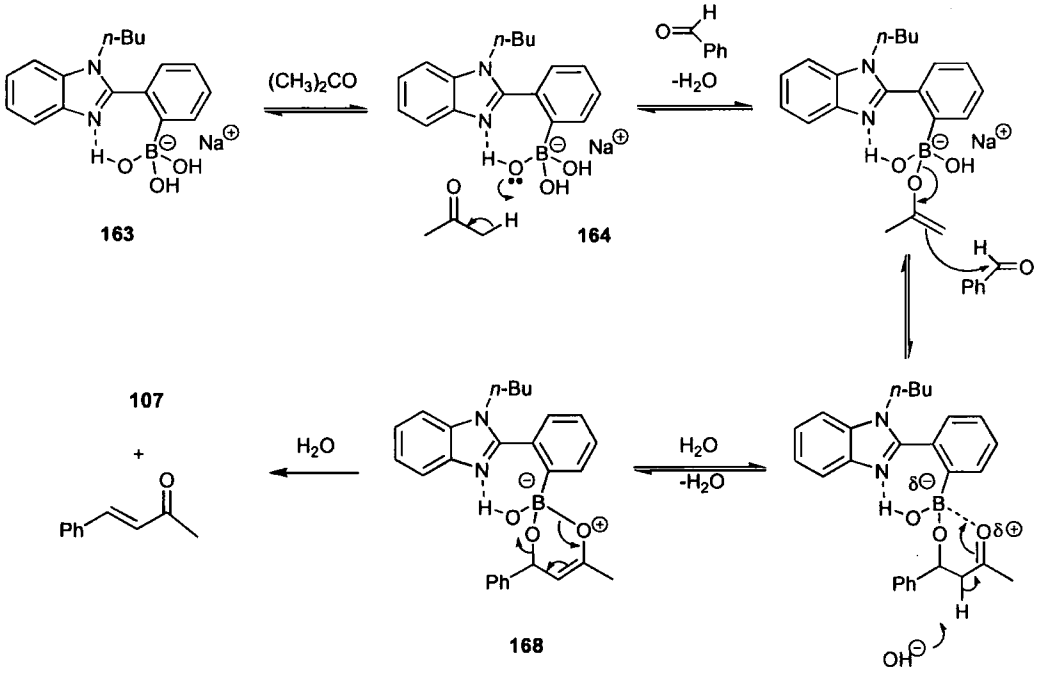
Graph 16: Concentration of **158b** (M, 6.6 x 10^{-6} M error) against time (10^3 s)

The low levels of **158b** formed in this screening experiment (**Graph 12**) indicate that, for catalytic activity not only is an 'ate'-group and an amino group required, but also these functional groups must be present in the same molecule, i.e. bifunctionality is required. Although it is equally possible that the fragments **150** and **165** had reacted together under the reaction conditions as shown in **Scheme 30** to form an inactive adduct, if the adduct **167** had been formed during the reaction, the aldol condensation product **158b** would still have been expected to be formed due to the presence of 15 mol% of sodium hydroxide. The fact that only low levels of activity were observed implies that **167** was formed during the reaction, but was only poorly active without the intramolecular interaction with an amino group. The low levels of activity of **167** could have been due to intermolecular interactions with amino groups, or due to residual hydroxide in solution.



Scheme 30

From the results obtained in the four screening experiments described above it can be deduced that the complex **107** catalyses the aldol condensation reactions of **156a** and **156b** with acetone, through a bifunctional mechanism, which involves the interaction of the amino and the boronate group of **107** with the nucleophile, or with each other, rather than with the substrate. The promotion of the reaction in this way could occur either through the deprotonation of both acetone and the aldol product **157b** by the complex **163** behaving as a base, or alternatively could involve complexation of the acetone enolate and aldol product to the boronate group. A possible mechanism for catalysis in this way is shown in **Scheme 31**. However, to further elucidate the mechanism more investigations are necessary.



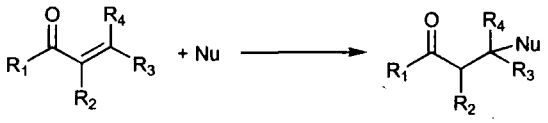
Scheme 31

Section 3.4

In our previous investigations we had found that the benzimidazole **107** was capable of promoting the aldol reaction of 4-anisaldehyde **156a** and benzaldehyde **156b** with acetone and it was hoped, that other, similar reactions might also be promoted by **107**. Therefore, investigations into the ability of **107** to behave as a catalyst in a variety of reactions were made, with particular emphasis on synthetically important reactions. The approach taken in this investigation was the design and implementation of a series of screening experiments, the reactions from which would be studied further if evidence of reaction was observed. Therefore, a number of reactions were chosen which could be susceptible to promotion by the complex **107**. The reactions selected were those which involved the formation of enolates or the activation of a carbonyl group through coordination to a Lewis acid, and particular interest was placed upon reactions which were known to be promoted by both Lewis acids and bases.

These factors led to the selection of a number of reactions which would provide a suitable starting point for the investigation of the ability of **107** to behave as a versatile, bifunctional catalyst. Of those considered, the reactions selected for this investigation were the Knoevenagel, Michael and Darzens reactions as well as the coupling of phenylacetylene with aldehydes.[87,88,89,90,91] As well as potentially being susceptible to promotion by a bifunctional catalyst, these reactions were chosen as they are valuable synthetic tools; for example, the Knoevenagel reaction provides a route to highly substituted alkenes (**Equation 82**), and the Michael reaction is an important carbon-carbon bond forming reaction (**Equation 83**).[87,88]

Equation 82



R_1 = Alkyl, aromatic
R_2, R_3, R_4 = H, alkyl, aromatic
X= Electron withdrawing group

Equation 83

The investigation into the ability of **107** to behave as a versatile catalyst, initially focused on the Knoevenagel reaction.[87] This offered an excellent starting point for the investigation, due the similarity between this reaction and the aldol reactions previously studied as well as the susceptibility of this reaction to catalysis by both Lewis acids and bases. Although a great deal of research has been conducted into the development of novel catalysts for the Knoevenagel reaction, the development of a water tolerant, environmentally friendly catalyst for this reaction remains a worthwhile synthetic target.[87] Therefore, if complex **107** was found to be capable of promoting the Knoevenagel reaction, then this would be of considerable interest as it would allow a new range of catalysts for this reaction to be prepared.

Section 3.4.1

The approach taken in the investigation into **107** as a potential catalyst for the Knoevenagel reaction was through the design and implementation of a screening experiment. A range of aldehydes were chosen, and these were reacted with a number of nucleophiles both with and without the presence of 8.8 mol% **107,** in a range of solvents. The aldehydes chosen for this experiment were the aromatic aldehydes 4-anisaldehyde **156a**, benzaldehyde **156b** and 4-nitrobenzaldehyde **156d**, and the alkyl aldehyde propionaldehyde **156e**. These aldehydes were reacted with the nucleophiles dimethyl malonate **169** and methyl cyanoacetate **170 (Table 14)** in parallel on a 100 μmol scale using a Robbins block™, and were shaken for 7 days at room temperature. The reactions were worked-up in parallel by filtration through a complimentary Robbins block™ packed with silica and analysed by LCMS.

Entry	156	R^2	107	Solvent	Knoevenagel product[a]
1	4-(MeO)C_6H_4 **156a**	CO_2Me **169**	-	H_2O	No
2				1:1 MeCN:H_2O	No
3		CN **170**	-	H_2O	No
4				1:1 MeCN:H_2O	Yes
5		**169**	8.9 mol%	H_2O	Yes
6				1:1 MeCN:H_2O	Yes
7		**170**	8.9 mol%	H_2O	Yes
8				1:1 MeCN:H_2O	Yes
9	Ph **156b**	**169**	-	H_2O	No
10				1:1 MeCN:H_2O	No
11		**170**	-	H_2O	No
12				1:1 MeCN:H_2O	No
13		**169**	8.9 mol%	H_2O	Yes
14				1:1 MeCN:H_2O	Yes
15		**170**	8.9 mol%	H_2O	Yes
16				1:1 MeCN:H_2O	Yes
17	4-(NO_2)C_6H_4 **156d**	**169**	-	H_2O	No
18				1:1 MeCN:H_2O	No
19		**170**	-	H_2O	No
20				1:1 MeCN:H_2O	No
21		**169**	8.9 mol%	H_2O	No
22				1:1 MeCN:H_2O	No
23		**170**	8.9 mol%	H_2O	No
24				1:1 MeCN: H_2O	No
25	CH_3CH_2 **156e**	**169**	-	H_2O	No
26				1:1 MeCN: H_2O	No
27		**170**	-	H_2O	No
28				1:1 MeCN:H_2O	No
29		**169**	8.9 mol%	H_2O	No
30				1:1 MeCN:H_2O	No
31		**170**	8.9 mol%	H_2O	No
32				1:1 MeCN:H_2O	No

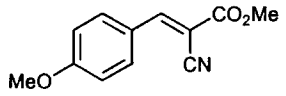
Table 14: Reaction of 4-anisaldehyde **156a**, benzaldehyde **156b**, 4-nitrobenzaldehyde **156d** and propionaldehyde **156e** with dimethyl malonate **169** and methyl cyanoacetate **170** in the presence of the benzimidazole **107**. [a] Products observed by LCMS and results confirmed by ^1H NMR.

Unfortunately, there were concerns that working-up the reactions in this way did not give consistent levels of recovery of either the starting materials or of the products. In isolated cases it could be seen that, even after the application of a great deal of pressure, not all of the reaction mixture could be pushed through the silica gel plugs. The large inconsistencies observed in a small number of reactions might also have been occurring in the bulk of the reactions but to a lesser extent. Due to this it was not appropriate to represent the recovery of the crude products as accurate. Therefore, the screening experiment described above

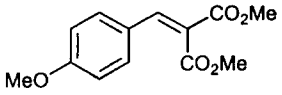
(**Table 14**) served as an indicator of the ability of **107** to promote the Knoevenagel reaction, and it is necessary to repeat any reactions which display activity on a larger scale to allow the yield to be determined and full characterisation of the products to be obtained.

The results obtained in this screening experiment (**Table 14**) indicate that the complex **107** is capable of promoting the Knoevenagel reaction. In the reactions of benzaldehyde **156b** and 4-anisaldehyde **156a** with methyl cyanoacetate and dimethyl malonate performed in the presence of the benzimidazole **107** (**Entries 4, 5, 6, 7, 8, 13, 14, 15** and **16, Table 14**) the Knoevenagel product had been observed by LCMS.

In the reaction of 4-Anisaldehyde **156a** with methyl cyanoacetate **170** in acetonitrile and water, even without addition of the benzimidazole **107**, the product **171** been observed by LCMS and ^{1}H NMR (**Entry 4, Table 14**).[92] The crude product of this reaction was found by ^{1}H NMR to contain the alkene **171** by comparison with literature values of similar molecules, and was formed with only low levels of impurities identified by weak peaks between δ_H 3-4 ppm.[92] Such high levels of purity were also observed when the reaction was repeated in the presence of **107** (**Entry 8, Table 14**). However, as the Knoevenagel product had been formed in the absence of benzimidazole **107** (**Entry 4, Table 14**), the role of **107** was not clear. Under aqueous conditions, it was clear that **107** was promoting the Knoevenagel reaction of 4-Anisaldehyde **156a** with methyl cyanoacetate **170**. When this reaction was performed in the presence of **107**, the product **171** was observed by LCMS and ^{1}H NMR, however, in the absence of **107** no evidence of **171** was found (**Entries 3** and **7, Table 14**).



171



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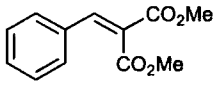
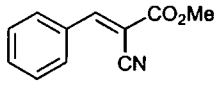


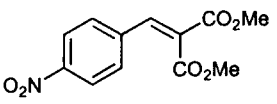
173



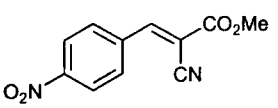
174

Clear evidence was also obtained for the promotion of the reaction of **156a** with dimethyl malonate **169** by **107**. The crude product obtained from the reaction performed in the presence of **107** in acetonitrile and water (**Entry 6, Table 14**), was found by LCMS and ^{1}H NMR to contain the product **172** alongside remaining 4-anisaldehyde **156a** and impurities which appeared to be derived from it.[23,92] These impurities were observed to a greater

extent in the reactions of **156a** and **169** performed in the presence of **107** under aqueous conditions. The reactions of benzaldehyde with dimethyl malonate **169** and methyl cyanoacetate **170** were also found to be promoted by **107** (**Entries 9-13, Table 14**); the Knoevenagel products **173** and **174** were identified by the observation of ions with masses consistent with the molecular ions of **173** and **174** by LCMS (ES +) and confirmed by ^{1}H NMR (**Entries 13, 14, 15** and **16, Table 14**).[93,94]

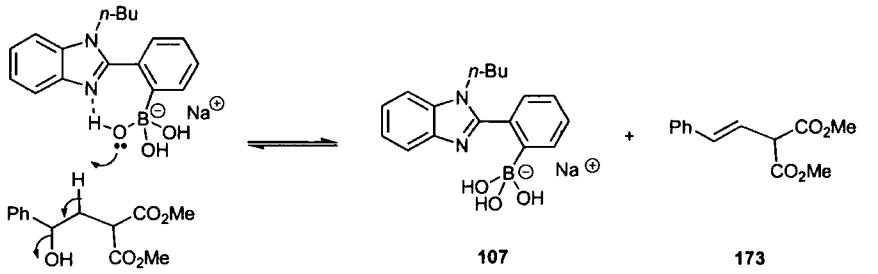


175



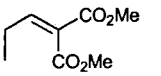
176

In the reactions of 4-nitrobenzaldehyde **156d** there was no evidence found for the formation of the Knoevenagel products **175** and **176** (**Entries 17-24, Table 14**). However, in these reactions partial loss of the starting material **156d** was observed, as well as formation of a number of products, some of which appeared by ^{1}H NMR to be derived from **156d**.[95] The loss of **156d** was highest in the reactions performed in the presence of **107** in acetonitrile and water (**Entries 23** and **24, Table 14**). The results of the reactions of 4-nitrobenzaldehyde were surprising. It was expected, that these reactions would be more active than the corresponding reactions of 4-anisaldehyde **156a** and benzaldehyde **156b** due to the greater electrophilicity of the aldehyde carbon of **156d**. A possible explanation for this counterintuitive result could be the poor solubility of nitrobenzaldehyde under the reaction conditions. It had been noticed during this screening experiment, that the reactions which contained **156d** still contained small amounts of particulate matter though to be the aldehyde. However, after 12 hours all solutions were found to be homogeneous. Therefore, as the reactions were ran for 7 days, it is unlikely that the initial differences in solubility of the aldehydes could have had much effect on the reactions. Instead, these results could indicate that **107** promotes the second step of the reaction; the dehydration of the alcohol, which would be faster in the electron rich aldehydes **156a** and **156b**. A possible mechanism for this promotion is shown in **Equation 84.**

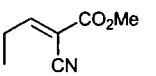


Equation 84

In the reactions of propionaldehyde **156e** with dimethyl malonate **169** and methyl cyanoacetate **170**, no evidence obtained by LCMS or ^{1}H NMR for the formation of the Knoevenagel products **177** and **178** (**Entries 25-32, Table 14**). As in the reactions of **156d** with dimethyl malonate and methyl cyanoacetate, loss of **156e** was observed as well as the formation of impurities which appeared to be derived from it by ^{1}H NMR. Again, the loss of **156e** was found to be the highest in the reactions performed in the presence of **107**.



177

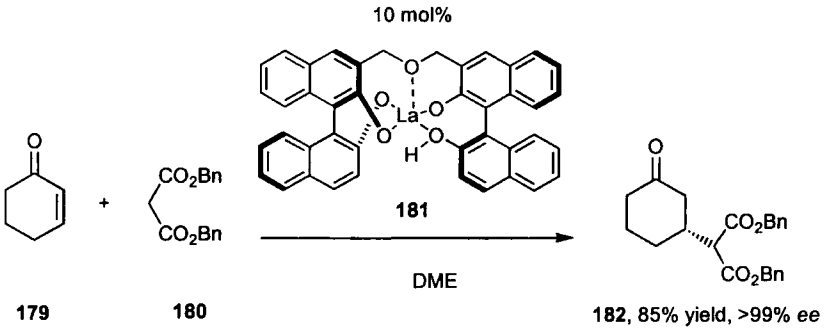


178

Despite the need for further investigation into these reactions, the initial results were exciting. The benzimidazole **107** had been shown to be capable of promoting the Knoevenagel reactions of 4-anisaldehyde **156a** and benzaldehyde **156b** with dimethyl malonate **169** and methyl cyanoacetate **170**, even under aqueous conditions. However, it is recognised that to confirm these results, the Knoevenagel reactions of **156a** and **156b** with **169** and **170** must be repeated on a larger scale. After the repetition of these reactions, and optimisation of the reaction conditions, this complex could be capable of promoting the Knoevenagel reaction of a wide range of aldehydes under aqueous conditions, potentially offering a recoverable and reusable environmentally friendly catalyst.

Section 3.4.2

Following the successful application of **107** to the Knoevenagel reaction, the investigation into the effect of benzimidazole **107** on other organic reactions was continued. The Michael reaction was chosen as a candidate for catalysis by **107**, as it is an important method of carbon-carbon bond formation, and is known to be promoted by both Lewis acids and bases.[88] Indeed, in research performed by Shibasaki *et al.* asymmetric bifunctional catalysts have been successfully applied to the Michael reaction.[47] These complexes are capable of promoting the reaction with yields and levels of enantioselectivity which rival those of enzymatic transformations.[44,47] The most effective catalyst reported by Shibasaki *et al.* for the Michael addition was the chiral complex **181**, which was shown to promote the Michael reaction of the enone **179** and the nucleophile **180**, giving the Michael adduct **182** in 94 % yield with an *e.e.* of over 99 % (**Equation 85**).[47]



Equation 85[47]

The Michael reaction involves the reaction of an α,β-unsaturated carbonyl compound with a nucleophile, often this results in the formation of new chiral centres including chiral quaternary carbon centres.[88] Due to this, extensive research has been conducted into the development of enantioselective Michael reactions, and many successful asymmetric catalysts have been developed.[88]

To investigate whether the benzimidazole complex **107** was capable of promoting the Michael reaction, a screening experiment was designed and performed. In this experiment a range of conjugated alkenes were reacted with a series of nucleophiles in the presence of the benzimidazole **107** in both aqueous conditions and in a mixture of acetonitrile and

water. The conjugated alkenes chosen for this experiment were cyclohexenone **179**, *trans*-chalcone **183**, methylcinnamate **184** and nitrostyrene **185**, which were intended to represent a diverse range of conjugated alkenes which would allow an accurate investigation to be performed. The conjugated alkenes were reacted with acetone, 2-siloxypropene **186** and methylcyanoacetate **170**, both with and without 8.8 mol% of the complex **107** as shown in **Table 15**. The reactions were performed in parallel using a Robbins block™ as the reaction vessel, over a 7 day period at room temperature, and were worked-up in parallel by filtration through silica, and analysed by LCMS. In reactions that were found to contain new compounds by mass spectrometry, the residues were analysed by ^{1}H NMR. The reactions that were carried out without the benzimidazole **107** were found to be inactive by LCMS, and therefore have not been included in **Table 15**.

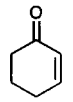
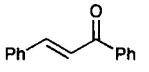
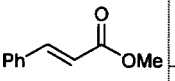
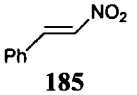
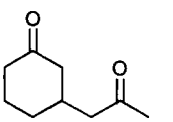
Entry	Substrate	Nucleophile	Solvent	Michael adduct[a]
1	 **179**	Acetone	H_2O	Yes
2			1:1 MeCN:H_2O	Yes
3		Methyl cyanoacetate **170**	H_2O	No
4			1:1 MeCN:H_2O	No
5		2-Siloxypropene **186**	H_2O	Yes
6			1:1 MeCN:H_2O	Yes
7	 **183**	Acetone	H_2O	No
8			1:1 MeCN:H_2O	No
9		Methylcyanoacetate **170**	H_2O	No
10			1:1 MeCN:H_2O	No
9		2-Siloxypropene **186**	H_2O	No
10			1:1 MeCN:H_2O	No
11	 **184**	Acetone	H_2O	Yes
12			1:1 MeCN:H_2O	Yes
13		Methylcyanoacetate **170**	H_2O	No
14			1:1 MeCN:H_2O	No
15		2-Siloxypropene **186**	H_2O	Yes
16			1:1 MeCN:H_2O	Yes
17	 **185**	Acetone	H_2O	No
18			1:1 MeCN:H_2O	No
19		Methylcyanoacetate **170**	H_2O	No
20			1:1 MeCN:H_2O	No
21		2-Siloxypropene **186**	H_2O	No
22			1:1 MeCN:H_2O	No

Table 15: Reaction of the alkenes cyclohexenone **179**, *trans*-chalcone **183**, methylcinnamate **184** and *trans*-nitrostyrene **185** with the nucleophiles acetone, methylcyanoacetate **170** and 2-siloxypropene **186** in the presence of **107**. [a] Product observed by LCMS.

The reactions of cyclohexenone **179** and methylcinnamate with acetone and 2-siloxypropene **186** (**Entries 1, 2, 5, 6, 11, 12, 15** and **16 Table 15**), were found to be promoted by **107**. In the presence of **107**, the reactions of cyclohexenone **179** with acetone and 2-siloxypropene **186** (**Entries 1, 2, 5** and **6, Table 15**) were found to produce the Michael product **187** identified by LCMS (ES +), due to the observation of ions at *m/z* 195.12 and 196.12, consistent with **187**. However, this could be an anomalous result, as they were also observed in the LCMS of **Entries 3** and **4**, which even if successful, would not lead to a product with these masses. When the residues obtained from these reactions were analysed by ^{1}H NMR they were found to contain a mixture of products which appeared to be starting materials, low levels of compounds derived from the starting materials, residual solvents and acetone self condensation products, but not the Michael adduct **187**.[23,80,96]

In the reactions of methylcinnamate **184** with acetone and 2-siloxypropene **186** (**Entries 11, 12, 15** and **16, Table 15**) in the presence of **107**, LCMS (ES +) revealed ions at *m/z* 218, consistent with the expected Michael product **188**.[97] As in the reactions of **179** (**Entry 1, 2, 5 and 6, Table 15**), these results could be anomalous, as ions with the same masses were also observed in the reaction of methylcinnamate **188** with methylcyanoacetate **170** (**Entries 13** and **14, Table 15**). Analysis of the residues obtained from the reactions of **186** with acetone and 2-siloxypropene **186** (**Entries 11, 12, 15** and **16, Table 15**) by ^{1}H NMR revealed a very complex mixture of compounds, most of which appeared to be derived from **184**, and none of which appeared to be the Michael adduct **188**.[23,97]



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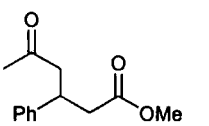
Although the analysis of this screening experiment by LCMS had allowed the effective generation of results, it had highlighted the need for care to be taken when using this method of analysis. In each of the reactions that had been found by LCMS to give the desired Michael adducts, there had been no evidence for the formation of these products observed in the ^{1}H NMR.[96,97] Although it is possible that the complexity of the NMR spectra of the residues obtained from the reactions which were found to be active might have resulted in the peaks due to the Michael adducts not being visible, these reactions

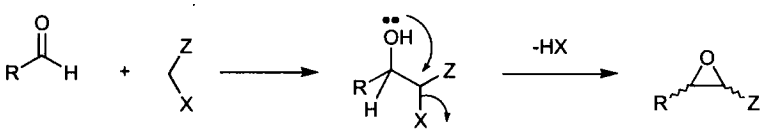


188

could simply have been inactive. To determine if the Michael reactions did occur in these reactions (**Entries 1, 2, 5, 6, 11, 12, 15** and **16, Table 15**), they must be repeated on a large enough scale that each product can be separated and characterised.

Section 3.4.3

Attempts were also made to investigate the effect that the benzimidazole **107** has on the Darzens reaction.[89] This reaction provides a method of preparation of epoxides through an aldol reaction, followed by an internal S_N2 reaction to form an epoxide as shown in the generic reaction in **Scheme 32**.



R= Alkyl, aromatic
Z= Electron withdrawing group
X= Leaving group

Scheme 32

Epoxides are key structural units; present in many medically important compounds and also as precursors in synthesis. The formation of an epoxide potentially allows the generation of two chiral centres in one step, and therefore the development of asymmetric catalysts, which would allow the enantioselective synthesis of epoxides are of great interest.[98,99]

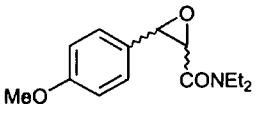
To investigate the effect that the benzimidazole **107** has on the Darzens reaction, a screening experiment was designed and performed in which a range of aldehydes were reacted with chloroacetonitrile **189** and N,N-diethyl-2-chloroacetamide **190,** both with and without the benzimidazole **107** (**Equation 86, Table 16**). The reactions in this screening experiment were performed in parallel using a Robbins block^{TM}, were mixed at room temperature for 7 days, and analysed by LCMS (ES +).

Equation 86

Entry	R	Nucleophile	**107**	Solvent	Darzens product[a]

1	4-$(MeO)C_6H_4$ **156a**	chloroacetonitrile **189**	-	H_2O	No
2			-	1:1 MeCN:H_2O	No
3			8.8 mol%	H_2O	No
4			8.8 mol%	1:1 MeCN:H_2O	No
5		N,N-Diethyl-2-Chloroacetamide **190**	-	H_2O	Yes
6			-	1:1 MeCN:H_2O	Yes
7			8.8 mol%	H_2O	Yes
8			8.8 mol%	1:1 MeCN:H_2O	Yes
9	Ph **156b**	**189**	-	H_2O	No
10			-	1:1 MeCN:H_2O	No
11			8.8 mol%	H_2O	No
12			8.8 mol%	1:1 MeCN:H_2O	No
13		**190**	-	H_2O	No
14			-	1:1 MeCN:H_2O	No
15			8.8 mol%	H_2O	Yes
16			8.8 mol%	1:1 MeCN:H_2O	Yes
17	4-$(NO_2)C_6H_4$ **156d**	**189**	-	H_2O	No
18			-	1:1 MeCN:H_2O	No
19			8.8 mol%	H_2O	Yes [a]
20			8.8 mol%	1:1 MeCN:H_2O	Yes [a]
21		**190**	-	H_2O	No
22			-	1:1 MeCN:H_2O	No
23			8.8 mol%	H_2O	Yes
24			8.8 mol%	1:1 MeCN:H_2O	Yes
25	CH_3CH_2 **156e**	**189**	-	H_2O	No
26			-	1:1 MeCN:H_2O	No
27			8.8 mol%	H_2O	No
28			8.8 mol%	1:1 MeCN:H_2O	No
29		**190**	-	H_2O	No
30			-	1:1 MeCN:H_2O	No
31			8.8 mol%	H_2O	No
32			8.8 mol%	1:1 MeCN:H_2O	No

Table 16: Reactions of the aldehydes 4-anisaldehyde **156a**, benzaldehyde **156b**, 4-nitrobenzaldehyde **156d** and propionaldehyde **156e** with chloroacetonitrile **189** and N,N-diethyl-2-chloroacetamide **190** were performed in the presence of 8.8 mol% of the complex **107**. [a] Product observed by LCMS.



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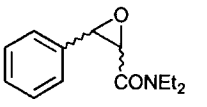
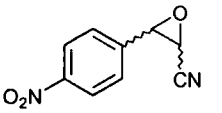
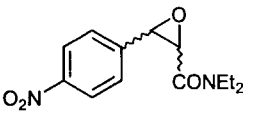
From the results obtained in this screening experiment it appeared that the Darzens reaction could indeed be promoted by **107**, but that the conditions used in the screen were far from optimum. In the reaction of 4-anisaldehyde **156a** with N,N-diethyl-2-chloroacetamide **190** (**Entry 5, 6, 7** and **8 Table 16**), evidence for the formation of the Darzens product **191** was obtained by LCMS even when **107** was not present in the reaction mixture. LCMS (ES +) of the crude products of the reactions performed in the absence of **107** (**Entries 5** and **6, Table 16**)



192



193



194

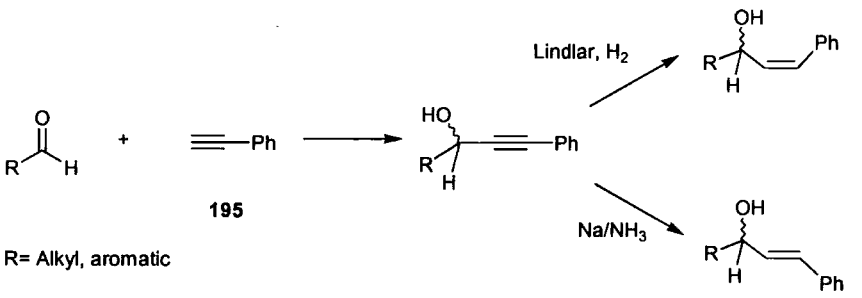
revealed an ion at *m/z* 249.14 consistent with the molecular ion of **196**, however, this product was not observed by ^{1}H NMR, which instead revealed residual starting materials and the hydrate of 4-anisaldehyde in a ratio of 1:12.4 for **Entry 5** and 1:10.7 for **Entry 6**.[23,78,99] The hydrate was identified by ^{1}H NMR due to the observation of peaks in at 8.07 (d, *J* 8.8 Hz, 2 H) and 7.85 (d, *J* 8.7 Hz, 2 H), and a new peak at 3.88 ppm (s, 3 H) due to the methoxide unit of the hydrate.[78] Due to the absence of peaks in the alkyl region of the ^{1}H NMR spectra, or those diagnostic of carbonyl compounds in the ^{13}C NMR spectra (180-200 ppm), it was thought that **156a** had reacted with water to form the hydrate rather than with N,N-diethyl-2-chloroacetamide **190**. in the presence of **107** the reactions of **156a** with N,N-diethyl-2-chloroacetamide **190** (**Entries 7** and **8**, **Table 16**), were also found to contain the Darzens product **191** by LCMS (ES+) due to the observation of ions at *m/z* 250.14 (MH^+), however, this could not be confirmed by ^{1}H NMR; the peaks due to the epoxide protons were absent from the spectra, only singlets were present in these positions.[99] From these results, it is not possible to determine whether the Darzens product had formed, as the observation of an ion with the same mass might be coincidental.

When the reactions of benzaldehyde and **190** were performed in the absence of **107**, the Darzens product **192** was not observed by either LCMS or by ^{1}H NMR, although partial loss of **156b** did occur and a number of products were observed in low levels.[100] In the presence of the benzimidazole **107**, these reactions were found by LCMS (ES +) to contain the Darzens product **192** alongside a number of other products, but again this was not supported by ^{1}H NMR.[100] The Darzens product **193** was observed by LCMS (ES +) in the reactions of 4-nitrobenzaldehyde **156d** with chloroacetonitrile **189**, in the presence of **107** (**Entries 19** and **20**, **Table 16**), however, this could not be confirmed by ^{1}H NMR spectra of the crude products were found to be very complex, containing residual starting materials as well other compounds.[23] Although it appeared that there were peaks characteristic of the epoxide present in the spectra, due to their complexity, these peaks could have been attributable to other species. Evidence for the formation of the Darzens product **194** was also observed by LCMS (ES +) in the reaction of **156d** with N,N-diethyl-2-chloroacetamide **190** in the presence of **107** (**Entries 23** and **24**, **Table 16**), however, the complexity of the ^{1}H NMR spectra of the crude products again prevented the identification of the Darzens product.[101]

From these results, it could not be conclusively determined if benzimidazole **107** was capable of promoting the Darzens reaction. If the benzimidazole **107** had promoted the Darzens reactions of benzaldehyde **156b** and 4-nitrobenzaldehyde **156d**, the products might have been formed in such low levels, and alongside so many impurities, that they could not be identified by ^{1}H NMR. To establish whether **107** is capable of promoting the Darzens reactions, repetition of the reactions on a larger scale is necessary so that each component of the crude product can be isolated and analysed.

Section 3.4.4

Our attention was now turned towards the ability of **107** to promote the coupling of phenylacetylene **195** with aldehydes.[102] The coupling of acetylene units to carbonyl compounds is of considerable interest, as the products generated can be versatile reagents for further synthetic transformations.[102] Not only does the coupling of acetylene units with carbonyl compounds result in the formation of a chiral centre, but also the acetylene unit can be selectively reduced to either a *cis*- or *trans*-alkene providing access to a wide range of chemistry (**Scheme 33**).[103]

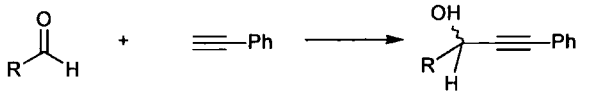


Scheme 33

Unlike the aldol, Knoevenagel, Michael and Darzens reactions previously studied, this reaction does not involve the formation of enolates.[102] However, the coupling of phenylacetylene **195** to aldehydes might still be susceptible to promotion by the complex **107**, due to the possible activation of aldehydes through complexation to the boron atom of **107** or a related compound.[102] If this reaction was found to be promoted by **107**, this would

suggest that activation of the carbonyl groups was responsible for the activity of **107** observed in the Knoevenagel, Michael and Darzens reactions (**Tables 14, 15** and **16**).

To investigate the effect of **107** on the coupling of phenylacetylene to aldehydes a screening experiment was designed in which the reaction of the aldehydes 4-anisaldehyde **156a**, benzaldehyde **156b**, 4-nitrobenzaldehyde **156d** and propionaldehyde **156e** with phenylacetylene **195**, were performed both with and without **107**. The reactions were performed in parallel using a Robbins block™, and were analysed by LCMS (**Equation 87**, **Table 17**).



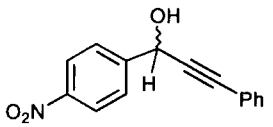
156 **195**

Equation 87

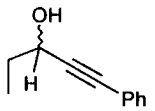
Entry	**156**	**107**	Solvent	Observation of Product.[a]
1	4-(MeO)C_6H_4 **156a**	-	H_2O	No
2		-	1:1 MeCN:H_2O	No
3		8.8 mol%	H_2O	No
4		8.8 mol%	1:1 MeCN:H_2O	No
5	Ph **156b**	-	H_2O	No
6		-	1:1 MeCN:H_2O	No
7		8.8 mol%	H_2O	No
8		8.8 mol%	1:1 MeCN:H_2O	No
9	4-(NO_2)C_6H_4 **156d**	-	H_2O	No
10		-	1:1 MeCN:H_2O	No
11		8.8 mol%	H_2O	Yes
12		8.8 mol%	1:1 MeCN:H_2O	Yes
13	CH_3CH_2 **156e**	-	H_2O	No
14		-	1:1 MeCN:H_2O	No
15		8.8 mol%	H_2O	Yes
16		8.8 mol%	1:1 MeCN:H_2O	Yes

Table 17: Reactions of the aldehydes 4-anisaldehyde **156a**, benzaldehyde **156b**, 4-nitrobenzaldehyde **156d**, and propionaldehyde **156e** with phenylacetylene **195**, both with and without 10 mol% of **107**. [a] Products identified by LCMS.

The reactions in this experiment were performed using the procedure from previous screening experiments (**Tables 14, 15** and **16**). The reactions were shaken to mix the reactions for 7 days at room temperature, after which the reactions were worked-up in parallel by filtration of the reaction mixtures short silica plugs (40 Å, MeCN), and analysed by LCMS. The results obtained indicated that under these conditions 4-anisaldehyde **156a** and benzaldehyde **156a** with **195** were inactive even in the presence of the benzimidazole **107** (**Entries 1-8, Table 17**). Although consumption of starting material was observed in these reactions, it was thought that the hydrates of **156a** and **156b** had been formed, rather than the products **196** and **197** due to the observation of peaks in the ^{1}H NMR spectra obtained, consistent with those observed in the Darzens reactions of **156a** and **156b** (**Table 17**).

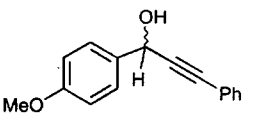


198

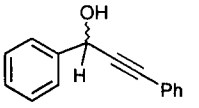


199

In the reactions of 4-nitrobenzaldehyde **156d** and propionaldehyde **156e** with phenylacetylene **195** in the presence of **107**, evidence for the formation of the products **193** and **194** were obtained by LCMS (ES +) (**Entries 11, 12, 15** and **16, Table 17**). However, problems were again encountered when attempting to confirm these results by ^{1}H NMR. When the reaction of 4-nitrobenzaldehyde **156d** with phenylacetylene **195** was performed in the presence of **107** (**Entries 11** and **12, Table 17**), the LCMS (ES +) revealed ions at *m/z* 253.07 and 277.31 attributable to **198** ions $(M\text{-}H)^+$ and MNa^+ respectively.[102c] Unfortunately, the residues obtained on work-up of these reactions (**Entries 11** and **12, Table 17**), were found by ^{1}H NMR to contain many products, which prevented the formation of **198** being confirmed.[102c] This problem was also encountered in the reactions of propionaldehyde **156e** with **195** in the presence of **107** (**Entries 15** and **16, Table 17**). The LCMS (ES +) revealed ions at *m/z* 160.09 consistent with the molecular ion of **199**, however, when these residues were analysed by ^{1}H NMR the spectra were very complex and the presence of **199** could not be confirmed.[104]



196



197

Although a number of false positive results appear to have been generated during the investigation into the activity of **107**, this approach had been found to be very effective. It has been found that the boronate complex

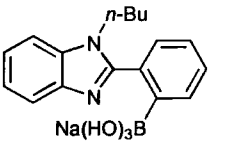
107 is capable of promoting the Knoevenagel reaction, and might be capable of promoting the Michael and Darzens reactions and the coupling of phenylacetylene to aldehydes. If these results can be confirmed and the conditions optimised then potentially, **107** could be an effective catalyst for these reactions.

Although a few problems had been encountered with the instrumentation used, such as the inconstancies in the work-up procedure used, this strategy has given an insight into the potential of this complex. If this investigation had been attempted using a wide ranging combinatorial screen, it might not have been as successful. For instance, if dimethyl malonate had been reacted with only benzaldehyde, no activity would have been observed and it might have been thought that the complex **107** was incapable of promoting the Knoevenagel reaction.

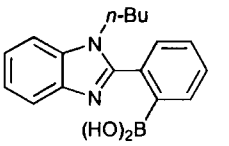
Chapter 4

Section 4.1

During our investigations into the potential of bifunctional molecules based on the benzimidazole core to behave as bifunctional catalysts, several compounds had been prepared based on the benzimidazole backbone (**Chapter 2**). Due to the potential of these compounds, the preparation of analogues of them is an exciting prospect. Indeed, it should be possible to prepare a wide range of analogues of these compounds, allowing the activity of **107** to be tailored to individual reactions through the investigation of structure-activity relationships, as well as allowing chiral and solid supported analogues of these compounds to be prepared.



107



118

One of the most promising analogues that had been considered was a solid supported version of the bifunctional complex **107**. The preparation of solid supported reagents and catalysts is one of the important advances in modern synthetic chemistry.[105] Solid supported catalysts and reagents are known to offer greater experimental ease and efficiency as well as having environmental benefits.[105] Therefore, if a supported version of **107** could be prepared, and was found to have the same activity as the free complex **107**, then it could be used in water and removed from reaction mixtures through a simple filtration. As well as the benefits that a solid supported version of **107** would provide, it could also have the advantage of allowing greater ease in the investigation of the activity of **107**. This would also be of benefit in the investigation into the activity of the parent structure **117** and related analogues, the handling of which had been found to be difficult. Tethering the monomer units to a solid support would mean that these molecules would be separated and therefore unable to form boroxine and dimer complexes. The use of solid supported resins might also allow the problems associated with solubility of the benzimidazole **117** to be avoided.

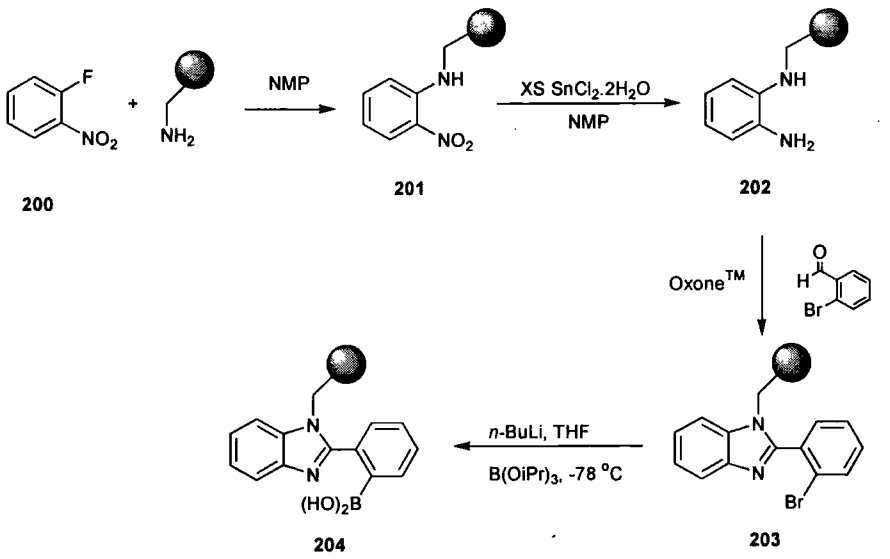
Section 4.1.1

Attempts to prepare a solid supported version of the benzimidazole **107** were made using the resin Argogel^{TM}-NH_2. This resin was chosen as the solid support, as it has similar swelling properties as other PEG based solid supports, such as Tentagel^{TM}, but has better mechanical stability, which would hopefully allow it to be stirred and shaken more than other, similar resins.[106,107] Attempts to prepare a solid supported version of the benzimidazole **107** were focused on the attachment of **107** to the Argogel^{TM}-NH_2 resin through the side chain of **107**. Tethering **107** to the resin in this way, should have less impact on the ability of the molecule to behave as a catalyst than if the attachment was made through the benzimidazole backbone.

There are two obvious approaches to the synthesis of solid supported versions of **107**; either through the attachment of the resin to 2-arylbenzimidazoles such as **133** or **145** or through the preparation of the benzimidazole on the surface of the resin from phenylenediamine **202**. After preparation of the supported benzimidazoles by either route, the boronic acid could be installed through lithium-halogen exchange, followed by quenching with triisopropyl borate, or through directed metalation followed by quenching with triisopropyl borate. These approaches should be possible due to the tolerance of Argogel^{TM} to organometallic compounds.[108] However, there were concerns that the installation of the boronic acid group in either of these ways could be difficult due to the presence of heteroatoms in the Argogel^{TM}-NH_2 resin, which might interfere with the metalation as had been observed in the preparation of the benzimidazole **137**.

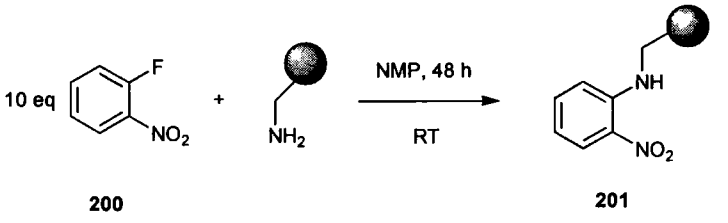
The approach taken in the preparation of a solid supported version of **107** was the construction of the benzimidazole on the surface of the resin from the phenylenediamine **202**. This was due to the fact that large quantities of reagents are required for these reactions to ensure all of the sites on the resin surface have reacted. If the attachment of **107** is performed after the 2-phenylbenzimidazoles have been synthesised, there could potentially be a large amount of these compounds wasted. By preparing the solid supported version of **107** stepwise from tethered phenylenediamine **202**, only relatively inexpensive reagents would be wasted. This synthesis was expected to be far more efficient than that of

the unsupported **107** prepared by this route due to the ability to work-up these reactions by simple filtration.



Scheme 34

Therefore, in an attempt to prepare the solid supported benzimidazole **204**, the Argogel^{TM}-NH_2 resin was reacted with an excess of 2-fluoronitrobenzene in NMP as shown in **Equation 88**. The reaction was performed through the treatment of a mixture of the resin in NMP with 2-fluoronitrobenzene under argon. The mixture was stirred gently, to prevent damage of the resin beads and after stirring for 12 hours the resin was isolated from the reaction mixture by filtration, washed with NMP, and the reaction repeated however this time the mixture was stirred for 24 hours. By repeating the reaction, we were attempting to ensure that all of the amine sites on the resin had reacted with the halide **200**.

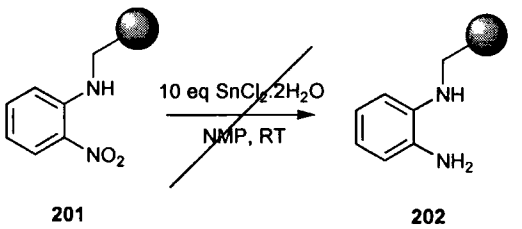


Equation 88

After the isolation of the resin by filtration the resin was washed with NMP, DCM, a mixture of MeOH:DCM and MeOH successively, to remove all unreacted 2-fluoronitrobenzene **200**. However, our attempts to analyse the resin obtained after drying

under reduced pressure (0.5-2 mmHg) met with difficulties. Attempts to analyse the material attached to the resin through the cleavage of a small portion of the resin was unsuccessful, using sodium potassium butoxide under reflux, only small amounts of material were recovered which appeared to be unrelated to the 2-nitrobenzene unit.[106] This indicated that the aryl compound had not become attached to the solid support. Direct analysis of the resin was then tried, using IR, ^{13}C and magic angle spinning ^{1}H NMR.[109] Due the flexibility of the polyethylene glycol chains of Argogel™, compounds attached to this resin can be observed by gel phase ^{13}C NMR since on this time scale they behave as if they are dissolved.[109] When the resin obtained from the reaction described above was analysed by ^{13}C gel phase NMR the spectrum obtained revealed signals characteristic of 2-nitroanilines at 114.3, 115.8, 127.3, 136.6 and 145.8 ppm. This was confirmed by MAS ^{1}H NMR which revealed peaks at 6.63-6.68 (m, Ar), 6.86 (d, *J* 7.5 Hz, Ar), 7.40-7.45 (m, Ar) and 8.18 ppm (d, *J* 7.5 Hz, Ar).

Attempts were then made to reduce the nitro group, as in the preparation of the unsupported benzimidazoles, to give the supported phenylene diamine **202** (**Equation 89**). There are many literature examples of reductions of this type using a wide range of reagents, of these, the reagent $SnCl_2.2H_2O$ in NMP was chosen as this system was known to have been successful in the reduction of similar supported nitrobenzene compounds.[110,111] This reaction was performed through the treatment of a solvated mixture of **201** in NMP, with $SnCl_2.2H_2O$ and the mixture shaken to mix the reaction for 12 hours at room temperature. The resin was isolated by filtration and after washing with NMP was again reacted with $SnCl_2.2H_2O$ in NMP at room temperature. After which, the resin was isolated by filtration, and washed with NMP, DCM, and a mixture of MeOH:DCM, MeOH, water, Et_2O and again with DCM.



201 **202**

Equation 89

Unfortunately, when the resin recovered from this reaction was analysed by IR, gel phase ^{13}C and magic angle spinning NMR, there was no evidence of the diamine **202** observed; the only peaks observed were those due to the starting material **201**. Although the reason for the lack of activity observed in these reactions was not clear, it is possible that the tin(II) chloride could have become associated with the oxygen atoms of the Argogel™ resin, effectively removing the tin from the reaction mixture and preventing reduction.

Further attempts to reduce **201** were made using tin(II) chloride under other reaction conditions.[110,111] These reactions were performed on a small scale (0.1 g) and were used to determine if any reduction was occurring under the conditions attempted. The reactions were run in parallel and involved the use of $SnCl_2$ and $SnCl_2.2H_2O$ in NMP, DMF and diethyl ether (**Table 18**). The reactions were performed through the treatment of the solvated resin with 2 equivalents of the tin salts and the reactions stirred gently at room temperature for 12 hours. After this period the resins were isolated by filtration and washed with NMP, DCM, and a mixture of MeOH:DCM, MeOH, water and Et_2O.

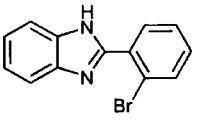
Entry	Solvent	$SnCl_2$ (Eq)	$SnCl_2.2H_2O$ (Eq)	Observation of **202**[a]
1	DMF	2	-	No
2	DMF	-	2	No
3	DMF:H_2O (10:1)	-	2	No
4	NMP	2	-	No
5	NMP	-	2	No
6	NMP:H_2O (10:1)	-	2	No
7	Diethyl ether	-	2	No

Table 18: Attempted reduction of **201** using tin salts in a range of solvents. [a] Identification of **202** attempted using IR.

The products of these reactions were analysed by IR, unfortunately, no evidence of **202** was obtained. Using this method of analysis, the presence of an aromatic nitro compound could be observed due to a signal at ν_{max} 1452.9 cm^{-1} indicating unreacted starting material, and no evidence of primary amine was observed.

Despite the difficulty encountered in the synthesis of a solid supported version of **107**, it was still thought that such a synthesis was possible. There are many reagents that allow the

reduction of nitrobenzene compounds, and a number of literature precedents for the reduction of supported nitrobenzene compounds of this type.[110] Therefore, it should be possible to find conditions suitable for the preparation of **202**, and from this material prepare the solid supported benzimidazole **204**. Even if this approach was not successful, the preparation of this material is also possible through the reaction of the 2-(2-bromobenzene)benzimidazole **133**, which after lithium-halogen exchange and subsequent quenching with triisopropyl borate should give the boronic acid **204**.



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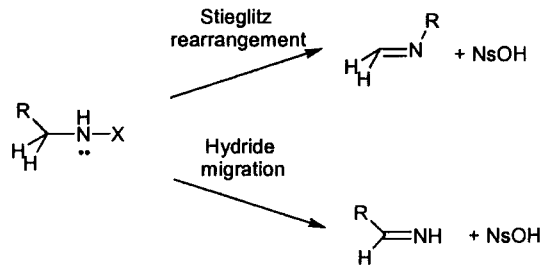
Conclusion

Section 4.2

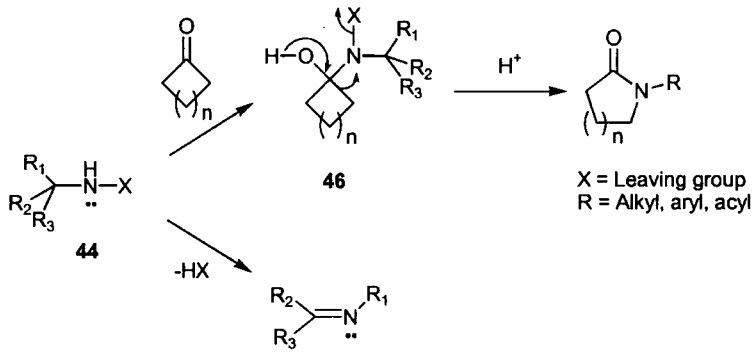
During our attempts to develop an aza-version of the Baeyer-Villiger reaction, problems had been encountered with the techniques used. Although the use of screening experiments was the most effective approach, many of the reagents used in our investigations were corrosive, hydrophobic and often violently unstable. However, the problems that this presented were minor and easily overcome. One of the difficulties associated with conducting our investigation in this way was the analysis of such large numbers of reactions. In theory the analysis of screening experiments by LCMS or GC is fast and accurate, however to analyse the experiments using these methods took an inordinate length of time due to the need to perform an additional work-up step. This meant that, although the results obtained were of a high quality, the analysis of the reactions by this method was often rather cumbersome. In many experiments this created a bottle-neck as the time required for analysis limited the number of reactions that could be run. This problem was solved by following some of the screening experiments using LCMS and GC, whilst at the same time following others by TLC. In this way we were able to perform what is thought to have been an extensive investigation into the reactivity of the compounds selected as possible reagents for an aza-Baeyer-Villiger reaction.

During our investigations, the major difficulty encountered had been the selection of compounds capable of behaving as nitrogen containing per-acid equivalents. If a molecule could be found which displayed the desired reactivity this species would be prone to decomposition. The balance between the lability of the leaving group, the nucleophilicity of the nitrogen centre and stability in suitable candidates is very fine. Molecules with very labile leaving groups are expected to undergo facile decomposition through Stieglitz rearrangements or through hydride migration (**Scheme 35**), a problem which is exacerbated by high electron density at the nitrogen centre.



Scheme 35

However, if the electron density is low or the leaving group is not labile then the molecule would be poorly nucleophilic and rearrangement may not occur. A molecule is required which decomposes only after attacking a carbonyl compound and in which the decomposition occurs with selective migration of a carbon originating from the carbonyl compound (**Scheme 36**).



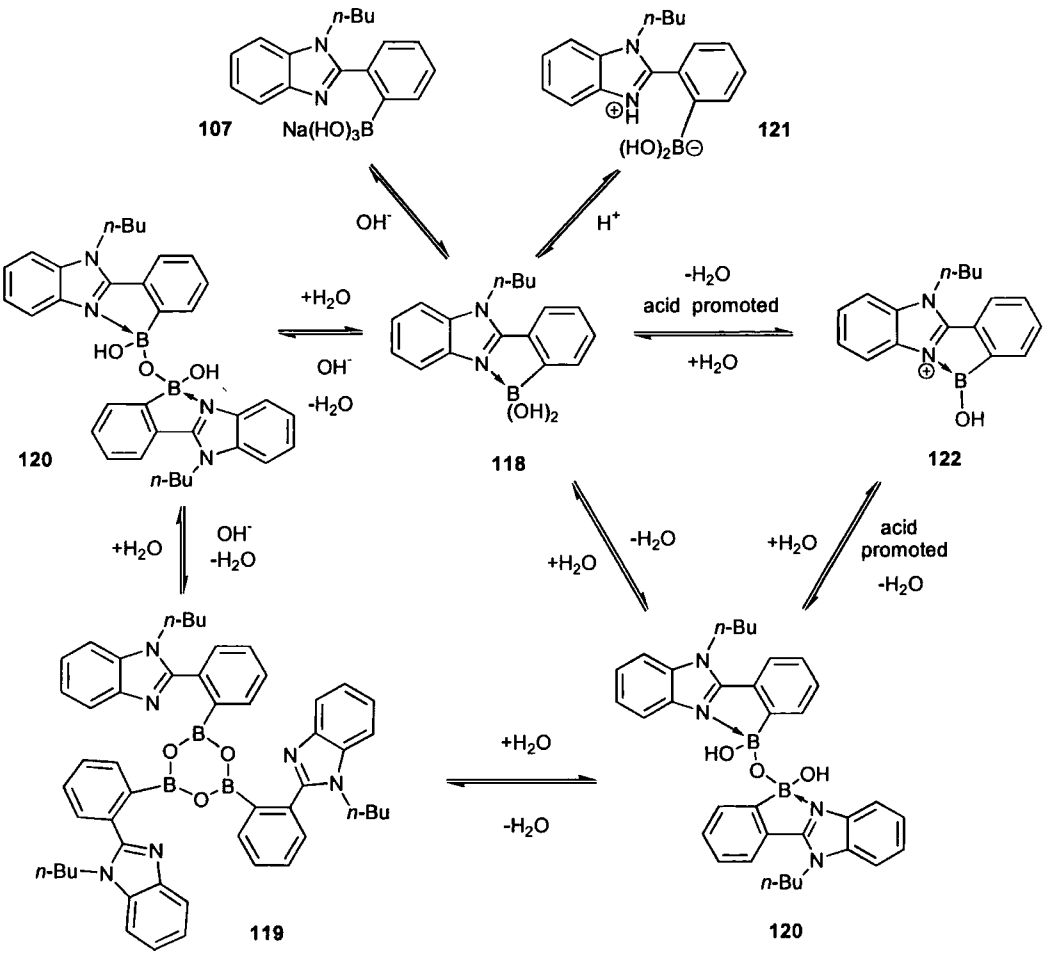
Scheme 36

Due to the complete lack of reactivity observed in the reactions of the potential nitrogen containing per-acid equivalents studied, it is unlikely that the development of a robust, selective and mild reaction of this type is possible. The literature precedents which exist for nitrogen insertion reactions of N-substituted reactions typically employ either azides, or are intramolecular reactions. However, it may be possible to achieve a reaction similar to the desired aza-Baeyer-Villiger reaction using metal nitrenoids. During our investigations we had found no evidence for the insertion reactions of nitrenoids derived from chloroamine T into carbonyl bonds, regardless, this behaviour has been suggested in a number of systems reported in the literature.[112] To perform an investigation of this chemistry would require an enormous screening program. Not only are there a large range

of species from which the metal nitrenoids could be formed, but these would have to be tested with a range of metal complexes under a number of different conditions.[37,38,39,112] Even with such a large screening program, the desired reactivity may still not be found as the specific conditions and the metal complexes necessary for reactivity may not be selected.

Section 4.3.1

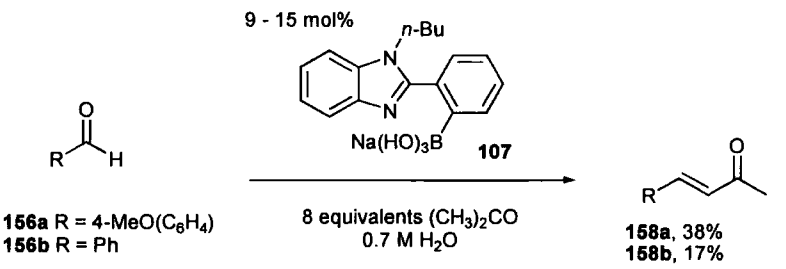
Our investigations into the behaviour and activity of the bifunctional benzimidazole **107** has revealed some very interesting chemistry. Not only does the benzimidazole **107** exist in a number of forms, but these forms are related to each other through a network of reactions. Although our early attempts to analyse this material and understand its behaviour were problematic due to the poor solubility of this material under neutral conditions, through a series of detailed studies and by comparison with the behaviour of similar compounds reported in the literature, it is thought that an accurate picture of the structures of these species and their behaviour has been constructed (**Scheme 37**).



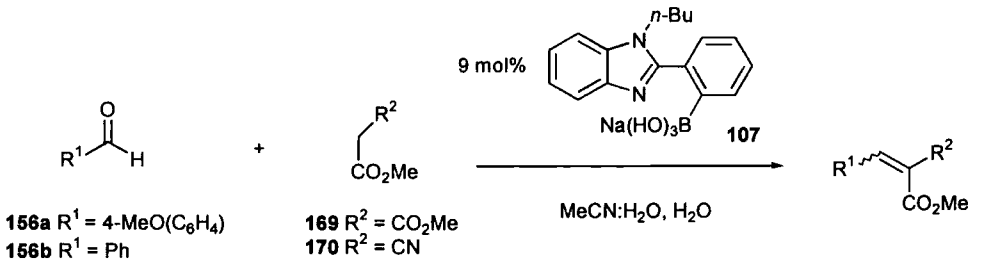
Scheme 37

Section 4.3.2

During our investigations into the ability of amino-boronate benzimidazoles to behave as bifunctional catalysts, a number of encouraging and interesting results were obtained. The benzimidazole **107** has been shown to be capable of catalysing the aldol condensation of benzaldehyde **156b** and 4-anisaldehyde **156a** with acetone (**Chapter 3**), and has also been found to promote the Knoevenagel reaction of **156a** and **156b** with methylcyanoacetate and dimethyl malonate (**Equation 91**).

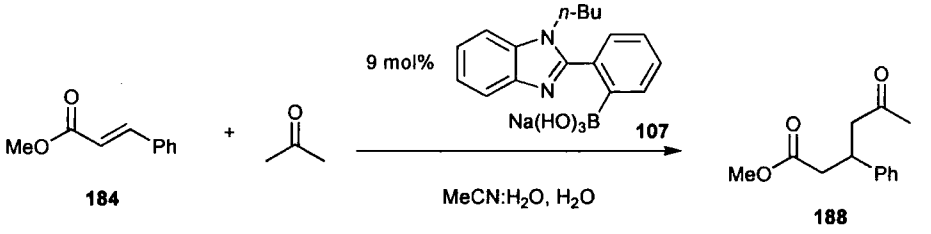


Equation 90 (Section 3.2.1)



Equation 91 (Section 3.4.1)

It is also thought that the complex **107** may capable of promoting the Michael reaction and the coupling of phenylacetylene to aldehydes. Although unconfirmed, evidence for the presence of **188** had been observed by LCMS in the reactions of methyl cinnamate **184** with acetone or 2-siloxypropene **186** performed in the presence of **107** (**Section 3.4.2**).



Equation 92 (Section 3.4.2)

As well as appearing to be an active catalyst for these reactions, what was even more exciting was that **107** appeared to be promoting these reactions under aqueous conditions. Potentially, **107** could be a versatile, water tolerant and even an environmentally friendly catalyst.

Although the results obtained through these investigations are promising, further work is required to confirm the activity of **107** observed in the screening experiments. Evidence of

reaction had been observed by LCMS in a number of the Michael reactions, in the coupling of phenylacetylene to a number of aldehydes, and in the Knoevenagel reactions of **156a** and **156b** by LCMS and ^{1}H and ^{13}C NMR. Unfortunately, due to the temperamental nature of the work-up procedure used, accurate yields could not be obtained. Also, in the Michael reactions and the coupling reactions of phenylacetylene, despite being observed by LCMS, the products of these reactions were either present in very low levels or were not present at all, as they could not be observed by ^{1}H NMR. Therefore, these reactions must be also performed on a larger scale.

Section 4.3.3

Although a complete mechanism for the aldol condensation reactions performed in the presence of **107** could not be determined, we have shown that the 'ate'-complex is the active species in these reactions. During our investigation into the identity of the active species in these reactions, the possibility had been considered that they were promoted by hydroxide impurities present in the reactions. However, when the reaction of **156a** with acetone was performed in the presence of equimolar quantities of **107** and sodium hydroxide, no activity was observed (**Section 3.2.4**). Instead of forming the boronate **107** in these reactions, due to the internal donation and the possible presence of dehydrated forms of **117**, sodium hydroxide had reacted with this material to form the 'ate'-complexes of the dimer or trimer complexes. This indicated that **117** had effectively 'scavenged' hydroxide from the reaction mixture was not released as part of an equilibrium process.

The presence of low levels of the internally bonded form **107** in the compound **107** (**Section 2.1.4**) identified by the peak at 5.6 ppm, implies that there is in fact a deficiency of hydroxide in **107**.[55] Therefore, hydroxide cannot have been present in the reactions performed in the presence of **107** as an impurity as it would be scavenged by **118**. Due to the lack of activity observed in (**Section 3.2.4**), it is also not reasonable to expect that it would be released as part of an equilibrium process.

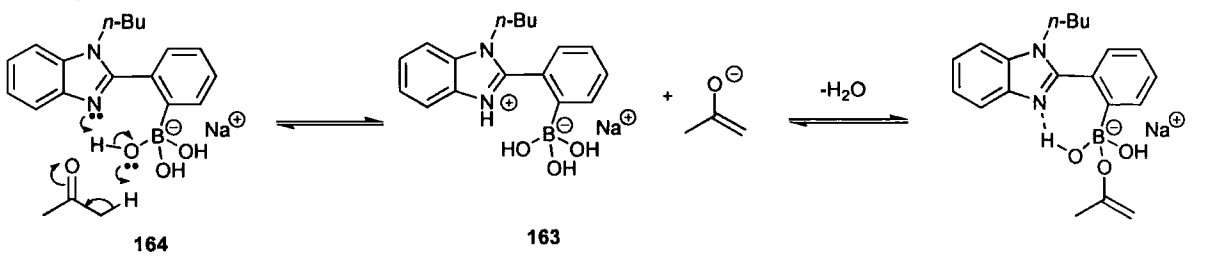
This was supported by our kinetic investigations. When the reaction of **156b** with acetone was performed in the presence of sodium hydroxide and followed by HPLC, the formation

of **158b** was found to have a rate constant almost five times that observed when the reaction was performed in the presence of **107** (**Table 19**). The kinetic studies also revealed that although the reactions performed in the presence of **107** and sodium hydroxide appeared similar, there are some clear differences. In the reactions promoted by **107** the k_1 value calculated by least squares fitting, was almost ten times larger than the k_2 value, however, in the reactions promoted by sodium hydroxide the k_1 value was only four times the k_2 value. This indicates that the conversion of the aldol product to the condensation product is slower in the reactions promoted by **107**, and occurs in a very different way to the conversion promoted by sodium hydroxide.

Catalyst	Consumption of **156b**	Formation of **158b**
	k_1 s^{-1} (sd)	k_2 s^{-1} (sd)
NaOH	1.1×10^{-3} (2.51×10^{-4})	2.77×10^{-4} (1.65×10^{-5})
107	5.58×10^{-4} (4.90×10^{-5})	5.59×10^{-5} (1.14×10^{-5})

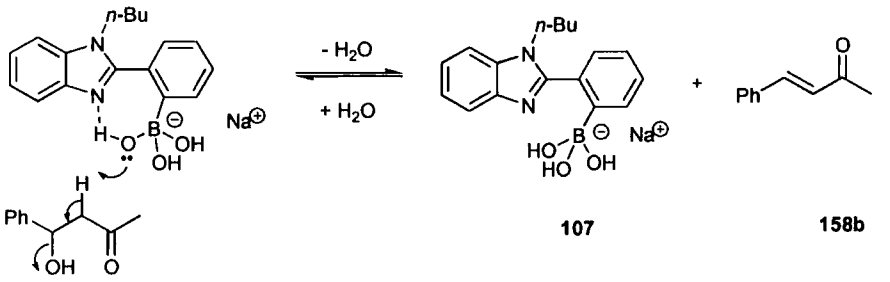
Table 19: Rate constants of the aldol condensation reaction of **156b** and acetone.

The mechanism was further elucidated when the reaction of **156b** and acetone was performed in the presence of **150**, **165** and sodium hydroxide. In this experiment only low levels of activity were observed, indicating that the complex **107** had promoted the aldol condensation reactions of **156a** and **156b** with acetone through a bifunctional mechanism. However, instead of the interaction of the boronate and nitrogen functional groups with the substrate molecules, the results obtained during our investigations suggest that the two functional groups promote the reaction by interacting cooperatively with a hydroxide ion, in a similar way to that suggested by Letsinger *et al.* for the hydrolysis of chloroalcohols by **95**.[53b] As well as deprotonating acetone to form the enolate the complex **163** (**Scheme 38**), this species may also deprotonate the aldol product **157a** as shown in **Equation 93**.



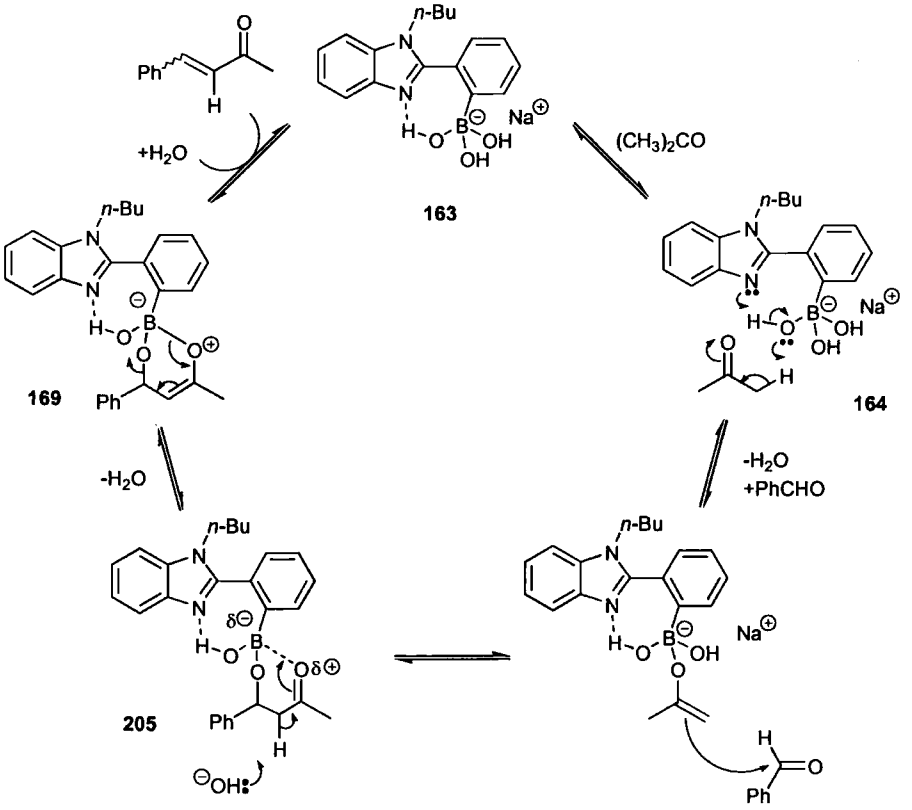
164 163

Scheme 38



Equation 93

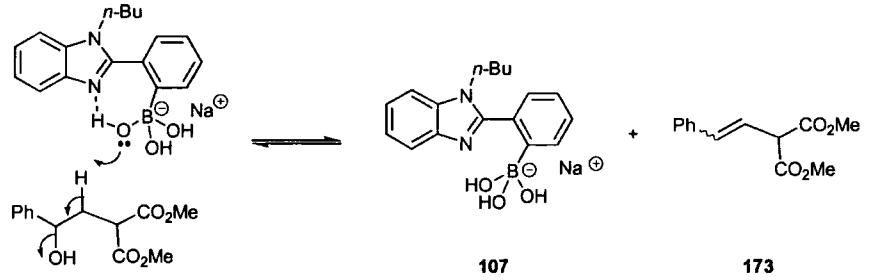
Beyond these steps, the mechanism by which the aldol condensation is promoted by **107** can only be speculated upon. Instead of proceeding through an acyclic transition state as shown in **Equation 93**, the aldol product could become complexed to the boronate group before undergoing deprotonation. This mechanism is certainly plausible as the acetone enolate formed could become complexed to the boronate (**Scheme 38**). If this boron enolate then reacted with benzaldehyde, as can be seen in **Scheme 39**, the aldol product could become complexed to the boronic acid to form a six-membered, cyclic transition state.



Scheme 39

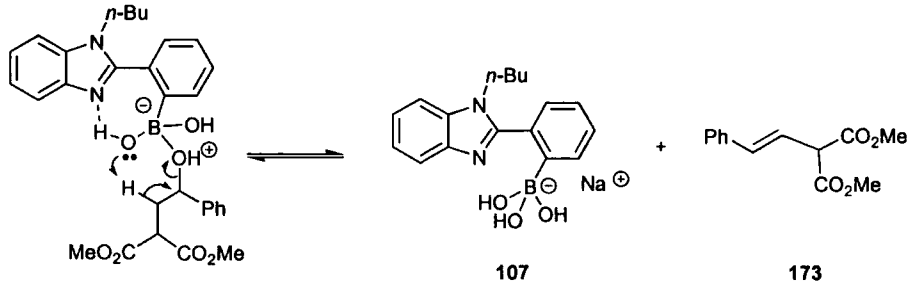
Without further investigation it is not possible to conclude which mechanism occurs in the aldol condensation reactions promoted by **107**. However, it is likely that both of these mechanisms operate, as in the mechanism shown in **Scheme 39**, the acetone enolate and aldol product **157b** would be in competition with hydroxide for complexation to the boronate. Both of the proposed mechanisms would account for the much lower k_2 value calculated in the aldol condensation reactions promoted by **107**, compared to that calculated for the reactions promoted by sodium hydroxide (**Table 19**). In the mechanism suggested in **Scheme 38** and **Equation 93**, the reduced rate of the second step may be due to the need to regenerate the boronate **163** after deprotonation of acetone. Alternatively, if the reaction proceeds through the mechanism shown in **Scheme 39**, then the reduced rate could be due to the formation of the complex **205**, deprotonation and elimination of the condensation product.

Although no mechanistic investigations have been made into the promotion of the Knoevenagel reaction by **107**, due to the similarity between this reaction and the aldol condensation reaction it is likely to proceed though a similar mechanism. As with the mechanism previously suggested, this can only be speculated upon, however, it is expected that the complex **107** would behave in a similar way to that suggested above (**Scheme 39**). Two possible mechanisms for this process are suggested below (**Equations 94 and 95**).



107 **173**

Equation 94



107 **173**

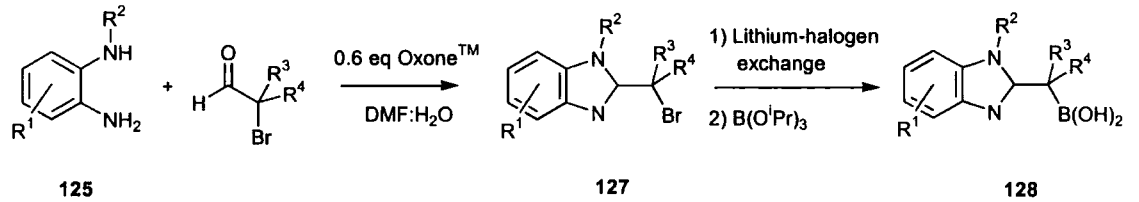
Equation 95

Section 4.4

As well as the development of the reactions in which **107** is known to be active; this complex may also be active in a number of other reactions. Due to the success of the approach used previously in the investigations into the use of **107** as a catalyst, it was thought this would be the most appropriate approach to take in future investigations. As well as the nitro-aldol reaction, which previous research performed within the research group has indicated may be susceptible to catalysis by **107**, a number of other promising reactions have been considered.[55] Amongst these were the Baylis-Hillman reaction, the Mukaiyama aldol, vinylogous Mukaiyama aldol and possibly the Baeyer-Villiger reaction, and it was even thought that the benzimidazole **107** may be capable of promoting cascade reactions similar to these such as the Mannich and Maitland-Japp reactions.[113,114,115,116] These reactions are either known to be promoted by both acids and bases, or appear to be amenable to bifunctional catalysis.

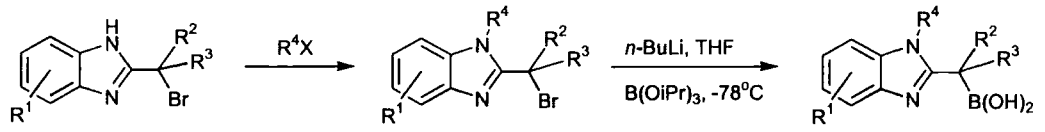
Section 4.4.1

During our investigations into the potential of the bifunctional benzimidazoles to behave as catalysts, a number of synthetic approaches to these compounds had been developed. The flexibility offered by these alternative approaches potentially allows an extensive range of analogues based on these benzimidazoles structures to be prepared (**Chapter 2**). The approaches can be split into two categories; those in which the backbone of the benzimidazole can be altered for example **Scheme 40**, and those in which the side chain can be altered (**Scheme 41**). By using both of these approaches it should be possible to prepare an extensive range of analogues.



125 **127** **128**

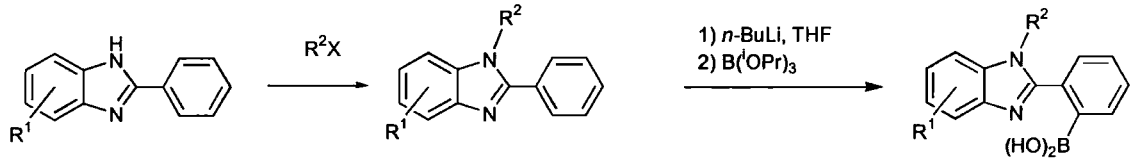
Scheme 40



130 131 128

Scheme 41

It had also been found that these compounds could be accessed by directed metalation, which does not require the preparation of a bromide such as **131**. This approach to the synthesis of analogues of **107**, was very interesting as it could potentially be achieved through a one-pot reaction (**Scheme 42**). However, a disadvantage of this route is that it may be difficult if the benzimidazole contains directing groups other than the nitrogen atoms of the benzimidazole backbone, which would interfere with the directed metalation.



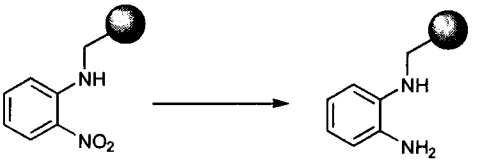
207 207 208

Scheme 42

The complementary use of these approaches may allow the synthesis of analogues with novel backbone substitution patterns and structures as well as a range of side chains. As well as allowing analogues of **107** with novel structures and activities to be prepared, it is hoped that the preparation analogues of **117** will allow the structure-activity relationships of these compounds to be investigated. By optimising the structure of the boronate, as well as the reaction conditions, it should be possible to prepare an effective range of catalysts based on **107**.

Although our attempts to prepare a solid supported version of **107** faltered when we were unable to find suitable conditions for the reduction of the pendant 2-nitrobenzene **201**, it is thought that this can be achieved through the use of other reagents such as Wilkinson's catalyst, or through transfer hydrogenation.[110] From the diamine **202**, we are confident that the supported benzimidazole **204** can be prepared as well as a range of analogues. As well

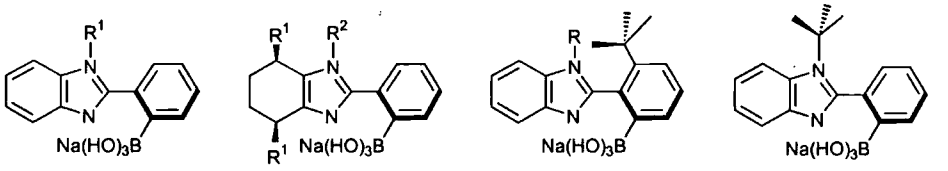
as the preparation of solid supported benzimidazoles using the resin Argogel^{TM}-NH_2, it was thought that other resins, possiby macroporous resins such as Argopore^{TM}, could be used and may display interesting activities.



201 202

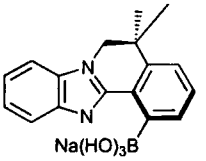
Equation 96

As well as the development of solid supported versions of the complex **107**, it may also be possible to prepare chiral versions of these benzimidazoles. As the complex **107** has already been found to be active in a number of reactions, it is thought that it may also have activity in reactions that result in the formation of chiral centres. As the complex **107** is thought to be active due to the delivery of a hydroxide group held within in the molecule, between the amino group and the boronic acid, then it is thought that a chiral version of **107** may be capable of delivering hydroxide in an asymmetric way.



209 210 211 212

Due to the formation of internal nitrogen to boron donation in compounds such as **107**, it is thought that the development of catalysts such as **209** in which the chirality is based on the twist of the biaryl system would be unsuitable. Therefore, although chirality can be introduced into these molecules in a number of ways, the most effective ways are thought to be through the backbone of the molecule through the introduction of pendant chiral groups as shown in **210** or **211**, through the side chain **212**, perhaps by tethering the two rings together as shown in **213**.



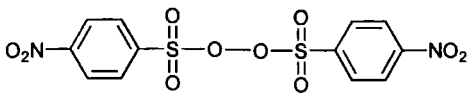
213

Experimental Section

General Experimental

All starting materials were obtained commercially from Aldrich, Lancaster or Fluka and were used as received or prepared by known methods, unless otherwise stated. Solvents were also used as received or dried by known methods, unless otherwise stated. In the case of DCM and toluene this involved refluxing over $CaCO_3$ under argon and in the case of ether and THF involved refluxing over sodium and benzophenone under argon. Purification by column chromatography was performed using Lancaster silica gel with pore size 60 Å, 40 Å or Florasil®. TLC was carried out using Merck aluminium-backed or plastic-backed pre-coated plates. TLC plates were analysed by UV at 254 and 365 nm, and visualisation was performed using standard solutions of 4-anisaldehyde, vanillin or PMA. NMR spectra were recorded at 200, 300 or 400 MHz using a Varian Mercury 200 MHz spectrometer, Varian Unity 300 MHz spectrometer or a Brucker 400 MHz spectrometer, respectively, unless otherwise stated. Electrospray (ES) mass spectra were recorded using a Micromass LCT spectrometer. Infra red spectra were obtained using FT1600 series spectrometer. Ultra-violet spectra were measured using a Unicam UV-Vis UV2 spectrometer. Melting points were measured with an Electrothermal apparatus and were uncorrected. Evaporations were carried out at 20 mmHg using a Büchi rotary evaporator and water bath, followed by evaporation to dryness under vacuum (<2 mmHg). Chloroform used in the preparation of the phosphoryl compounds was Aldrich HPLC grade 99.9% stabilised with amylases.

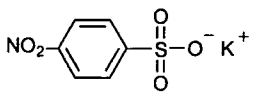
Experiment 1 (Equation 7, Section 1.2.1): *Preparation of 4-(nitrobenzenesulfonyl)peroxide* ***50a.***



50a

To a solution of K_2CO_3 (5.10 g, 36.9 mmol) in H_2O (76 ml), ethanol (38 ml) and hydrogen peroxide (35%, 8.75 g) at -20 °C a cooled solution (-20 °C) of

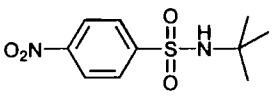
4-nitrobenzenesulfonyl chloride (7.88 g, 35.6 mmol) in chloroform (10 ml) was added and the suspension was mixed at full power for 1 minute using a Breville Classique™ blender. Ethanol (80 ml) was added, the solution was mixed for 4 minutes at low power, followed by filtration and recovery of the yellow precipitate formed by filtration. The recovered precipitate was washed with distilled water and recrystallized (acetone) to give **50a** as a yellow solid (2.22 g, 31%). All spectroscopic and analytical properties were identical to those in the literature, except the unreported values given below;[24,25] mp 109.3-112.7 °C (lit.[25]); ν_{max} (nujol)/cm^{-1} *inter alia* 3103, 3065 (Ar), 2921 (CH), 1529 (NO_2), 1461 (SO_2) and 819 (*para*-substituted aromatic); δ_H (200 MHz, $CDCl_3$) 8.18 (d, *J* 9 Hz, 2 H, ArH), 8.48 (d, *J* 9 Hz, 2 H, ArH); δ_C (100 MHz, $CDCl_3$) 123.5 ($PhSO_2$), 126.0 (*C*H aromatic), 140.0 (*C*H aromatic), 148.0 ($PhNO_2$).



52

The filtrate of the reaction mixture was set aside at -20°C for 24 hours and 4-nitrobenzenesulfonic acid potassium salt monohydrate **52** was obtained as yellow crystals which were collected on filtration (0.160 g, 1%). All spectroscopic and analytical properties were identical to those in the literature;[26] mp >320 °C (lit.[26])

Experiment 2 (Equation 8, Section 1.2.1): *Synthesis of N-*tert*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine **51a**.*



51a

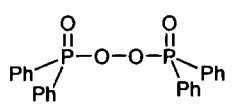
To a stirred, cooled (-78 °C) suspension of **50a** (1.15 g, 2.83 mmol) in anhydrous DCM (75 ml) under argon, *t*-butylamine (0.316 g, 4.23 mmol) was carefully added. After 2 hours, the reaction mixture was filtered through a short silica gel column (DCM as eluent) and the solvent was evaporated to give **51a** as a pale yellow solid (0.230 g, 60%), which on standing decomposed quickly at room temperature. All characterisation and analytical data was identical to that reported in the literature,[24] except the following unreported values below; δ_H (200 MHz, $CDCl_3$) 0.97 (s, 9 H, $C(CH_3)_3$), 8.19 (d, *J* 9.2 Hz, 2 H, ArH) and 8.40 (d, *J* 9 Hz, 2 H, ArH); δ_C (200 MHz, $CDCl_3$) 26.0 (CH_3C), 57.5 (CH_3C), 124.0 (ArH), 129.0 (ArH), 131.3 ($ArSO_2$) and 141.0 ($ArNO_2$).

Experiment 3 (Equation 11, Section 1.2.1): *Attempted synthesis of N-(4-methoxybenzene)-O-(4-nitrobenzenesulfonyl)hydroxylamine* ***51d.*** To a cooled (-40 °C) suspension of **50a** (2.68 g, 6.63 mmol) in anhydrous diethyl ether (70 ml) under argon, 4-methoxyaniline (0.957 ml, 13.3 mmol) was carefully added. The solution was stirred at -40 °C for 2 hours, and was then filtered through a short silica gel column (40 Å, diethyl ether eluent, -20 °C). The residue obtained was evaporated to dryness at -20 °C to give a white waxy solid (0.46 g). No evidence for the formation of **50a** was found except for the data given below; *m/z* ES (+) 325.6 (MH, 13.3%) 226.0 (NsONa, 27.7%).

Experiment 4 (Equation 12, Section 1.2.2): *Reaction of N-*tert*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine* ***51a*** *with cyclobutanone.* A cooled (-78 °C) solution of **51a** (0.293 g, 1.07 mmol) in anhydrous dichloromethane (3 ml) was treated with 0.9 equivalents of cyclobutanone (0.073 ml, 0.965 mmol). The resultant solution was warmed slowly to room temperature whilst being shaken to mix. Triethylamine (0.410 ml, 2.94 mmol) was added and after stirring for 30 min the solvent was removed under reduced pressure to give a pale yellow oil (0.032 g), which was subjected to Krugelröhr distillation (5-2 mmHg).

Experiment 5 (Equation 13, Section 1.2.2): *Reaction of N-*tert*-butyl-O-(4-nitrobenzenesulfonyl)hydroxylamine* ***51a*** *with cyclobutanone.* A cooled (-50 °C) solution of **51a** (0.088 g, 0.32 mmol) in $CDCl_3$ (0.7 ml) under argon, was treated with cyclobutanone (0.023 ml, 0.30 mmol). The reaction was slowly warmed to room temperature and mixed by shaking. The resultant solution was treated with triethylamine (0.122 ml, 0.88 mmol) and the reaction was analysed by ^{1}H NMR ($CDCl_3$) over a period of 42 hours. As no reaction was observed by ^{1}H NMR during this time, the reaction was not worked-up.

Experiment 6 (Equation 15, Section 1.2.3): *Synthesis of diphenylphosphinic peroxide* ***60.***

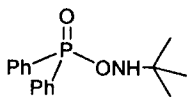


60

To a cold (-5 °C) solution of sodium peroxide 98% (1.468 g, 19.0 mmol) in H_2O (34 ml), a solution of diphenyl phosphinic chloride (5.69 ml, 23.6 mmol) in toluene (14 ml) was added drop-wise. The

solution was stirred for 20 minutes at 0 °C, insoluble impurities were removed by filtration, and the solvent was evaporated yielding the peroxide **60** as a white powder (1.94 g, 47%), which decomposed quickly at room temperature. Due to the thermal instability of this peroxide and the possible risk of explosion, the melting point was not recorded. However, all other characterisation data was found to be consistent with that reported in the literature.[34]

Experiment 7 (Equation 16, Section 1.2.3): *Synthesis of* N-tert-*butyl-O-(diphenylphosphoryl)hydroxylamine* ***58a.***



58a

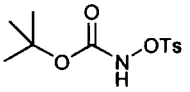
To a stirred, cooled (-78 °C) suspension of **60** (1.15 g, 2.83 mmol) in DCM (75 ml) under argon, *t*-butylamine (0.316 g, 4.23 mmol) was carefully added. After 2 hours, the reaction mixture was filtered through a short Florasil® column (DCM eluent, -40 °C) and the solvent was evaporated to give **58a** as a pale yellow solid (0.230 g, 60%), which decomposed quickly on standing at room temperature. The characterisation data of **58a** which could be obtained was found to be identical to that reported in the literature, except the following unreported data;[32a] δ_C (200 MHz, $CDCl_3$) 26.8 [C(CH_3)$_3$], 56.6 [C(CH_3)$_3$], 124.9 [PhP(O)], 128.8 (Ph), 131.7 (Ph) and 132.2 (Ph).

Experiment 8 (Equation 18, Section 1.2.3): *Attempted synthesis of N-(prop-3-ene)-O-(diphenylphosphoryl)hydroxylamine* ***58c.*** A suspension of the peroxide **60** (0.673 g, 1.55 mmol) at -78 °C, in HPLC grade chloroform (15 ml) under argon, was treated carefully with allyl amine (0.237 ml, 3.10 mmol). The resultant solution was stirring at -40 °C for 2 hours, after which the solvent was removed under reduced pressure and a white residue was obtained (0.066 g), which was thought to contain, amongst other compounds **58c**, due to the observation of data consistent with the values expected for this compound;[32] *m/z* ES (+) 296.1 (MNa, 77.1%) 226.0 (NsONa, 27.7%).

Experiment 9 (Equation 19, Section 1.2.4): *Reaction of* N-tert-*butyl-O-(diphenylphosphoryl)hydroxylamine* ***58a*** *with cyclobutanone.* To a cooled (-55 °C) solution of **58a** (0.039 g, 0.136 mmol) in $CDCl_3$ (0.7 ml) under argon, cyclobutanone was

added (0.009ml, 0.122 mmol). The reaction was slowly warmed to room temperature and mixed by shaking, after which triethylamine (0.038 ml, 0.272 mmol) was added and the reaction analysed by ^{1}H and ^{31}P NMR ($CDCl_3$) over a period of 3 days. As no reaction was observed by ^{1}H NMR during this time, the reaction was not worked-up.

Experiment 10 (Equation 20, Section 1.2.5): *Synthesis of N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61**.*



61

Method A: To a solution of Boc-hydroxylamine **62** (0.781 g, 5.75 mmol) in anhydrous dichloromethane (10 ml) under argon, a solution of tosyl chloride (1.051 g, 5.46 mmol) in anhydrous dichloromethane (8 ml) was added. The resultant solution was stirred at <0 °C for 20 minutes, after which triethylamine (0.72 ml, 5.14 mmol) was added. The reaction mixture was allowed to warm to room temperature, stirred for 1 hour, quenched with H_2O (10 ml) and the aqueous layer was extracted into diethyl ether (3 x 30 ml). The combined organic extracts were washed with saturated bicarbonate solution (3 x 9 ml), 5% HCl (3 x 9 ml) and brine (3 x 9 ml). After drying ($MgSO_4$) and evaporation, the resulting solid was recrystallized (diethyl ether:hexane) to give pale yellow crystals of **61** (0.170 g, 10%). The characterisation data which could be obtained was found to be identical to the literature, unreported values are given below except the melting point which, due to the thermal instability of this peroxide and the possible risk of explosion, was not recorded;[37] ν_{max}/cm^{-1} *inter alia* 3192 (amide), 3117 (Ar), 2934 (CH), 2856 (CH), 1706 (CO), 1153 (ester), 1192 (ester) and 819 (*para*-Ar); δ_H (200 MHz, $CDCl_3$), 1.30 (s, 9 H, $C(CH_3)_3$], 2.43 (s, 3 H, CH_3), 7.36 (d, *J* 8.4 Hz, 2 H, ArH) 7.60 (s, 1 H, NH) and 7.88 [d, *J* 8.4 Hz, 2 H, ArH); δ_C ($CDCl_3$, 100 MHz), 22.0 (CH_3), 27.9 ($C(CH_3)_3$), 84.1 ($OC(CH_3)_3$), 129.8 (ArH), 129.9 (ArH), 130.8 ($ArCH_3$), 146.2 ($ArSO_2$) and 154.4 (NHC(O)O); *m/z* ES(+) *inter alia* 285.9 (M-H, 40.3%) and 309.9 (MNa, 92.7%).

Method B: To a solution of Boc-hydroxylamine **62** (2.047 g, 15.1 mmol) in a mixture of toluene and dichloromethane (1:3, 25 ml), was added a solution of tosyl chloride (2.906 g, 15.1 mmol) in a mixture of toluene and dichloromethane (1:3, 20 ml). The resultant solution was stirred at <0°C for 20 minutes, after which triethylamine (1.9 ml, 13.6 mmol)

was added. The reaction mixture was allowed to warm to room temperature, stirred for 3 hours, quenched with H_2O (10 ml) and the aqueous layer extracted into diethyl ether. The organic layer was washed with saturated bicarbonate solution (3 x 9 ml), 5% HCl (3 x 9 ml), and brine (3 x 9 ml). The organic layer was dried ($MgSO_4$), evaporated and the crude solid (1.60 g) recrystallized (diethyl ether:hexane) to give pale yellow crystals (1.00 g, 37.5%). All spectroscopic and analytical properties were found to be identical to that reported in the literature and to that obtained from the experiment described above.[37]

Experiment 11 (Table 1, Section 1.2.6): *Screening experiment **61** with benzophenone, cyclobutanone and chalcone in the presence of copper(II) complexes, pyridine and triphenylphosphine.* Reactions performed using $CuCl_2$ (0.012 g, 0.008 mmol) were carried out in 1.5 ml screw-top vials which were charged with the metal complex and then treated with solutions of either pyridine (0.6 µl, 0.008 mmol) in DCM (0.1 ml), triphenylphosphine (0.009 g, 0.03 mmol) in DCM (0.1 ml), blank solvent DCM (0.1 ml) or a combination thereof. The resultant solutions were treated with **61** (0.01 g, 0.03 mmol) and one of the carbonyl compounds: benzophenone (0.006 g, 0.03 mmol), cyclobutanone (0.003 ml, 0.03 mmol) or chalcone (0.007 g, 0.03 mmol) in DCM (0.2 ml). The solution was stirred at room temperature for 1 week, after which the reactions which appeared to have undergone reaction by TLC, were worked-up by filtration through a short plug of silica (60 Å) and Amberlite® (MB-1) with DCM. The reactions which used $Cu(OTf)_2$ were performed in small screw-top vials which had been charged with the copper complex (0.001 g, 0.0028 mmol), followed by pyridine (6.7 µl, 0.008 mmol) in DCM (0.1 ml), triphenylphosphine (0.087 g, 0.33 mmol) in DCM (0.1 ml), blank solvent DCM (0.1 ml) or a combination thereof. The resultant solutions were then treated with **61** (0.079 g, 0.28 mmol) and one of the carbonyl compounds: benzophenone (0.006 g, 0.03 mmol), cyclobutanone (0.003 ml, 0.03 mmol) and chalcone (0.007 g, 0.03 mmol) in DCM (0.2 ml).

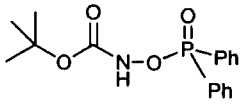
Experiment 12 (Equation 23, Section 1.2.6): *Reaction of N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** with cyclobutanone in the presence of $BF_3.OEt_2$ and $(^iPr)_2NEt$.* To a solution of **61** (0.038 g, 0.135 mmol) and cyclobutanone (10.3 µl, 0.135 mmol) in dichloromethane (1 ml), was added diisopropylethylamine (21.7 µl, 0.135 mmol) and $BF_3.OEt_2$ (17.3 µl, 0.139 mmol) at room temperature. The resulting solution

was stirred at room temperature for 24 hours. As no evidence of reaction had been observed during this time, the reaction was not worked-up.

Experiment 13 (Equation 24, Section 1.2.6): *Reaction of N-Boc-O-(4-methylbenzenesulfonyl)hydroxylamine **61** with cyclobutanone in the presence of TsOH.* A solution of cyclobutanone (10.3 µl, 0.135 mmol) in DCM (1 ml) at 0 °C was treated with 10 mol% tosic acid (0.004 g, 0.019 mmol). Followed by a solution of **61** (0.055 g, 0.190 mmol) in DCM (2 ml). The resulting mixture stirred at room temperature for 2 hours and then refluxed for 22 hours. The solvent was evaporated and the residue obtained was partitioned between H_2O and DCM, neutralised with saturated aqueous Na_2CO_3. After separation of the layers, the aqueous layer was extracted twice more with DCM (30 ml), and the combined organic layers obtained were dried ($MgSO_4$) and evaporated to give a pale yellow oil (0.010 g). This crude product was found by NMR to contain only the starting materials.

Experiment 14 (Equation 25, Section 1.2.7): *Synthesis of N-Boc-O-(diphenylphosphoryl)hydroxylamine **65**.*

A solution of Boc-hydroxylamine **62** (6.39 g, 0.048 mol) in anhydrous DCM (160 ml) and anhydrous toluene (320 ml), was cooled to 0 °C under argon, and treated with 1.2 equivalents of triethylamine (6.021 g, 0.0595 mol). The resulting solution was stirred for 30 minutes and diphenylphosphinyl chloride (9.16 ml, 0.048 mol) was added and the solution warmed to room temperature and stirred for a further 72 hours. After evaporation, the resulting solid was recrystallized from dichloromethane to give white crystals of **65** (12.14 g, 76%). The characterisation data which could be obtained for this material is given below. However, due to the thermal instability of this peroxide and the possible risk of explosion, the melting point was not recorded; δ_H (200 MHz, $CDCl_3$) 1.39 [s, 9 H, $C(CH_3)_3$], 7.44-7.48 (m, 4 H, ArH) 7.53-7.57 (m, 2 H, ArH), 7.94-7.99 (m, 4 H, ArH) and 8.63 (broad s, 1 H, NH); δ_C (100 MHz, $CDCl_3$) 27.9 (CH_3), 83.1[$C(CH_3)_3$], 128.4 (ArH), 128.5 (ArH), 129.5 (ArP(O)), 132.4 (ArH), 132.8 (ArH) and 156.2 (ArH); δ_P (81 MHz, $CDCl_3$) 40.96; *m/z* ES (+) 233.3 (M-Boc, 82%) and 356.33 (45).



65

Experiment 15 (Table 2, Section 1.2.8): *Screening experiment of **65** with cyclobutanone in the presence of a range of Lewis acids and bases.* **a)** A 96 well Robbins Block™ was charged with **65** (0.033 g, 0.1 mmol) as solutions in either DCM (0.5 ml), MeOH (0.5 ml), MeCN (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). The mixtures were then treated with cyclobutanone (0.007 ml, 0.1 mmol), and the respective wells were treated with the metal complexes AgI (0.023 g, 0.1 mmol), $BF_3.OEt_2$ (0.0126 ml, 0.1 mmol), CuBr (0.014 g, 0.1 mmol), Cu(OTf) (0.052 g, 0.1 mmol), $CuBr_2$ (0.022 g, 0.1 mmol) or $Cu(OTf)_2$ (0.036 g, 0.1 mmol), either as solutions in the respective solvents as solids. The resultant mixtures were then treated with diisopropylethylamine (0.017 ml, 0.1 mmol) and the block was shaken to mix the reactions for 24 hours. The reaction mixtures were then filtered through a 96 well Robbins block™ packed with silica gel (40 Å, MeCN as eluent) and the solutions were evaporated to dryness before dilution and analysis by LCMS (ES +).

b) A 48 well Robbins Block™ was charged with portions of **65** (0.033 g, 0.1 mmol) as solutions in either dichloromethane (0.5 ml) or MeOH (0.5 ml). Cyclobutanone (0.007 ml, 0.1 mmol) was added to these mixtures and then the metal complexes; $FeBr_2$ (0.022 g, 0.1 mmol), $Fe(OAc)_2$ (0.018 g, 0.1 mmol), $FeBr_3$ (0.030 g, 0.1 mmol), $MnBr_2$ (0.026 g, 0.1 mmol), $MnCO_3$ (0.011 g, 0.1 mmol), $Pd(0)(PPh_3)_3$ (0.022 g, 0.1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), $PtBr_2$ (0.035 g, 0.1 mmol), $PtCl_4$ (0.034 g, 0.1 mmol), $RuCl_2(PPh_3)_3$ (0.096 g, 0.1 mmol) or $RuCl_3$ (0.021 g, 0.1 mmol) were added as solutions in MeOH or DCM (0.5 ml) or as solids followed by the solvent (0.5 ml). Finally the reaction mixtures were treated with triethylamine (15 µl, 0.1 mmol) and the reactions were shaken to mix for 24 hours. The reactions were worked-up by filtration through a Robbins block™ packed with silica gel (40 Å, MeCN as eluent) and the residues obtained on evaporation were diluted and analysed by LCMS (ES +).

Experiment 16 (Table 3, Section 1.2.9): *Screening experiment of **66** with cyclobutanone in the presence a range of Lewis acids and bases.* Small (2.5 ml) screw-top vials were charged with 10, 50 or 100 mol% of either $BF_3.OEt_2$ [(0.0038 ml, 0.03 mmol), (0.019 ml, 0.15 mmol) or (0.038 ml, 0.3 mmol)], $Ru(PPh_3)_2$(Salen) **68** [(0.032 g, 0.03 mmol), (0.155 g, 0.15 mmol) or (0.311 g, 0.3 mmol)], $RuCl_2(PPh_3)_3$ [(0.037 g, 0.03 mmol), (0.185 g, 0.15 mmol) or (0.367 g, 0.3 mmol)], or $CuClO_4.4MeCN$ [(0.010 g, 0.03 mmol), (0.049 g, 0.15 mmol) or (0.098 g, 0.3 mmol)]. To these metal complexes N-bromoacetamide **66** (0.043 g,

0.3 mmol) and cyclobutanone (22 μl, 0.3 mmol) were added as solutions in DCM (1.5 ml). Finally, 10, 50 and 100 mol% of either of the bases 2,6-lutidine [(0.004 ml, 0.03 mmol), (0.018 ml, 0.15 mmol) or (0.035 g, 0.3 mmol)], diisopropylethylamine [(0.005 ml, 0.03 mmol), (0.027 ml, 0.15 mmol) or (0.053 g, 0.3 mmol)] or N,N-diethyl aniline [(0.005 ml, 0.03 mmol), (0.024 ml, 0.15 mmol) or (0.048 g, 0.3 mmol)] were added. The reactions were stirred at room temperature for 24 hours during which samples were taken from the vials and filtered through columns containing silica gel (60 Å), Amberlite® (MB-1) and $MgSO_4$ layers separated by sand. The samples were pushed through these columns in parallel using a sample handling station (Supelco, Visiprep™ 24, DCM as eluent). The solvent was evaporated from each fraction, and the residues obtained were diluted and analysed by GC (initial temperature 60°C, hold time 5 minutes, rate 10 °C/min, final temperature 220 °C, column was 20 m carbowax/polyethylene gylcol).

Experiment 17 (Table 4, Section 1.2.9): *Screening experiment of **66** with cyclobutanone in the presence a range of Lewis acids and bases.* Small (2.5 ml) screw-top vials were charged with 10, 50 or 100 mol% of either $Yb(OTf)_3$ [(0.025 g, 0.042 mmol), (0.129 g, 0.208 mmol) or (0.243 g, 0.42 mmol)], MgI_2 [(0.013 g, 0.042 mmol), (0.056 g, 0.208 mmol) or (0.118 g, 0.42 mmol)] or PhCu(OTf) [(0.016 g, 0.042 mmol), (0.067 g, 0.208 mmol) or (0.132 g, 0.42 mmol)]. Or in the reactions which were performed in the presence of a number of different concentrations of diisopropylethylamine [(20 mol%, 0.01 ml, 0.069 mmol), (50 mol%, 0.03 ml, 0.208 mmol) or (100 mol%, 0.07 ml, 0.42 mmol)], N,N-diethylaniline [(5 mol%, 0.01 ml, 0.021 mmol), (50 mol%, 0.1 ml, 0.208 mmol) or (100 mol%, 0.3 ml, 0.42 mmol)] or pyridine [(50 mol%, 2 ml, 0.208 mmol) or (100 mol%, 3 ml, 0.42 mmol)]. Each reaction was then treated with a solution of acetophenone (0.05 g, 0.416 mmol) as a solution in either dichloromethane or MeOH (0.5 ml), followed by a solution of **66** (0.57 g, 0.416 mmol) in either DCM or MeOH (0.5 ml). The reactions were stirred at room temperature for 1 week, after which those reactions which appeared by TLC to have shown some conversion were worked-up by filtration through a short silica gel columns (60 Å, DCM as eluent).

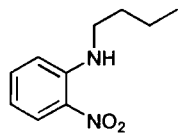
Experiment 18 (Table 5, Section 1.2.9): *Reaction of 67 with cyclobutanone in the presence of Cu(OTf)$_2$.Ph.* A solution of benzophenone (0.383 g, 2.10 mmol) by anhydrous MeCN (10 ml) was treated with chloroamine T **67** (1.435 g, 6.30 mmol) and Cu(OTf)$_2$.Ph (0.116 g, 2.07 mmol). The resultant solution was stirred at room temperature for 4 days. The reaction was then quenched by addition of saturated aqueous Na_2CO_3 solution (5 ml), followed by separation and extraction of the aqueous layer into diethyl ether (3 x 15 ml) and drying ($MgSO_4$). The crude product was obtained on evaporation of the solvents under reduced pressure (1.446 g), and was found by NMR spectroscopy to contain starting materials.

Experiment 19 (Table 6, Section 1.2.9): *Screening experiment of 67 with cyclobutanone in the presence the copper complex Cu(OTf)$_2$.Ph.* **a)** The wells of a 96 and 48 well Robbins blocks™ were charged with **67** (0.023 g, 0.1 mmol) as solutions in either DCM (0.5 ml), MeOH (0.5 ml), MeCN (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). The mixtures were then treated with a solution (0.5 ml) of cyclobutanone (0.007 ml, 0.1 mmol), and the respective wells were treated with the metal complexes; AgI (0.023 g, 0.1 mmol), CuBr (0.014 g, 0.1 mmol), Cu(OTf) (0.052 g, 0.1 mmol), $CuBr_2$ (0.022 g, 0.1 mmol), Cu(OTf)$_2$ (0.036 g, 0.1 mmol), $RuCl_2(PPh_3)_3$ (0.096 g, 0.1 mmol), $RuCl_3$ (0.021 g, 0.1 mmol), $Pd(PPh_3)_4$ (0.022 g, 0.1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), $PtBr_2$ (0.035 g, 0.1 mmol), $PtCl_4$ (0.034 g, 0.1 mmol), $MnCO_3$ (0.011 g, 0.1 mmol), $MnBr_2$ (0.026 g, 0.1 mmol), $Fe(OAc)_2$ (0.018 g, 0.1 mmol), $FeBr_2$ (0.022 g, 0.1 mmol), $FeBr_3$ (0.030 g, 0.1 mmol),or $BF_3.OEt_2$ (0.013 ml, 0.1 mmol), either as solutions in the respective solvents or as solids followed by the solvent (0.5 ml). The resultant mixtures were then treated with diisopropylethylamine (0.017 ml, 0.1 mmol) or the corresponding solvent. The Robbins blocks™ were sealed and then shaken to mix the reactions for 24 hours. The reaction mixtures were then pushed through complimentary Robbins blocks™ packed with silica gel (40 Å, MeCN as eluent) and the solutions collected were evaporated to dryness before being diluted and analysed by LCMS.

b) The wells of a 64 well Robbins Block™ were charged with **67** (0.023 g, 0.1 mmol), followed by either DCM (0.5 ml) or MeOH (0.5 ml). The mixtures were then treated with a solution (0.5 ml) of cyclobutanone (0.007 ml, 0.1 mmol), and the metal complexes; $RuCl_2(PPh_3)_3$ (0.096 g, 0.1 mmol), $RuCl_3$ (0.021 g, 0.1 mmol), $Pd(PPh_3)_4$, (0.022 g, 0.1

mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), $PtBr_2$ (0.035 g, 0.1 mmol), $PtCl_4$ (0.034 g, 0.1 mmol), $MnCO_3$ (0.011 g, 0.1 mmol), $MnBr_2$ (0.026 g, 0.1 mmol), $Fe(OAc)_2$ (0.018 g, 0.1 mmol), $FeBr_2$ (0.022 g, 0.1 mmol), or $FeBr_3$ (0.030 g, 0.1 mmol) either as solutions in the respective solvents or as solids followed by the solvent (0.5 ml). The reactions were then treated with triethylamine (0.015 ml, 0.1 mmol) or the respective solvent alone and the Robbins blocks™ were shaken to mix the reactions for 24 hours. The reaction mixtures were then pushed through a complimentary Robbins block™ packed with silica gel (40 Å, MeCN as eluent) and the solutions collected were evaporated to dryness before being diluted and analysed by LCMS.

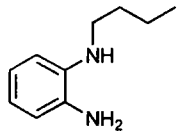
Experiment 20 (Equation 34, Section 2.2.1): *Synthesis of 2-(N-n-butylamine)nitrobenzene **109.***



109

A solution of 2-bromonitrobenzene (18.3 ml, 90.5 mmol) in DMSO (100 ml), was treated with *n*-butylamine (36.0 ml, 360.2 mmol) and the solution refluxed for 20 hours. After cooling to room temperature, the reaction was quenched with H_2O (300 ml), extracted into dichloromethane (3 x 200 ml), the organic extracts were combined and washed with brine (3 x 100 ml), dried ($MgSO_4$) and evaporated to give **109** as a dark brown oil (18.065 g, 102%). The characterisation data for this compound was found to be consistent with the literature data.[55] This compound was used in later stages without further purification.

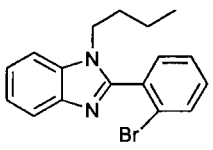
Experiment 21 (Equation 35, Section 2.2.1): *Synthesis of 2-(N-n-butylamine)aniline **110.***



110

A mixture of **109** (18.065 g, 93.10 mmol), 10% Pd/C (1.943 g, 1.83 mmol) and MeOH (75 ml) was saturated with H_2 (1 atm). The mixture was shaken under H_2 for 8 hours, after which the reaction mixture was filtered through Celite® and the solvent evaporated to provide **110** (14.958 g, 98%) as a black solid. The characterisation data of this material was found to be consistent with the literature,[55] and was used in subsequent steps without further purification.

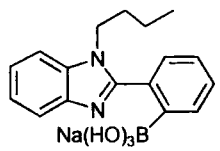
Experiment 22 (Equation 37, Section 2.2.1): *Synthesis of the 2-(2-bromophenyl)-N-n-butylbenzimidazole 111.*



111

A solution of **110** (4.977 g, 30.40 mmol) in DMF (50 ml) and H_2O (1.6 ml), was treated with 2-bromobenzaldehyde (3.5 ml, 30.4 mmol) and Oxone™ (11.008 g, 18.2 mmol). After stirring at room temperature for 12 hours, the reaction was carefully quenched by the addition of an aqueous solution of K_2CO_3 (0.04 M, 310 ml). The resulting suspension was extracted with ethyl acetate (3 x 150 ml) and the combined organic extracts dried ($MgSO_4$) and evaporated. The resulting residue was purified by silica gel chromatography (60 Å, hexane:ethyl acetate, gradient elution) to provide **111** as a viscous pale brown oil (6.936 g, 69%). The characterisation data of this material was found to be consistent with that of **111** prepared previously within the group;[55] ν_{max}/cm^{-1} *inter alia* 3661 (amine), 3391 (amine), 3059 (Ar), 2958 (CH), 2931 (CH), 2871 (CH), 1613 (Ar), 1599 (Ar), 1453, 1393 (CH), 1281 (benzimidazole), 1243 (benzimidazole), 1026 (benzimidazole) and 706 (ArBr); δ_H (400 MHz, $CDCl_3$) 0.71 (t, *J* 7.4 Hz, 3 H, CH_3), 1.11 (hextet, *J* 7.5 Hz, 2 H, $CH_3CH_2CH_2$), 1.61 (quintet, *J* 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 3.98 (t, *J* 7.2 Hz, 2 H, NCH_2CH_2), 7.25-7.46 (m, 6 H, ArH), 7.64-7.66 (m, 1 H, ArH) and 7.76-7.80 (m, 1 H, ArH); δ_C (100 MHz, $CDCl_3$) 13.5 (CH_3), 20.0 (CH_2), 31.5 (CH_2), 44.4 (CH_2), 110.2 (Ar), 120.2 (Ar), 122.4 (Ar), 123.0 (Ar), 124.0 (Ar), 127.4 (Ar), 131.4 (Ar), 132.4 (Ar), 132.9 (Ar), 134.4 (Ar), 145.6 (Ar) and 152.3 (Ar); *m/z* EI (+) inter alia 206.0 (M – CH_2CHCH_2Br, 91%), 284.7 (M-CH_2CHCH_2, 56%), 286.7 (M-CH_2CHCH_2, 56%), 327.8 (MH, 100%) and 329.8 (MH, 99%); HMRS found *m/z* EI (+) 327.8722 (M - H, 95.57%) 329.8390 (M - H, 89.07%) $C_{17}H_{17}N_2Br$ requires 328.2487 and 330.2467.

Experiment 23 (Equation 38, Section 2.2.2): *Synthesis of the 2-(2-boronophenyl)-N-n-butylbenzimidazole sodium hydroxide salt 107.*

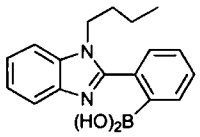


107

A solution of benzimidazole **111** (0.223 g, 0.677 mmol) in ether (7 ml) at -78°C under argon was treated with *t*-BuLi (1.69 ml, 0.52 M in pentane, 0.879 mmol) over a period of 15 minutes. The resultant solution was stirred at -78 °C for 1 hour, treated with $B(O^iPr)_3$ (0.355 ml, 1.54 mmol) and the solution stirred for 48 hours during which it was allowed to warm

slowly from -78 °C to room temperature. NaOH (20% w/v, 7 ml) was then added, and the mixture was stirred at room temperature for 1 hour. The yellow precipitate that formed, was filtered, washed with ether and dried under reduced pressure to give **107** as a white solid (0.161 g, 109%) which was found have similar characterisation data to the material previously prepared within the group;[55] mp 147.7 – 148.9 °C; λ_{max} (EtOH)/nm 225sh, 245sh, 252sh, 297sh and 316 (ε/dm^3 mol^{-1} cm^{-1} 15 015, 9 610, 8 408, 10 811 and 13 513); ν_{max} (KBr)/ cm^{-1} *inter alia* 3418 (amine), 3044 (Ar), 2959 (CH), 2931 (CH), 2873 (CH), 1455, 1397 (CH), 1284 (benzimidazole), 1204, 1173, 1059 (benzimidazole), 959, 897, 866 and 745; δ_H (400 MHz, D_2O) 0.71 (t, *J* 7.4 Hz, 3 H, CH_3), 1.14 (hextet, *J* 7.5 Hz, 2 H, $CH_3CH_2CH_2$), 1.64 (quintet, *J* 7.5 Hz, 2 H, NCH_2CH_2), 3.99 (m, 2 H, NCH_2CH_2), 7.25-7.32 (m, 4 H, ArH), 7.39-7.43 (m, 1 H, ArH), 7.54-7.57 (m, 1 H, ArH), 7.64-7.66 (m, 1 H, ArH) and 7.70 (d, *J* 7.2 Hz, 1 H, ArH); δ_C (400 MHz, CD_3CN:D_2O, 3:1) 10.2, 16.7, 28.3, 41.6, 108.5, 115.3, 119.9, 120.0, 122.7, 126.2, 126.5, 129.0, 129.7, 131.9 and 159.0; δ_B (128 MHz, D_2O) 1.7, 2.9 and 5.6; *m/z* ES (-) 309.5 (M - Na, 22%), 293.5 (M - NaOH, 100%); *m/z* ES (+) 611.4 (2M - Na - 2OH, 35%), 317.2 (M - OH, 100%); HMRS ES (+) found 295.1627, $C_{17}H_{20}O_2N_2B$ requires 295.1630.

Experiment 24 (Equation 39, Section 2.2.3): *Synthesis of the 2-(2-boronophenyl)-N-*n*-butylbenzimidazole **118**.*

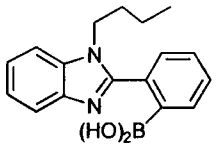


118

A solution of **111** (0.369 g, 1.12 mmol) in diethyl ether (3 ml) at -78°C under argon, was treated with *n*-BuLi (0.90 ml, 2.5 M in pentane, 2.24 mmol) over 30 minutes, and the resultant solution stirred for 1 hour. $B(O^iPr)_3$ (0.52 ml, 2 x 1.12 mmol) was added and the solution stirred for 4 hours at -78°C and allowed to warm to room temperature. The solution was quenched with aqueous NaOH (10% w/v, 2 ml), and stirred at room temperature for 15 minutes. The pH of the solution was adjusted to pH 7 with aqueous HCl (10% w/v) and the resulting precipitate was filtered, washed (diethyl ether) and dried under reduced pressure, giving **118** as a white solid (0.261 g, 79%); mp 235.6 – 239.9 °C; ν_{max} (KBr)/ cm^{-1} *inter alia* 3439 (amine), 3049 (Ar), 2957 (CH), 2930 (CH), 2872 (CH), 1636, 1616 (Ar), 1524, 1461, 1360, 1300 ($ArB(OH)_2$), 1171, 1007 (boroxine) and 953; δ_H (400 MHz, CD_3CN:D_2O, 3:1) 0.90 (t, *J* 7 Hz, 3 H, CH_3), 1.40 (hextet, *J* 7.5 Hz, 2 H, CH_2), 1.90 (quintet, *J* 8 Hz, 2 H, CH_2), 4.55

(t, *J* 7 Hz, 2 H, NCH_2), 7.41-7.51 (m, 4 H, Ar), 7.64-7.67 (m, 2 H, Ar) and 7.79-7.83 (m, 2 H, Ar); δ_C (400 MHz, CD_3CN:D_2O, 3:1) 12.7, 19.3, 31.0, 44.3, 111.3, 114.4, 116.4, 123.0, 123.5, 124.4, 127.5, 129.3, 130.16, 131.0, 133.1, 136.1 and 159; δ_B (128 MHz, CD_3CN:D_2O, 3:1) 12.5, 19.7 and 32.8; *m/z* ES (+) 553.4 (2M - 2OH, 100%), 317.2 (47) and 295.2 (25); Found: C, 60.6; H, 5.2; N, 7.29%. $C_{17}H_{19}O_2N_2B$ requires C, 69.4; H, 6.5; N, 9.5%.

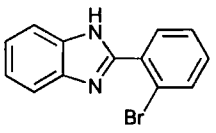
Experiment 25 (Equation 41, Section 2.2.4): *Synthesis of the 2-(2-boronophenyl)-N-*n*-butylbenzimidazole **118**.*



118

A cooled (-78 °C) solution of benzimidazole **111** (0.777 g, 2.36 mmol) in ether (7.3 ml) under argon, was treated with *n*-BuLi (1.90 ml, 2.5 M in pentane, 4.72 mmol) and the resultant solution was stirred for 1 hour. $B(O^iPr)_3$ (1.09 ml, 4.72 mmol) was added and the solution allowed to warm from -78 °C to room temperature over four hours. The solution was then treated with aqueous HCl (20% w/v, 2 ml) until pH 6, and stirred at room temperature for 15 minutes. The pH of the solution was adjusted to pH 7 using aqueous NaOH (20% w/v) and the light brown precipitate formed was filtered, washed with diethyl ether and H_2O and dried in air to give **118** (0.386 g, 56%). This material was found have similar characterisation data to that observed for the material prepared previously (**Experiment 24**), with the exception of the values reported below; mp 231.3 - 236.6 °C; δ_B (128 MHz, CD_3CN:D_2O, 3:1) 10.4 and 33.4; *m/z* ES (+) 277.4 (M - OH, 99.4%).

Experiment 26 (Equation 44, Section 2.3.1): *Synthesis of 2-(2-bromophenyl)benzimidazole **133**.*

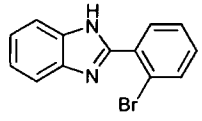


133

A solution of phenylenediamine (1.858 g, 17.2 mmol) in 30:1 DMF:H_2O (31 ml) was treated with 2-bromobenzaldehyde (1.8 ml, 15.5 mmol) and Oxone® (8.13 g, 13.2 mmol). The reaction mixture was stirred at RT for 8 hours, after which the reaction was carefully quenched with an aqueous solution of NaOH (300 ml, 0.04 M). The resulting mixture was extracted into ethyl acetate (3 x 700 ml), separated, dried ($MgSO_4$) and evaporated to give a brown oil (2.348 g) which was subjected to silica gel chromatography (60 Å, hexane:ethyl acetate, gradient elution), followed by

recrystallisation (hexane:ethyl acetate) to give benzimidazole **133** as a pale brown crystalline solid (1.232 g, 26%): mp 229.2-233.8 °C; λ_{max} (EtOH)/nm 206.0sh, 286.6 (ε/dm^3 mol^{-1} cm^{-1} 40 780, 12 012); ν_{max}/cm^{-1} *inter alia* 3661 (amine), 3391 (amine), 3059 (Ar), 2958 (Ar), 1613 (Ar), 1599 (Ar), 1563 (benzimidazole), 1523 (Ar), 1453, 1393, 1365, 1330 (benzimidazole), 1281, 1257 (benzimidazole), 1243, 1024 and 766 (ArBr); δ_H (400 MHz, $CDCl_3$) 7.31-7.34 (m, 3 H, ArH), 7.42-7.44 (m, 1 H, ArH), 7.67-7.71 (m, 3 H, ArH), 8.23-8.25 (m, 1 H, ArH); δ_c (400 MHz, $CDCl_3$) 115.5 (PhBr), 120.4 (*Ar*C), 123.3, 127.2 (ArH), 128.0 (ArN), 130.5 (ArH), 131.2 (ArH), 132.8 (ArH), 134.0 (ArH), 149.8 (*C*Ph); *m/z* (EI) 273.95 (M^+ 100%), 271.94 (M^+ 99%), 193.03 (83); Found: C, 57.1; H, 3.3; N, 10.3%. $C_{13}H_9N_2Br$ requires C, 57.2; H, 3.3; N, 10.3%.

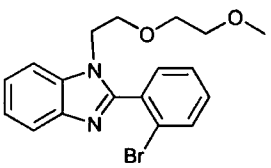
Experiment 27 (Equation 45, Section 2.3.1): *Synthesis of 2-(2-bromophenyl)benzimidazole **133**.*



133

A stirred solution of phenylenediamine (1.377 g, 0.0128 mmol) in anhydrous pyridine (90 ml) under argon was treated with 2-bromobenzaldehyde (7.40 ml, 0.0638 mol). The resultant solution was refluxed for 7 hours and stirred at room temperature for 72 hours. The solution was evaporated to give a crude product (12.629 g) which was purified by recrystallisation (chloroform:toluene) to give **133** (1.070 g, 33%), and was found to have identical characterisation data to that obtained from the experiment as shown above (**Experiment 26**).

Experiment 28 (Equation 46, Section 2.3.2): *Synthesis of 2-(2-bromophenyl)-N-PEG-benzimidazole **136**.*

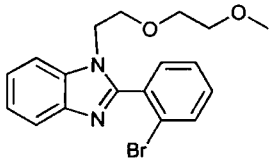


136

A solution of **133** (0.047 g, 0.172 mmol) in anhydrous DMF (1 ml) was treated with K_2CO_3 (0.126 g, 0.86 mmol) and 1-bromo-3,6-dioxaheptane **135** (0.070 ml, 0.516 mmol). The resultant mixture was refluxed for 5 hours diluted with DCM (6 ml), quenched with H_2O (6 ml), and neutralisation with aqueous HCl (10% w/v). The layers were separated, the aqueous layer was extracted with DCM (2 x 2 ml), and the combined organic layers were then dried ($MgSO_4$), and evaporated to give the crude product (0.793 g). The

benzimidazole **136** (0.061 g, 94%) was isolated as an oil after silica gel chromatography (60 Å, chloroform:MeOH, 8:1); λ_{max} (EtOH)/nm 210.7, 217.9 and 273.2 (ε/dm^3 mol^{-1} cm^{-1} 208 986, 256 0084 and 205 771); ν_{max} (Nujol)/cm^{-1} *inter alia* 3177 (amine), 3056 (Ar), 3016 (Ar), 2919 (CH), 2823 (CH), 1669, 1452, 1258 (benzimidazole), 1210, 1129 (ether), 968, 758 (C-Br) and 694; δ_H (400 MHz, $CDCl_3$) 3.28 (s, 3 H), 3.37-3.42 (m, 4 H), 3.69 (t, *J* 6.0 Hz, 2 H), 4.26 (t, *J* 6.0 Hz, 2 H), 7.31-7.57 (m, 6 H, ArH), 7.70-7.72 (m, 1 H, ArH) and 7.84-7.86 (m, 1 H, ArH); δ_c (100 MHz, $CDCl_3$) 44.4 (CH_2), 59.0 (CH_2), 69.2 (CH_2), 70.6 (CH_2), 71.8 (CH_3), 100.0 (Ar), 110.4 (Ar), 114.0 (Ar), 115.6 (Ar), 120.0 (Ar), 122.4 (Ar), 123.0 (Ar), 123.8 (Ar), 127.3 (Ar), 131.5 (Ar), 132.7 (Ar), 132.8 (Ar), 134.7 (Ar); *m/z* ES (+) 375.1 (MH, 89.1%) and 377.1 (MH, 100%); HRMS ES (+) 375.0715 (MH) and 377.0686 (MH) $C_{18}H_{19}O_2N_2Br$ requires 374.2740 and 376.3933.

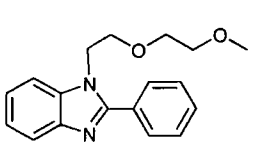
Experiment 29 (Equation 47, Section 2.3.2): *Synthesis of 2-(2-bromo phenyl)-N-PEG-benzimidazole **136**.*



136

A stirred solution of **133** (0.563 g, 2.06 mmol) in THF (5 ml) was treated with a suspension of NaH (0.10 g, 4.12 mmol) in THF (10 ml) under argon, followed by the addition of solid 15-crown-5 (1.23 ml, 5.59 mmol) and 1-bromo-3,6-dioxaheptane (0.84 ml, 6.18 mmol). The mixture was stirred for 4 h, quenched with H_2O (5 ml), the organic layer was separated and washed with distilled water (5 ml). The aqueous washings were combined and re-extracted with DCM (3 x 20 ml), neutralised by addition of aqueous HCl (10% w/v) and re-extracted with DCM (3 x 20 ml). The combined organic extracts were combined, dried ($MgSO_4$) and evaporated to give a crude oil (0.752 g) which was subjected to silica gel chromatography (60 Å, petroleum ether:hexane, gradient elution) to give the benzimidazole **136** as a pale brown oil (0.839 g, 109%). All spectroscopic and analytical details were found to be identical to that obtained from the experiment described above (**Experiment 28**).

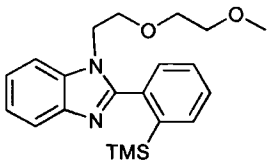
Experiment 30 (Equation 51, Section 2.3.3): *Synthesis of 2-phenyl-N-PEG-benzimidazole **146**.*



146

A stirred solution of 2-phenylbenzimidazole **145** (0.604 g, 3.11 mmol), K_2CO_3 (2.152 g, 15.6 mmol) and DMAP (0.196 g, 1.61 mmol) in anhydrous DMF (30 ml) under argon, was treated with 1-bromo-3,6-dioxaheptane (0.70 ml, 5.15 mmol) and the mixture was refluxed for 5 hours. After evaporation the residue obtained was partitioned between DCM (50 ml) and H_2O (3 x 20 ml), the organic layer was dried ($MgSO_4$), and evaporated to give the crude product (1.522 g). This product was purified by silica gel chromatography (60 Å, hexane:ethyl acetate, gradient elution), to give **146** as a pale yellow oil which solidified upon drying to give oily crystals (0.773 g, 84%); λ_{max} (EtOH)/nm 267.9 (ε/dm^3 mol^{-1} cm^{-1} 1 396); ν_{max} /cm^{-1} *inter alia* 3381.9 (amine), 3185.8 (amine), 3061.1 (Ar), 2923.2 (CH), 2876.3 (CH), 1460.4, 1443.8, 1388.9, 1330.2 (benzimidazole), 1115.2 (ether) and 1025.5; δ_H (400 MHz, $CDCl_3$) 3.31 (s, 3 H, OCH_3), 3.42-3.44 (m, 2 H, OCH_2CH_2OMe), 3.50-3.52 (m, 2 H, OCH_2CH_2OMe), 3.88 (t, *J* 5.8 Hz, 2 H, NCH_2CH_2OR), 4.45 (t, *J* 6.0 Hz, 2 H, NCH_2CH_2OR), 7.31-7.33 (m, 2 H, ArH) 7.51-7.53 (m, 4 H, ArH) and 7.81-7.84 (m, 3 H, ArH); δ_C (100 MHz, $CDCl_3$) 44.7 (CH_2), 59.1 (CH_3), 69.4 (CH_2), 70.8 (CH_2), 71.9 (CH_2), 110.4 (Ph), 120.0 (Ph), 122.5 (Ph), 122.7 (Ar), 128.6 (ArH), 129.7 (ArH), 129.8 (ArH), 130.4 (*Ph*C), 135.8 (ArN), 143.1 (ArN) and 154.2 (Ph*Ar*); *m/z* EI(+) 296.2 (M$^+$, 47%), 221.1 (M - Ar, 30%) and 207.1 (M - C_7H_9, 100%); HRMS EI(+) found 296.1638 (M$^+$, 46.61%), $C_{18}H_{20}N_2O_2$ requires 296.3637.

Experiment 31 (Equation 52, Section 2.3.3): *Synthesis of 2-(2-trimethylsilylphenyl)-N-PEG-benzimidazole **147**.*

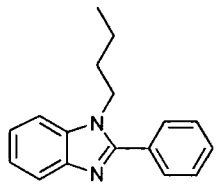


147

A stirred solution of **146** (0.151 g, 0.51 mmol) in anhydrous THF (5 ml) at -78 °C under argon, was treated with *n*-BuLi (0.22 ml, 2.5 M solution in pentane) over a period of 20 minutes. The solution was stirred at -78 °C for 1 hour, after which freshly distilled TMSCl (0.07 ml, 0.56 mmol) was added drop-wise and the mixture stirred for 1 hour at -78 °C. After warming to room temperature, the reaction was quenched with distilled water (25 ml), extracted with EtOAc (3 x 50 ml), the combined extracts were dried

($MgSO_4$), and evaporated to give an oil (0.149 g). This product was purified by silica gel chromatography (60 Å, hexane:ethyl acetate, gradient elution), to give benzimidazole **147** as an oily yellow crystalline solid (0.045 g, 24%); λ_{max} (EtOH)/nm 212.5sh 273.2 and 283.9 (ε/dm^3 mol^{-1} cm^{-1}, 2 778, 2 099 and 2469); (ν_{max}/cm^{-1} *inter alia* 3166 (amine), 3054 (Ar), 2949 (CH), 2802 (CH), 1633 (Ar), 1457, 1382, 1245, 1170 (ether), 1127 (ether) and 981; δ_H (400 MHz, $CDCl_3$) 0.01 (s, 9 H, Si(CH_3)$_3$), 3.33 (s, 3 H, OCH_3), 3.45-3.53 (m, 4 H, OCH_2CH_2O), 3.75 (t, *J* 6.2 Hz, 2 H, NCH_2CH_2O), 4.19 (t, *J* 6.2 Hz, 2 H, NCH_2CH_2O), 7.32-7.34 (m, 2 H, ArH), 7.45-7.53 (m, 4 H, ArH), 7.70-7.72 (m, 1 H, ArH) and 7.82-7.87 (m, 1 H, ArH); δ_C ($CDCl_3$, 100 MHz) 0.0 ($SiCH_3$), 44.7 (CH_2), 59.5 (CH_3), 69.8 (CH_2), 71.1 (CH_2), 72.3 (CH_2), 93.9 ($PhSiMe_3$), 110.8 (PhH), 120.4 (PhH), 122.8 (PhH), 123.2 (ArH), 128.8 (ArH), 129.8 (ArH), 130.7 (*Ph*Ar), 135.4 (ArN), 142.0 (ArN) and 156.1(*Ar*Ph); *m/z* EI(+) 353.1539 (M-CH_3, 100%) and 207.1046 (M - $C_6H_6SiMe_3$, 95%), $C_{21}H_{28}O_2N_2Si$ requires 368.5493.

Experiment 32 (Equation 53, Section 2.3.3): *Synthesis of 2-phenyl-N-*n*-butylbenzimidazole **150**.*

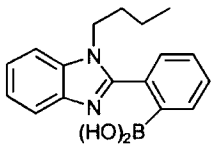


150

To a stirred solution of **145** (0.2.36 g, 12.10 mmol) in anhydrous DMF (60 ml), K_2CO_3 (8.254 g, 60.5 mmol), DMAP (0.741 g, 6.05 mmol) under argon, *n*-butyl bromide (0.198 ml, 18.15 mmol) was added. The resultant mixture was refluxed 2 hours, and cooled to room temperature for 8 hours. The reaction mixture was condensed and the crude residue was diluted with DCM (40 ml), washed with distilled water (3 x 10 ml) and dried ($MgSO_4$). Evaporation gave the crude product (3.100 g) which was purified by silica gel chromatography (60 Å, hexane:ethyl acetate, gradient elution) to provide **150** as a pale yellow oil that solidified on drying to give an oily solid (2.594 g, 85%); λ_{max} (EtOH)/nm 239.0sh, 287.0 (ε/dm^3 mol^{-1} cm^{-1} 8 806, 10 966); ν_{max}/cm^{-1} *inter alia* 3188 (amine), 3046 (Ar), 2915 (CH), 1456, 1376, 1328 (benzimidazole), 1275 and 922; δ_H (400 MHz, $CDCl_3$) 0.88 (t, *J* 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.26-1.32 (m, 2 H, $CH_2CH_2CH_3$), 1.78-1.84 (m, 2 H, $CH_2CH_2CH_3$), 4.25 (t, *J* 7.6 Hz, 2 H, NCH_2CH_2), 7.31-7.33 (m, 2 H, ArH), 7.42-7.45 (m, 1 H, ArH) 7.52-7.54 (m, 3 H, ArH), 7.71-7.74 (m, 2 H, ArH) and 7.83-7.85 (m, 1 H, Ar); δ_C ($CDCl_3$, 100 MHz) 13.6 (CH_3), 20.0 (CH_2), 31.9 (CH_2), 44.5 (CH_2), 110.1 (Ph), 120.0 (Ph), 122.3 (Ph), 122.6 (ArH), 128.7 (ArH), 129.4 (ArH), 129.7 (ArH), 130.7 (*Ph*Ar), 135.6

(ArN), 143.1 (ArN) and 153.7 (*Ar*Ph); *m/z* EI (+) 250.1290 (M^+, 85.72%) $C_{17}H_{18}N_2$ requires 250.3383.

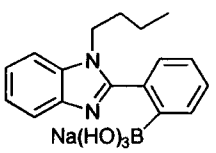
Experiment 33 (Equation 54, Section 2.3.3): *Synthesis of the 2-(2-boronophenyl)-N-n-butylbenzimidazole **118**.*



107

A stirred solution of benzimidazole **150** (0.438 g, 1.75 mmol) in diethyl ether (17.5 ml) at -78 °C under argon, was treated with *t*-BuLi (5.06 ml, 0.52 M in pentane, 2.63 mmol) over a period of 20 minutes. The resultant solution was stirred at -78 °C for 2 hours, treated with $B(O^iPr)_3$ (0.81 ml, 3.50 mmol) and allowed to warm slowly to room temperature over 12 hours. The reaction was quenched with dilute aqueous NaOH (10% w/v, 11 ml), and the reaction stirred at room temperature for 10 minutes. The mixture was then neutralised with dilute aqueous HCl (10% w/v) and the precipitate that formed was collected by filtration, washed with diethyl ether, distilled water and dried in air to give **118** as a white hydrated solid (0.664 g, 120 %). All spectroscopic and analytical data was identical to that of the material prepared previously (**Equations 39** and **41**).

Experiment 34 (Equation 55, Section 2.3.3): *Synthesis of the 2-(2-boronophenyl)-N-n-butylbenzimidazole sodium hydroxide salt **107**.*



107

A stirred solution of benzimidazole **150** (2.036 g, 8.14 mmol) in diethyl ether (90 ml) was cooled (-78 °C) under argon and treated with *t*-BuLi (1.18 ml, 1.7 M in pentane, 12.2 mmol) over a period of 20 minutes. The resultant solution was stirred at -78 °C for 4.5 hours, treated with $B(O^iPr)_3$ (3.76 ml, 16.3 mmol) and allowed to warm slowly to room temperature over 12 hours. After quenching with aqueous NaOH (20% w/v, 85 ml) and stirring at room temperature for 1.5 hours, the off-white precipitate that had formed was collected by filtration, washed with diethyl ether, distilled water and dried in air to give **107** as a white solid (2.795 g, 103%). All spectroscopic and analytical data was identical to that of the material prepared previously (**Experiment 26, Section 2.2.4**).

Experiment 35 (Table 9, Section 3.1.1): *Screening experiment of N-Boc-O-(diphenylphosphoryl)hydroxylamine **65** and chloroamine T **67** with cyclobutanone in the presence of **107**.* All of the wells of a 64 well Robbins block™ were charged with **65** (0.033 g, 0.100 mmol) or chloroamine T **67** (0.023 g, 0.100 mmol) in MeOH or DCM (0.5 ml). To these mixtures either a solution of **107** (0.029 g 0.0879 mmol), triethylamine (0.015 ml, 0.100 mmol) or a combination of these were added. The reactions were mixed by shaking at room temperature for 24 hours. After this time, the reactions were filtered through a complimentary Robbins block™ packed with silica gel (40 Å, MeCN as eluent), and the solutions obtained were evaporated, diluted (0.05 M) and analysed by LCMS (ES +).

Experiment 36 (Table 10, Section 3.1.2): *Screening experiment of N-Boc-hydroxylamine **62** with cyclobutanone, benzophenone and chalcone in the presence of Cu(OTf).Ph and $(^{i}Pr)_2NEt$.* To solutions of **62** (0.005 g, 0.038 mmol) in MeCN:H_2O (9:1, 0.1 ml), cyclobutanone (0.0027 ml, 0.038 mmol), benzophenone (0.0069 ml, 0.038 mmol) or chalcone (0.0055 ml, 0.038 mmol) were added as solutions in MeCN:H_2O (9:1, 0.2 ml). The solutions were then treated with either the copper complex Cu(OTf).Ph (0.001 g, 0.0038 mmol) as a solution in MeCN:H_2O (9:1, 0.1 ml), diisopropylethylamine (0.0065 ml, 0.038 mmol), 0.1 ml of solvent (MeCN:H_2O, 9:1) or a combination thereof. The reactions were then stirred at room temperature for 4 days during which they were analysed by TLC.

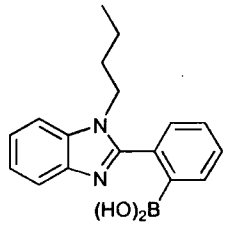
Experiment 37 (Table 11, Section 3.1.2): *Screening experiment of N-Boc-hydroxylamine **62** with cyclobutanone, benzophenone and chalcone in the presence of **107**.* Solutions of **62** (0.005 g, 0.038 mmol) in MeCN (0.1 ml) were prepared in 1.5 ml screw-top vials, these were treated with cyclobutanone (0.0027 ml, 0.038 mmol), benzophenone (0.0069 ml, 0.038 mmol) or chalcone (0.0055 ml, 0.038 mmol) as solution in either MeCN or MeCN:H_2O (9:1, 0.1 ml). These solutions were then treated with either a solution of **107** (0.001 g, 0.0033 mmol), diisopropylethylamine (0.0066 ml, 0.038 mmol), 0.1 ml of solvent or a combination thereof. The reactions were then stirred at room temperature for 5 days during which they were analysed by TLC.

Experiment 38 (Entry 1, Table 12, Section 3.2.1): *Reaction of 4-anisaldehyde with acetone in the presence of **107**.* Benzimidazole **107** (0.017 g, 0.058 mmol) was treated with acetone (0.35 ml) and D_2O (0.55 ml) giving a cloudy mixture that was sonnicated for 5 minutes. To this mixture 4-anisaldehyde **156a** (0.072 ml, 0.588 mmol) was added and the biphasic solution stirred at room temperature for 5 days. The biphasic mixture was separated, the aqueous layer neutralised with dilute aqueous HCl (10% w/v), diluted with DCM (10 ml) and extracted into DCM (3 x 30 ml) and ethylacetate (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), and evaporated to give a residue (0.010 g) which was purified by column chromatography (60 Å, hexane:ethyl acetate, gradient elution), to give the ketone **158a** as a pale brown oil (0.040 g, 38%). All spectroscopic and analytical data were identical to those reported in the literature.[77]

Experiment 39 (Entry 2, Table 12, Section 3.2.1): *Reaction of benzaldehyde with acetone in the presence of **107**.* A stirred solution of benzaldehyde (0.075 ml, 0.733 mmol) in a mixture of D_2O and acetone (1:1.6, 1.1 ml), was treated with the benzimidazole **107** (0.037 g, 0.11 mmol). The mixture was shaken periodically over a period of 72 hours at room temperature during which the reaction was analysed by ^1H NMR, which indicated that **158b** was present (estimated yield; 17%).[79]

Experiment 40 (Equation 60, Section 3.2.2): *Reaction of 4-anisaldehyde with acetone in the presence of NaOD.* A stirred solution of 4-anisaldehyde **156a** (0.32 ml, 2.64 mmol) in acetone (1.51 ml) and D_2O (2.37 ml) was treated with NaOD (0.033 g, 0.330 mmol). The resultant solution was then stirred at room temperature for 4 days. The biphasic mixture was then extracted with dichloromethane (3 x 3 ml), neutralised with dilute aqueous HCl (10% w/v) and extracted with DCM (3 x 3 ml). The combined organic extracts were dried ($MgSO_4$), and evaporated to give **158a** as a yellow crystalline solid (0.556 g, 63.4%). All spectroscopic and analytical data was identical to that of the material prepared previously and reported in the literature.[77]

Experiment 41 (Equation 63, Section 3.2.3): *Synthesis of 2-(2-boronophenyl)-N-n-butylbenzimidazole 118.*



106b

A stirred cooled (-78 °C) solution of **150** (0.369 g, 1.12 mmol) in diethyl ether (3 ml) under argon, was treated with *n*-BuLi (0.896 ml, 2.5 M in pentane, 2.24 mmol) over 30 minutes. The resultant solution was stirred for 1 hour at -78 °C, treated with $B(O^iPr)_3$ (0.52 ml, 2.24 mmol) and stirred for 4 hours, whilst warming slowly to room temperature. The reaction was quenched with dilute aqueous NaOH (10% w/v, 2 ml), and stirred at room temperature for 15 minutes. The solution was adjusted to pH 7 with dilute aqueous HCl (10% w/v), and the off white precipitate which formed was collected by filtration, washed with diethyl ether and dried in air to give **118** as a white solid (0.261 g, 79%). All spectroscopic and analytical data was identical to that of the material prepared previously, except for the following data; δ_B (128 MHz, D_2O) 12.2; (128 MHz, CD_3CN:D_2O, 3:1) 6.3; *m/z* ES (+) 553.34 (2M - 2OH, 35%) and 295.20 (MH, 100%).

Experiment 42 (Equation 65, Section 3.2.4): *Reaction of 4-anisaldehyde with acetone in the presence of 118 and NaOD.* A stirred solution of 4-anisaldehyde **156a** (0.23 ml, 1.89 mmol) in acetone (1.1 ml) and D_2O (1.76 ml) was treated with **118** (0.066 g, 0.223 mmol) and NaOD (0.024 g, 0.59 mmol). The resultant solution was then stirred at room temperature for 2 days, and the biphasic mixture extracted with DCM (3 x 3 ml), neutralised with dilute aqueous HCl (10% w/v) and extracted with DCM (3 x 3 ml). The combined organic extracts were dried ($MgSO_4$), and evaporated to give **158a** as a yellow crystalline solid (0.264 g, 79.4%). All spectroscopic and analytical data was identical to that of the material prepared previously and reported in the literature.[77]

Experiment 43 (Equation 67, Section 3.3.1): *Screening experiment of 4-anisaldehyde with acetone in the presence of NaOH.* 112 GC vials (1.5 ml) were charged with benzaldehyde (0.0356 ml, 0.336 mmol), acetone (0.26 ml, 3.5 mmol) and toluene (0.037 ml, 0.35 mmol). The resultant solutions were treated with an aqueous solution of sodium hydroxide (0.24 ml, 0.22 M), and the reactions were stirred at room temperature over a period of 24 hours. Individual reactions were worked-up and analysed by the addition of diethyl ether (0.5 ml), shaking and sampling of the organic layer (15 µl). The samples were

diluted (MeCN:H_2O, 70:30, 0.002 M) and analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30).

Experiment 44 (Equation 76, Section 3.3.2): *Screening experiment of 4-anisaldehyde with acetone in the presence of **107**.* 74 GC vials (1.5 ml) were charged with benzaldehyde (0.0341 ml, 0.336 mmol), acetone (0.20 ml, 2.5 mmol) and toluene (0.037 ml, 0.35 mmol). These solutions were then treated with **107** (0.017 g, 0.0505 mmol) in H_2O (0.24 ml) and the reactions stirred at room temperature over a period of 72 hours. Individual reactions were worked-up and analysed by the addition of diethyl ether (0.5 ml), shaking the solutions and sampling of a portion of the organic layer (15 µl). The samples were diluted (MeCN:H_2O, 70:30, 0.002 M) and analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30).

Experiment 45 (Equation 79, Section 3.3.3): *Screening experiment of 4-anisaldehyde with acetone in the presence of **150** and **165**.* 21, 1.5 ml GC vials were charged with solutions of benzaldehyde (0.037 ml, 0.35 mmol), acetone (0.26 ml, 3.5 mmol) and toluene (0.037 ml, 0.35 mmol), and were treated with a solution of phenylboronic acid **165** (0.006 g, 0.0525 mmol) and **150** (0.013 g, 0.0525 mmol) in H_2O (0.24 ml). The resultant solutions were stirred at room temperature over a period of 6 days. Individual reactions were worked-up and analysed through the addition of diethyl ether (0.5 ml), shaking the solutions and sampling of a portion of the organic layer (15 µl). The samples were diluted (MeCN:H_2O, 70:30, 0.002 M) and analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30).

Experiment 46 (Equation 81, Section 3.3.4): *Screening experiment of 4-anisaldehyde with acetone in the presence of **150**, **165** and NaOH.* 27, 1.5 ml GC vials were charged with solutions of benzaldehyde (0.037 ml, 0.35 mmol), acetone (0.13 ml, 1.75 mmol) and toluene (0.037 ml, 0.35 mmol). These solutions were treated with phenylboronic acid **165** (0.006 g, 0.0525 mmol) and **150** (0.013 g, 0.0525 mmol) as a solution in acetone (0.13 ml, 1.75 mmol). The reaction mixtures were then treated with aqueous solutions of sodium hydroxide (0.24 ml, 0.22 M) and were stirred at room temperature over a period of 6 days. Individual reactions were worked-up and analysed through the addition of diethyl ether (0.5 ml), shaking the solutions and sampling of a portion of the organic layer (15 µl). The

samples were diluted (MeCN:H_2O, 70:30, 0.002 M) and analysed by HPLC (Phenomenex 18 C Luna, MeCN:H_2O, 70:30).

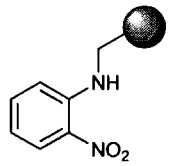
Experiment 47 (Table 14, Section 3.4.1): *Assessment of **107** as a catalyst for the Knoevenagel reaction.* The wells of a 46 well Robbins block™ were charged with 4-anisaldehyde (0.0120 ml, 0.100 mmol), benzaldehyde (0.0102 ml, 0.100 mmol), 4-nitrobenzene (0.0161 ml, 0.100 mmol) or propionaldehyde (0.010 ml, 0.100 mmol) as solutions in H_2O (0.5 ml) or a mixture of MeCN and H_2O (1:1, 0.5 ml). The corresponding wells were then treated with solutions of dimethyl malonate (0.012 g, 0.100 mmol) or methylcyanoacetate (0.0177 ml, 0.100 mmol) in H_2O (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). The resultant mixtures were then treated with either solutions of the complex **107** (0.029 g, 0.088 mmol) in the respective solutions or the solvent alone (0.5 ml). The Robbins block™ was sealed and shaken to mix for 6 days at room temperature. After this time, the reaction solutions were pushed through silica plugs which had been packed into a complimentary Robbins block™ (silica gel 40 Å, MeCN as eluent). The solvents were evaporated (Genevac™), diluted (MeCN, 0.02 M) and the residues obtained were analysed by LCMS (ES +).

Experiment 48 (Table 15, Section 3.4.2): *Assessment of **107** as a catalyst for the Michael reaction.* The wells of a 46 well Robbins block™ were charged with 2-cyclohexenone (0.0196 ml, 0.100 mmol), *trans*-chalcone (0.042 g, 0.100 mmol), methyl cinnamate (0.032 g, 0.100 mmol) or nitrostyrene (0.030 g, 0.100 mmol) as solutions in H_2O (0.5 ml) or a mixture of MeCN and H_2O (1:1, 0.5 ml). These mixtures were then treated with solutions of acetone (0.0073 ml, 0.100 mmol), methyl cyanoacetate (0.0177 ml, 0.100 mmol) or 2-siloxypropene (0.033 ml, 0.100 mmol) in H_2O (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). The corresponding solutions were then treated with solutions of the complex **107** (0.029 g, 0.088 mmol) or the solvent alone (0.5 ml). The Robbins block™ was sealed and shaken to mix for 6 days at room temperature. After this time, the reaction mixtures were filtered through a complimentary Robbins block™ packed with silica gel (40 Å, MeCN as eluent). The resulting solutions were evaporated (Genevac™), diluted (MeCN, 0.02 M) and the residues obtained were analysed by LCMS (ES +).

Experiment 49 (Equation 86, Table 16, Section 3.4.3): *Assessment of **107** as a catalyst for the Darzens reaction.* The wells of a 96 well Robbins block™ were charged with 4-anisaldehyde (0.0120 ml, 0.100 mmol), benzaldehyde (0.0102 ml, 0.100 mmol), 4-nitrobenzene (0.0161 ml, 0.100 mmol) or propionaldehyde (0.010 ml, 0.100 mmol) as solutions in H_2O (0.5 ml) or a mixture of MeCN and H_2O (1:1, 0.5 ml). The corresponding wells were then treated with solutions of chloroacetonitrile (0.010 ml, 0.100 mmol) or N,N-diethyl-2-chloroacetamide **190** (0.0137 ml, 0.100 mmol) in H_2O (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). The resultant solutions were then treated with solutions of the complex **107** (0.029 g, 0.088 mmol) in the respective solvent or 0.5 ml of the solvent alone. The Robbins block™ was then sealed and shaken for 6 days at room temperature, after which, the reactions were pushed through short silica plugs packed into a complimentary Robbins block™ (40 Å, MeCN as eluent), evaporated (Genevac™) and the residues diluted (MeCN, 0.02 M) and analysed by LCMS (ES +).

Experiment 50 (Equation 87, Table 17, Section 3.4.4): *Assessment of the ability of **107** to catalyse the coupling of phenylacetylene to aldehydes.* The wells of a 96 well Robbins block™ were charged with 4-anisaldehyde (0.0120 ml, 0.100 mmol), benzaldehyde (0.0102 ml, 0.100 mmol), 4-nitrobenzene (0.0161 ml, 0.100 mmol) or propionaldehyde (0.010 ml, 0.100 mmol) as solutions in H_2O (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). These solutions were then treated with solutions phenylacetylene **195** (0.011 ml, 0.100 mmol) in either H_2O (0.5 ml) or MeCN and H_2O (1:1, 0.5 ml). Selected solutions were then treated with solutions of the complex **107** (0.029 g, 0.088 mmol) in the corresponding solvent or with 0.5 ml of the solvent alone. The Robbins block™ was then sealed and shaken for 6 days at room temperature, after which, the reactions were filtered through short silica plugs packed in a complimentary Robbins block™ (silica gel 40 Å, MeCN as eluent), evaporated (Genevac™) and the residues diluted (MeCN, 0.02 M) and analysed by LCMS (ES +).

Experiment 51 (Equation 89, 4.1.1): *Synthesis of solid supported 2-(Argogel™-amine)nitrobenzene **201**.*



201

Argogel™-NH_2 (9.776 g, 4.15 mmol) was solvated with NMP (100 ml) and stirred gently under argon. The solvated beads were treated with 2-fluoronitrobenzene **200** (2.58 ml, 41.5 mmol) and the after 12 hours at room temperature, the resin was collected by filtration, washed with NMP (3 x 70 ml), re-solvated with NMP (100 ml) and treated again with 2-fluoronitrobenzene (2.58 ml, 41.5 mmol). After stirring for a further 24 hours under argon, the resin was filtered and washed with NMP (3 x 100 ml), DCM (3 x 100 ml), MeOH:DCM (1:1, 3 x 100 ml) and MeOH (3 x 100 ml). The resin obtained was dried under vacuum to give the functionalised Argogel™-NH_2 **201** with quantitative mass recovery; ν_{max} (solid phase)/cm^{-1} *inter alia* 3425.9 (Argogel™), 1637.9 (Argogel™), 1452.9 (Ar-NO_2), 1350.2 (C-N), 1298.1 (Ar-NO_2), 1250.4 (Ar-NO_2), 1103.5 (Argogel™); δ_H ($CDCl_3$, 300MHz, MAS) 1.49 (s, Argogel™), 3.49-3.78 (m, Argogel™), 6.63-6.68 (m, Ar), 6.86 (d, 7.5Hz, Ar), 7.40-7.45 (m, Ar) and 8.18 (d, 7.5Hz, Ar); δ_c ($CDCl_3$, 400MHz, gel phase) 43.1(Argogel™), 71.0 (Argogel™), 114.3, 115.8, 127.3, 136.6 and 145.8.

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Appendix 1: X-ray diffraction data for compound 52.

Table 20: Crystal data and structure refinement for **52**.

Empirical formula	$C_6 H_6 K N O_6 S$	
Formula weight	259.28	
Temperature	393(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.7936(9) Å	α = 90°.
	b = 7.1516(6) Å	β = 106.150(3)°.
	c = 12.4173(9) Å	γ = 90°.
Volume	920.68(13) $Å^3$	
Z	4	
Density (calculated)	1.871 Mg/m^3	
Absorption coefficient	0.812 mm^{-1}	
F(000)	528	
Crystal size	0.2 x 0.1 x 0.1 mm^3	
Theta range for data collection	1.96 to 27.50°.	
Index ranges	-14<=h<=13, -9<=k<=9, -16<=l<=15	
Reflections collected	9859	
Independent reflections	2117 [R(int) = 0.0668]	
Completeness to theta = 27.50°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2117 / 0 / 160	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0417, wR2 = 0.0864	
R indices (all data)	R1 = 0.0661, wR2 = 0.0947	
Largest diff. peak and hole	0.402 and -0.444 $e.Å^{-3}$	

Table 21: Bond lengths [Å] and angles [°] for **52**.

O(6)-K(1)	2.779(2)	K(1)-O(6)-K(1)#1	83.68(7)
O(6)-K(1)#1	2.955(3)	C(5)-C(4)-C(3)	120.9(3)
C(4)-C(5)	1.394(4)	C(5)-C(4)-S(1)	118.6(2)
C(4)-C(3)	1.401(4)	C(3)-C(4)-S(1)	120.5(2)
C(4)-S(1)	1.784(3)	C(6)-C(1)-C(2)	122.8(3)
C(1)-C(6)	1.385(4)	C(6)-C(1)-N(1)	118.9(3)
C(1)-C(2)	1.398(4)	C(2)-C(1)-N(1)	118.2(3)
C(1)-N(1)	1.471(4)	C(1)-C(6)-C(5)	118.6(3)
C(6)-C(5)	1.387(4)	C(2)-C(3)-C(4)	120.0(3)
C(3)-C(2)	1.380(4)	C(6)-C(5)-C(4)	119.6(3)
O(2)-N(1)	1.230(3)	C(3)-C(2)-C(1)	118.1(3)
O(2)-K(1)#2	2.802(2)	N(1)-O(2)-K(1)#2	175.71(19)
N(1)-O(1)	1.236(3)	O(2)-N(1)-O(1)	123.7(3)
S(1)-O(5)	1.451(2)	O(2)-N(1)-C(1)	118.3(2)
S(1)-O(4)	1.451(2)	O(1)-N(1)-C(1)	118.0(2)
S(1)-O(3)	1.457(2)	O(5)-S(1)-O(4)	113.24(12)
S(1)-K(1)#1	3.5242(10)	O(5)-S(1)-O(3)	112.86(12)
O(3)-K(1)#1	3.148(2)	O(4)-S(1)-O(3)	113.49(13)
O(5)-K(1)	2.711(2)	O(5)-S(1)-C(4)	105.63(13)
O(5)-K(1)#1	2.819(2)	O(4)-S(1)-C(4)	104.93(12)
O(4)-K(1)#3	2.765(2)	O(3)-S(1)-C(4)	105.72(13)
O(4)-K(1)#4	2.775(2)	O(5)-S(1)-K(1)#1	49.97(8)
K(1)-O(4)#5	2.765(2)	O(4)-S(1)-K(1)#1	140.26(9)
K(1)-O(4)#4	2.775(2)	O(3)-S(1)-K(1)#1	63.18(9)
K(1)-O(2)#6	2.802(2)	C(4)-S(1)-K(1)#1	114.13(9)
K(1)-O(5)#7	2.819(2)	S(1)-O(3)-K(1)#1	92.43(10)
K(1)-O(6)#7	2.955(3)	S(1)-O(5)-K(1)	162.37(12)
K(1)-O(3)#7	3.148(2)	S(1)-O(5)-K(1)#1	106.82(10)
K(1)-S(1)#7	3.5242(10)	K(1)-O(5)-K(1)#1	87.56(6)
K(1)-K(1)#1	3.8272(5)	S(1)-O(4)-K(1)#3	128.22(11)
K(1)-K(1)#7	3.8272(5)	S(1)-O(4)-K(1)#4	141.86(12)
		K(1)#3-O(4)-K(1)#4	87.39(6)

O(5)-K(1)-O(4)#5	87.92(6)	O(5)#7-K(1)-S(1)#7	23.21(4)
O(5)-K(1)-O(4)#4	78.99(6)	O(6)#7-K(1)-S(1)#7	80.36(5)
O(4)#5-K(1)-O(4)#4	151.04(3)	O(3)#7-K(1)-S(1)#7	24.39(4)
O(5)-K(1)-O(6)	66.45(7)	O(5)-K(1)-K(1)#1	47.38(4)
O(4)#5-K(1)-O(6)	81.81(7)	O(4)#5-K(1)-K(1)#1	46.41(4)
O(4)#4-K(1)-O(6)	115.28(7)	O(4)#4-K(1)-K(1)#1	126.37(5)
O(5)-K(1)-O(2)#6	128.10(7)	O(6)-K(1)-K(1)#1	50.13(5)
O(4)#5-K(1)-O(2)#6	134.61(7)	O(2)#6-K(1)-K(1)#1	138.25(5)
O(4)#4-K(1)-O(2)#6	71.79(6)	O(5)#7-K(1)-K(1)#1	137.76(5)
O(6)-K(1)-O(2)#6	88.54(7)	O(6)#7-K(1)-K(1)#1	94.31(5)
O(5)-K(1)-O(5)#7	146.95(5)	O(3)#7-K(1)-K(1)#1	108.68(4)
O(4)#5-K(1)-O(5)#7	91.86(6)	S(1)#7-K(1)-K(1)#1	126.91(3)
O(4)#4-K(1)-O(5)#7	85.63(6)	O(5)-K(1)-K(1)#7	106.44(5)
O(6)-K(1)-O(5)#7	146.11(7)	O(4)#5-K(1)-K(1)#7	115.92(5)
O(2)#6-K(1)-O(5)#7	72.37(6)	O(4)#4-K(1)-K(1)#7	46.20(4)
O(5)-K(1)-O(6)#7	85.46(7)	O(6)-K(1)-K(1)#7	161.31(6)
O(4)#5-K(1)-O(6)#7	74.71(6)	O(2)#6-K(1)-K(1)#7	82.79(5)
O(4)#4-K(1)-O(6)#7	78.55(7)	O(5)#7-K(1)-K(1)#7	45.06(4)
O(6)-K(1)-O(6)#7	143.93(7)	O(6)#7-K(1)-K(1)#7	46.19(5)
O(2)#6-K(1)-O(6)#7	127.38(7)	O(3)#7-K(1)-K(1)#7	92.38(4)
O(5)#7-K(1)-O(6)#7	62.76(7)	S(1)#7-K(1)-K(1)#7	67.99(2)
O(5)-K(1)-O(3)#7	156.06(6)	K(1)#1-K(1)-K(1)#7	138.23(4)
O(4)#5-K(1)-O(3)#7	70.29(6)		
O(4)#4-K(1)-O(3)#7	124.93(6)		
O(6)-K(1)-O(3)#7	99.66(7)		
O(2)#6-K(1)-O(3)#7	67.85(6)		
O(5)#7-K(1)-O(3)#7	47.52(6)		
O(6)#7-K(1)-O(3)#7	97.73(7)		
O(5)-K(1)-S(1)#7	164.34(5)		
O(4)#5-K(1)-S(1)#7	81.98(5)		
O(4)#4-K(1)-S(1)#7	104.44(5)		
O(6)-K(1)-S(1)#7	123.31(6)		
O(2)#6-K(1)-S(1)#7	66.81(5)		

Appendix 2: X-ray diffraction data for compound 61.

Table 22: Crystal data and structure refinement for **61**.

Empirical formula	$C_{12}\ H_{17}\ N\ O_5\ S$	
Formula weight	287.33	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/C	
Unit cell dimensions	a = 9.2654(3) Å	α= 90°.
	b = 20.3452(5) Å	β= 110.4220(10)°.
	c = 8.0209(2) Å	γ = 90°.
Volume	1416.96(7) $Å^3$	
Z	4	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	0.244 mm^{-1}	
F(000)	608	
Crystal size	0.3 x 0.07 x 0.06 mm^3	
Theta range for data collection	2.00 to 30.00°.	
Index ranges	-13<=h<=13, -27<=k<=28, -11<=l<=11	
Reflections collected	16849	
Independent reflections	4129 [R(int) = 0.0731]	
Completeness to theta = 30.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4129 / 0 / 176	
Goodness-of-fit on F^2	0.992	
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.0915	
R indices (all data)	R1 = 0.0702, wR2 = 0.0988	
Extinction coefficient	0	

Largest diff. peak and hole	0.384 and -0.423 e.Å^{-3}

Table 23: Bond lengths [Å] and angles [°] for **61**.

S(1)-O(3)	1.4210(11)	C(10)-H(10B)	0.9800
S(1)-O(1)	1.4213(11)	C(10)-H(10C)	0.9800
S(1)-O(2)	1.6286(11)	C(1)-H(1A)	0.9800
S(1)-C(5)	1.7470(15)	C(1)-H(1B)	0.9800
O(2)-N(1)	1.4227(15)	C(1)-H(1C)	0.9800
O(5)-C(8)	1.3162(17)	C(1)-H(1D)	0.9800
O(5)-C(9)	1.4955(19)	C(1)-H(1E)	0.9800
O(4)-C(8)	1.2167(18)	C(1)-H(1F)	0.9800
C(5)-C(4)	1.390(2)	C(11)-H(11A)	0.9800
C(5)-C(6)	1.390(2)	C(11)-H(11B)	0.9800
N(1)-C(8)	1.381(2)	C(11)-H(11C)	0.9800
N(1)-H(1N)	0.936(18)		
C(4)-C(3)	1.383(2)	O(3)-S(1)-O(1)	120.60(7)
C(4)-H(4A)	0.9500	O(3)-S(1)-O(2)	108.45(6)
C(2)-C(7)	1.390(2)	O(1)-S(1)-O(2)	101.33(6)
C(2)-C(3)	1.393(2)	O(3)-S(1)-C(5)	110.09(7)
C(2)-C(1)	1.510(2)	O(1)-S(1)-C(5)	110.79(7)
C(6)-C(7)	1.387(2)	O(2)-S(1)-C(5)	103.92(6)
C(6)-H(6A)	0.9500	N(1)-O(2)-S(1)	110.28(8)
C(3)-H(3B)	0.9500	C(8)-O(5)-C(9)	121.16(12)
C(9)-C(10)	1.509(2)	C(4)-C(5)-C(6)	121.52(14)
C(9)-C(12)	1.513(2)	C(4)-C(5)-S(1)	118.89(11)
C(9)-C(11)	1.514(2)	C(6)-C(5)-S(1)	119.56(12)
C(7)-H(7A)	0.9500	C(8)-N(1)-O(2)	114.93(11)
C(12)-H(12A)	0.9800	C(8)-N(1)-H(1N)	116.0(10)
C(12)-H(12B)	0.9800	O(2)-N(1)-H(1N)	109.4(10)
C(12)-H(12C)	0.9800	C(3)-C(4)-C(5)	118.79(15)
C(10)-H(10A)	0.9800	C(3)-C(4)-H(4A)	120.6

C(5)-C(4)-H(4A)	120.6	H(10B)-C(10)-H(10C)	109.5
C(7)-C(2)-C(3)	118.77(15)	C(2)-C(1)-H(1A)	109.5
C(7)-C(2)-C(1)	120.85(15)	C(2)-C(1)-H(1B)	109.5
C(3)-C(2)-C(1)	120.38(16)	H(1A)-C(1)-H(1B)	109.5
O(4)-C(8)-O(5)	127.72(14)	C(2)-C(1)-H(1C)	109.5
O(4)-C(8)-N(1)	119.47(14)	H(1A)-C(1)-H(1C)	109.5
O(5)-C(8)-N(1)	112.71(13)	H(1B)-C(1)-H(1C)	109.5
C(7)-C(6)-C(5)	118.42(14)	C(2)-C(1)-H(1D)	109.5
C(7)-C(6)-H(6A)	120.8	H(1A)-C(1)-H(1D)	141.1
C(5)-C(6)-H(6A)	120.8	H(1B)-C(1)-H(1D)	56.3
C(4)-C(3)-C(2)	121.14(15)	H(1C)-C(1)-H(1D)	56.3
C(4)-C(3)-H(3B)	119.4	C(2)-C(1)-H(1E)	109.5
C(2)-C(3)-H(3B)	119.4	H(1A)-C(1)-H(1E)	56.3
O(5)-C(9)-C(10)	102.21(12)	H(1B)-C(1)-H(1E)	141.1
O(5)-C(9)-C(12)	107.97(13)	H(1C)-C(1)-H(1E)	56.3
C(10)-C(9)-C(12)	111.36(15)	H(1D)-C(1)-H(1E)	109.5
O(5)-C(9)-C(11)	110.82(13)	C(2)-C(1)-H(1F)	109.5
C(10)-C(9)-C(11)	110.97(15)	H(1A)-C(1)-H(1F)	56.3
C(12)-C(9)-C(11)	112.96(15)	H(1B)-C(1)-H(1F)	56.3
C(6)-C(7)-C(2)	121.36(15)	H(1C)-C(1)-H(1F)	141.1
C(6)-C(7)-H(7A)	119.3	H(1D)-C(1)-H(1F)	109.5
C(2)-C(7)-H(7A)	119.3	H(1E)-C(1)-H(1F)	109.5
C(9)-C(12)-H(12A)	109.5	C(9)-C(11)-H(11A)	109.5
C(9)-C(12)-H(12B)	109.5	C(9)-C(11)-H(11B)	109.5
H(12A)-C(12)-H(12B)	109.5	H(11A)-C(11)-H(11B)	109.5
C(9)-C(12)-H(12C)	109.5	C(9)-C(11)-H(11C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(11A)-C(11)-H(11C)	109.5
H(12B)-C(12)-H(12C)	109.5	H(11B)-C(11)-H(11C)	109.5
C(9)-C(10)-H(10A)	109.5		
C(9)-C(10)-H(10B)	109.5		
H(10A)-C(10)-H(10B)	109.5		
C(9)-C(10)-H(10C)	109.5		
H(10A)-C(10)-H(10C)	109.5		

Appendix 3: X-ray diffraction data for compound 65.

Table 24: Crystal data and structure refinement for **65**.

Empirical formula	$C_{17}H_{20}NO_4P$	
Formula weight	333.31	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.1807(6) Å	α= 101.103(4)°.
	b = 13.7335(7) Å	β= 96.770(5)°.
	c = 16.5321(10) Å	γ = 92.927(4)°.
Volume	2687.1(3) $Å^3$	
Z	6	
Density (calculated)	1.236 Mg/m^3	
Absorption coefficient	0.171 mm^{-1}	
F(000)	1056	
Crystal size	0.2 x 0.17 x 0.12 mm^3	
Theta range for data collection	1.27 to 34.89°.	
Index ranges	-18<=h<=14, -18<=k<=21, -26<=l<=16	
Reflections collected	14862	
Independent reflections	14815 [R(int) = 0.0398]	
Completeness to theta = 34.89°	63.1 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14815 / 0 / 622	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1341	
R indices (all data)	R1 = 0.0679, wR2 = 0.1461	
Largest diff. peak and hole	0.731 and -0.657 $e.Å^{-3}$	

Table 25: Bond lengths [Å] and angles [°] for **65**.

P(1)-O(4)	1.4804(10)	C(23)-C(24)	1.398(2)
P(1)-O(3)	1.6149(12)	C(23)-C(28)	1.399(2)
P(1)-C(12)	1.7843(13)	O(2)-C(5)	1.2034(17)
P(1)-C(6)	1.7882(15)	C(46)-C(51)	1.393(2)
P(2)-O(8)	1.4778(10)	C(46)-C(47)	1.397(2)
P(2)-O(7)	1.6168(12)	C(12)-C(17)	1.3975(18)
P(2)-C(23)	1.7841(13)	C(12)-C(13)	1.3992(18)
P(2)-C(29)	1.7899(16)	O(10)-C(39)	1.2016(18)
P(3)-O(12)	1.4807(10)	C(13)-C(14)	1.3945(18)
P(3)-O(11)	1.6190(12)	C(13)-H(13A)	0.9500
P(3)-C(40)	1.7862(13)	C(24)-C(25)	1.392(2)
P(3)-C(46)	1.7906(15)	C(24)-H(24A)	0.9500
O(3)-N(1)	1.4395(14)	C(40)-C(41)	1.3978(19)
O(7)-N(2)	1.4351(14)	C(40)-C(45)	1.400(2)
O(11)-N(3)	1.4345(14)	C(14)-C(15)	1.389(2)
N(2)-C(22)	1.3841(18)	C(14)-H(14A)	0.9500
N(2)-H(2A)	0.8800	C(41)-C(42)	1.395(2)
O(5)-C(22)	1.3394(18)	C(41)-H(41A)	0.9500
O(5)-C(21)	1.4751(18)	C(17)-C(16)	1.3863(19)
O(9)-C(39)	1.3389(19)	C(17)-H(17A)	0.9500
O(9)-C(38)	1.4752(19)	C(27)-C(26)	1.382(2)
O(1)-C(5)	1.3385(17)	C(27)-C(28)	1.393(2)
O(1)-C(4)	1.4758(18)	C(27)-H(27A)	0.9500
N(1)-C(5)	1.3885(18)	C(28)-H(28A)	0.9500
N(1)-H(1A)	0.8800	C(34)-C(33)	1.395(2)
N(3)-C(39)	1.3816(18)	C(34)-H(34A)	0.9500
N(3)-H(3A)	0.8800	C(7)-C(8)	1.401(2)
C(29)-C(30)	1.391(2)	C(7)-H(7A)	0.9500
C(29)-C(34)	1.393(2)	C(15)-C(16)	1.392(2)
O(6)-C(22)	1.2024(17)	C(15)-H(15A)	0.9500
C(6)-C(11)	1.392(2)	C(16)-H(16A)	0.9500
C(6)-C(7)	1.396(2)	C(4)-C(1)	1.515(3)

C(4)-C(3)	1.519(2)	C(48)-H(48A)	0.9500
C(4)-C(2)	1.517(3)	C(9)-C(8)	1.369(3)
C(45)-C(44)	1.3945(19)	C(9)-C(10)	1.381(3)
C(45)-H(45A)	0.9500	C(9)-H(9A)	0.9500
C(21)-C(18)	1.511(3)	C(31)-C(32)	1.381(3)
C(21)-C(20)	1.518(2)	C(31)-H(31A)	0.9500
C(21)-C(19)	1.519(3)	C(37)-C(38)	1.520(3)
C(51)-C(50)	1.391(2)	C(37)-H(37A)	0.9800
C(51)-H(51A)	0.9500	C(37)-H(37B)	0.9800
C(50)-C(49)	1.389(3)	C(37)-H(37C)	0.9800
C(50)-H(50A)	0.9500	C(8)-H(8B)	0.9500
C(30)-C(31)	1.394(3)	C(10)-H(10A)	0.9500
C(30)-H(30A)	0.9500	C(33)-C(32)	1.379(3)
C(43)-C(44)	1.382(2)	C(33)-H(33A)	0.9500
C(43)-C(42)	1.388(3)	C(38)-C(35)	1.513(3)
C(43)-H(43A)	0.9500	C(38)-C(36)	1.530(3)
C(20)-H(20A)	0.9800	C(2)-H(2B)	0.9800
C(20)-H(20B)	0.9800	C(2)-H(2C)	0.9800
C(20)-H(20C)	0.9800	C(2)-H(2D)	0.9800
C(47)-C(48)	1.385(2)	C(19)-H(19A)	0.9800
C(47)-H(47A)	0.9500	C(19)-H(19B)	0.9800
C(26)-C(25)	1.393(3)	C(19)-H(19C)	0.9800
C(26)-H(26A)	0.9500	C(32)-H(32A)	0.9500
C(11)-C(10)	1.393(2)	C(1)-H(1B)	0.9800
C(11)-H(11A)	0.9500	C(1)-H(1C)	0.9800
C(44)-H(44A)	0.9500	C(1)-H(1D)	0.9800
C(42)-H(42A)	0.9500	C(35)-H(35A)	0.9800
C(25)-H(25A)	0.9500	C(35)-H(35B)	0.9800
C(49)-C(48)	1.389(2)	C(35)-H(35C)	0.9800
C(49)-H(49A)	0.9500	C(18)-H(18A)	0.9800
C(3)-H(3B)	0.9800	C(18)-H(18B)	0.9800
C(3)-H(3C)	0.9800	C(18)-H(18C)	0.9800
C(3)-H(3D)	0.9800	C(36)-H(36A)	0.9800

C(36)-H(36B)	0.9800	C(39)-N(3)-O(11)	112.16(11)
C(36)-H(36C)	0.9800	C(39)-N(3)-H(3A)	123.9
		O(11)-N(3)-H(3A)	123.9
O(4)-P(1)-O(3)	115.14(6)	C(30)-C(29)-C(34)	120.34(15)
O(4)-P(1)-C(12)	112.71(6)	C(30)-C(29)-P(2)	117.04(12)
O(3)-P(1)-C(12)	99.98(6)	C(34)-C(29)-P(2)	122.62(12)
O(4)-P(1)-C(6)	112.13(6)	C(11)-C(6)-C(7)	119.97(14)
O(3)-P(1)-C(6)	105.84(6)	C(11)-C(6)-P(1)	118.31(11)
C(12)-P(1)-C(6)	110.22(7)	C(7)-C(6)-P(1)	121.70(13)
O(8)-P(2)-O(7)	115.35(6)	C(24)-C(23)-C(28)	120.08(13)
O(8)-P(2)-C(23)	112.65(6)	C(24)-C(23)-P(2)	122.94(11)
O(7)-P(2)-C(23)	99.10(6)	C(28)-C(23)-P(2)	116.99(11)
O(8)-P(2)-C(29)	110.57(7)	C(51)-C(46)-C(47)	119.53(14)
O(7)-P(2)-C(29)	106.60(7)	C(51)-C(46)-P(3)	123.13(12)
C(23)-P(2)-C(29)	112.01(7)	C(47)-C(46)-P(3)	117.34(11)
O(12)-P(3)-O(11)	115.24(6)	C(17)-C(12)-C(13)	120.11(12)
O(12)-P(3)-C(40)	112.53(6)	C(17)-C(12)-P(1)	122.08(10)
O(11)-P(3)-C(40)	99.57(6)	C(13)-C(12)-P(1)	117.81(10)
O(12)-P(3)-C(46)	111.05(6)	C(14)-C(13)-C(12)	119.41(13)
O(11)-P(3)-C(46)	106.13(6)	C(14)-C(13)-H(13A)	120.3
C(40)-P(3)-C(46)	111.70(7)	C(12)-C(13)-H(13A)	120.3
N(1)-O(3)-P(1)	107.76(8)	O(6)-C(22)-O(5)	127.75(14)
N(2)-O(7)-P(2)	108.32(8)	O(6)-C(22)-N(2)	125.86(14)
N(3)-O(11)-P(3)	108.59(8)	O(5)-C(22)-N(2)	106.31(12)
C(22)-N(2)-O(7)	111.50(10)	C(25)-C(24)-C(23)	119.57(15)
C(22)-N(2)-H(2A)	124.2	C(25)-C(24)-H(24A)	120.2
O(7)-N(2)-H(2A)	124.2	C(23)-C(24)-H(24A)	120.2
C(22)-O(5)-C(21)	121.04(12)	C(41)-C(40)-C(45)	120.09(13)
C(39)-O(9)-C(38)	120.84(13)	C(41)-C(40)-P(3)	123.27(11)
C(5)-O(1)-C(4)	120.93(11)	C(45)-C(40)-P(3)	116.64(11)
C(5)-N(1)-O(3)	111.31(10)	C(15)-C(14)-C(13)	120.32(13)
C(5)-N(1)-H(1A)	124.3	C(15)-C(14)-H(14A)	119.8
O(3)-N(1)-H(1A)	124.3	C(13)-C(14)-H(14A)	119.8

C(42)-C(41)-C(40)	119.59(15)	O(1)-C(4)-C(2)	109.75(16)
C(42)-C(41)-H(41A)	120.2	C(1)-C(4)-C(2)	112.94(16)
C(40)-C(41)-H(41A)	120.2	C(3)-C(4)-C(2)	110.82(16)
C(16)-C(17)-C(12)	119.92(13)	C(44)-C(45)-C(40)	119.54(14)
C(16)-C(17)-H(17A)	120.0	C(44)-C(45)-H(45A)	120.2
C(12)-C(17)-H(17A)	120.0	C(40)-C(45)-H(45A)	120.2
C(26)-C(27)-C(28)	120.23(15)	O(5)-C(21)-C(18)	109.81(14)
C(26)-C(27)-H(27A)	119.9	O(5)-C(21)-C(20)	101.60(13)
C(28)-C(27)-H(27A)	119.9	C(18)-C(21)-C(20)	110.66(19)
C(27)-C(28)-C(23)	119.69(15)	O(5)-C(21)-C(19)	110.04(17)
C(27)-C(28)-H(28A)	120.2	C(18)-C(21)-C(19)	113.08(19)
C(23)-C(28)-H(28A)	120.2	C(20)-C(21)-C(19)	111.05(17)
O(2)-C(5)-O(1)	128.09(14)	C(50)-C(51)-C(46)	120.21(15)
O(2)-C(5)-N(1)	125.85(14)	C(50)-C(51)-H(51A)	119.9
O(1)-C(5)-N(1)	105.99(11)	C(46)-C(51)-H(51A)	119.9
C(33)-C(34)-C(29)	119.36(16)	C(49)-C(50)-C(51)	119.79(15)
C(33)-C(34)-H(34A)	120.3	C(49)-C(50)-H(50A)	120.1
C(29)-C(34)-H(34A)	120.3	C(51)-C(50)-H(50A)	120.1
C(6)-C(7)-C(8)	119.35(17)	C(31)-C(30)-C(29)	119.68(16)
C(6)-C(7)-H(7A)	120.3	C(31)-C(30)-H(30A)	120.2
C(8)-C(7)-H(7A)	120.3	C(29)-C(30)-H(30A)	120.2
C(14)-C(15)-C(16)	120.09(13)	C(44)-C(43)-C(42)	120.49(14)
C(14)-C(15)-H(15A)	120.0	C(44)-C(43)-H(43A)	119.8
C(16)-C(15)-H(15A)	120.0	C(42)-C(43)-H(43A)	119.8
O(10)-C(39)-O(9)	127.40(14)	C(21)-C(20)-H(20A)	109.5
O(10)-C(39)-N(3)	125.59(15)	C(21)-C(20)-H(20B)	109.5
O(9)-C(39)-N(3)	106.93(13)	H(20A)-C(20)-H(20B)	109.5
C(17)-C(16)-C(15)	120.15(14)	C(21)-C(20)-H(20C)	109.5
C(17)-C(16)-H(16A)	119.9	H(20A)-C(20)-H(20C)	109.5
C(15)-C(16)-H(16A)	119.9	H(20B)-C(20)-H(20C)	109.5
O(1)-C(4)-C(1)	109.69(14)	C(48)-C(47)-C(46)	120.25(14)
O(1)-C(4)-C(3)	101.84(12)	C(48)-C(47)-H(47A)	119.9
C(1)-C(4)-C(3)	111.23(17)	C(46)-C(47)-H(47A)	119.9

C(27)-C(26)-C(25)	120.30(14)	C(10)-C(9)-H(9A)	119.5
C(27)-C(26)-H(26A)	119.8	C(32)-C(31)-C(30)	119.73(17)
C(25)-C(26)-H(26A)	119.8	C(32)-C(31)-H(31A)	120.1
C(10)-C(11)-C(6)	119.81(16)	C(30)-C(31)-H(31A)	120.1
C(10)-C(11)-H(11A)	120.1	C(38)-C(37)-H(37A)	109.5
C(6)-C(11)-H(11A)	120.1	C(38)-C(37)-H(37B)	109.5
C(43)-C(44)-C(45)	120.22(15)	H(37A)-C(37)-H(37B)	109.5
C(43)-C(44)-H(44A)	119.9	C(38)-C(37)-H(37C)	109.5
C(45)-C(44)-H(44A)	119.9	H(37A)-C(37)-H(37C)	109.5
C(43)-C(42)-C(41)	120.07(15)	H(37B)-C(37)-H(37C)	109.5
C(43)-C(42)-H(42A)	120.0	C(9)-C(8)-C(7)	120.11(17)
C(41)-C(42)-H(42A)	120.0	C(9)-C(8)-H(8B)	119.9
C(26)-C(25)-C(24)	120.13(15)	C(7)-C(8)-H(8B)	119.9
C(26)-C(25)-H(25A)	119.9	C(9)-C(10)-C(11)	119.81(18)
C(24)-C(25)-H(25A)	119.9	C(9)-C(10)-H(10A)	120.1
C(50)-C(49)-C(48)	120.29(16)	C(11)-C(10)-H(10A)	120.1
C(50)-C(49)-H(49A)	119.9	C(32)-C(33)-C(34)	120.04(17)
C(48)-C(49)-H(49A)	119.9	C(32)-C(33)-H(33A)	120.0
C(4)-C(3)-H(3B)	109.5	C(34)-C(33)-H(33A)	120.0
C(4)-C(3)-H(3C)	109.5	O(9)-C(38)-C(35)	110.18(17)
H(3B)-C(3)-H(3C)	109.5	O(9)-C(38)-C(37)	101.63(14)
C(4)-C(3)-H(3D)	109.5	C(35)-C(38)-C(37)	111.1(2)
H(3B)-C(3)-H(3D)	109.5	O(9)-C(38)-C(36)	109.21(17)
H(3C)-C(3)-H(3D)	109.5	C(35)-C(38)-C(36)	113.8(2)
C(47)-C(48)-C(49)	119.93(16)	C(37)-C(38)-C(36)	110.21(19)
C(47)-C(48)-H(48A)	120.0	C(4)-C(2)-H(2B)	109.5
C(49)-C(48)-H(48A)	120.0	C(4)-C(2)-H(2C)	109.5
C(8)-C(9)-C(10)	120.93(17)	H(2B)-C(2)-H(2C)	109.5
C(8)-C(9)-H(9A)	119.5	C(4)-C(2)-H(2D)	109.5

Appendix 4: X-ray diffraction data for compound 117.

Table 26: Crystal data and structure refinement for **117.**

Empirical formula	$C_{51} H_{51} B_3 N_6 O_3$	
Formula weight	828.41	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.223(2) Å	α= 75.48(3)°.
	b = 13.252(3) Å	β= 73.58(3)°.
	c = 16.734(3) Å	γ = 70.65(3)°.
Volume	2218.3(8) $Å^3$	
Z	2	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	876	
Crystal size	0.22 x 0.06 x 0.03 mm^3	
Theta range for data collection	1.91 to 25.00°.	
Index ranges	-12<=h<=13, -15<=k<=15, -19<=l<=19	
Reflections collected	14759	
Independent reflections	7767 [R(int) = 0.0701]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.999 and 0.748	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7767 / 0 / 569	
Goodness-of-fit on F^2	0.892	
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1093	
R indices (all data)	R1 = 0.1428, wR2 = 0.1329	

Largest diff. peak and hole	0.314 and -0.250 e.Å^{-3}

Table 27: Bond lengths [Å] and angles [°] for **106**.

B(1)-O(1)	1.359(4)	C(8)-C(9)	1.477(6)	C(112)-C(113)	1.392(4)
B(1)-O(2)	1.359(4)	C(8)-C(9A)	1.695(11)	C(112)-C(117)	1.400(4)
B(1)-C(17)	1.585(4)	C(9)-C(10)	1.541(8)	C(113)-C(114)	1.390(4)
B(2)-O(3)	1.418(4)	C(10)-C(11)	1.543(8)	C(114)-C(115)	1.380(4)
B(2)-O(2)	1.458(4)	C(9A)-C(10A)	1.545(14)	C(115)-C(116)	1.388(4)
B(2)-C(117)	1.634(4)	C(10A)-C(11A)	1.494(14)	C(116)-C(117)	1.391(4)
B(2)-N(101)	1.665(4)	C(12)-C(13)	1.394(4)	N(201)-C(201)	1.328(4)
B(3)-O(3)	1.416(4)	C(12)-C(17)	1.396(4)	N(201)-C(206)	1.388(4)
B(3)-O(1)	1.479(4)	C(13)-C(14)	1.388(4)	N(202)-C(201)	1.349(4)
B(3)-C(217)	1.631(5)	C(14)-C(15)	1.384(4)	N(202)-C(207)	1.398(4)
B(3)-N(201)	1.641(4)	C(15)-C(16)	1.386(4)	N(202)-C(208)	1.475(4)
N(1)-C(1)	1.307(4)	C(16)-C(17)	1.404(4)	C(201)-C(212)	1.474(4)
N(1)-C(7)	1.387(4)	N(101)-C(101)	1.329(3)	C(202)-C(203)	1.376(5)
N(2)-C(1)	1.377(4)	N(101)-C(106)	1.389(4)	C(202)-C(207)	1.380(4)
N(2)-C(6)	1.383(4)	N(102)-C(101)	1.337(4)	C(203)-C(204)	1.395(5)
N(2)-C(8)	1.459(5)	N(102)-C(107)	1.416(4)	C(204)-C(205)	1.385(4)
C(1)-C(12)	1.483(4)	N(102)-C(108)	1.467(4)	C(205)-C(206)	1.382(4)
C(2)-C(7)	1.373(8)	C(101)-C(112)	1.470(4)	C(206)-C(207)	1.400(4)
C(2)-C(3)	1.374(11)	C(102)-C(103)	1.376(5)	C(208)-C(209)	1.522(4)
C(3)-C(4)	1.443(12)	C(102)-C(107)	1.393(4)	C(209)-C(210)	1.516(4)
C(4)-C(5)	1.384(12)	C(103)-C(104)	1.390(4)	C(210)-C(211)	1.525(4)
C(5)-C(6)	1.508(8)	C(104)-C(105)	1.384(4)	C(212)-C(213)	1.399(4)
C(2A)-C(3A)	1.404(12)	C(105)-C(106)	1.398(4)	C(212)-C(217)	1.400(4)
C(2A)-C(7)	1.513(9)	C(106)-C(107)	1.399(4)	C(213)-C(214)	1.388(5)
C(3A)-C(4A)	1.385(13)	C(108)-C(109)	1.516(4)	C(214)-C(215)	1.372(4)
C(4A)-C(5A)	1.426(12)	C(109)-C(110)	1.521(4)	C(215)-C(216)	1.383(4)
C(5A)-C(6)	1.322(9)	C(110)-C(111)	1.474(5)	C(216)-C(217)	1.381(4)

C(6)-C(7) 1.386(6)

O(1)-B(1)-O(2)	122.1(3)	C(101)-N(101)-B(2)	111.9(2)
O(1)-B(1)-C(17)	118.2(2)	C(106)-N(101)-B(2)	140.1(2)
O(2)-B(1)-C(17)	119.6(3)	C(101)-N(102)-C(107)	106.4(2)
O(3)-B(2)-O(2)	115.1(2)	C(101)-N(102)-C(108)	128.5(3)
O(3)-B(2)-C(117)	115.9(3)	C(107)-N(102)-C(108)	125.0(3)
O(2)-B(2)-C(117)	113.8(3)	N(101)-C(101)-N(102)	112.3(3)
O(3)-B(2)-N(101)	110.1(3)	N(101)-C(101)-C(112)	113.2(3)
O(2)-B(2)-N(101)	105.0(2)	N(102)-C(101)-C(112)	134.4(3)
C(117)-B(2)-N(101)	94.1(2)	C(103)-C(102)-C(107)	116.2(3)
O(3)-B(3)-O(1)	114.4(2)	C(102)-C(103)-C(104)	122.5(3)
O(3)-B(3)-C(217)	116.2(3)	C(105)-C(104)-C(103)	121.7(3)
O(1)-B(3)-C(217)	112.7(3)	C(104)-C(105)-C(106)	116.7(3)
O(3)-B(3)-N(201)	111.6(3)	N(101)-C(106)-C(105)	131.8(3)
O(1)-B(3)-N(201)	105.0(2)	N(101)-C(106)-C(107)	107.3(3)
C(217)-B(3)-N(201)	94.6(2)	C(105)-C(106)-C(107)	120.9(3)
B(1)-O(1)-B(3)	118.4(2)	C(102)-C(107)-C(106)	122.1(3)
B(1)-O(2)-B(2)	117.1(2)	C(102)-C(107)-N(102)	131.4(3)
B(3)-O(3)-B(2)	121.3(2)	C(106)-C(107)-N(102)	106.5(3)
C(1)-N(1)-C(7)	103.7(3)	N(102)-C(108)-C(109)	111.7(2)
C(1)-N(2)-C(6)	105.6(3)	C(108)-C(109)-C(110)	112.5(3)
C(1)-N(2)-C(8)	128.0(3)	C(111)-C(110)-C(109)	114.6(3)
C(6)-N(2)-C(8)	125.6(3)	C(113)-C(112)-C(117)	123.1(3)
N(1)-C(1)-N(2)	114.2(3)	C(113)-C(112)-C(101)	129.5(3)
N(1)-C(1)-C(12)	124.1(3)	C(117)-C(112)-C(101)	107.4(2)
N(2)-C(1)-C(12)	121.7(3)	C(114)-C(113)-C(112)	117.9(3)
C(7)-C(2)-C(3)	126.4(7)	C(115)-C(114)-C(113)	120.4(3)
C(2)-C(3)-C(4)	120.1(7)	C(114)-C(115)-C(116)	120.8(3)
C(5)-C(4)-C(3)	122.3(7)	C(115)-C(116)-C(117)	120.8(3)
C(4)-C(5)-C(6)	108.9(7)	C(116)-C(117)-C(112)	117.1(3)
C(3A)-C(2A)-C(7)	107.4(7)	C(116)-C(117)-B(2)	129.6(3)
C(4A)-C(3A)-C(2A)	123.0(9)	C(112)-C(117)-B(2)	113.3(3)

C(3A)-C(4A)-C(5A)	121.5(8)	C(201)-N(201)-C(206)	107.9(2)
C(6)-C(5A)-C(4A)	123.7(8)	C(201)-N(201)-B(3)	112.3(3)
C(5A)-C(6)-N(2)	143.1(6)	C(206)-N(201)-B(3)	139.2(2)
C(5A)-C(6)-C(7)	111.7(5)	C(201)-N(202)-C(207)	106.6(2)
N(2)-C(6)-C(7)	105.3(3)	C(201)-N(202)-C(208)	127.6(3)
C(5A)-C(6)-C(5)	21.6(5)	C(207)-N(202)-C(208)	125.7(3)
N(2)-C(6)-C(5)	121.6(5)	N(201)-C(201)-N(202)	111.5(3)
C(7)-C(6)-C(5)	133.1(5)	N(201)-C(201)-C(212)	112.5(3)
C(2)-C(7)-C(6)	109.0(5)	N(202)-C(201)-C(212)	136.0(3)
C(2)-C(7)-N(1)	139.5(5)	C(203)-C(202)-C(207)	116.4(3)
C(6)-C(7)-N(1)	111.2(3)	C(202)-C(203)-C(204)	122.5(3)
C(2)-C(7)-C(2A)	26.2(4)	C(205)-C(204)-C(203)	120.9(3)
C(6)-C(7)-C(2A)	132.1(5)	C(206)-C(205)-C(204)	116.9(3)
N(1)-C(7)-C(2A)	116.0(5)	C(205)-C(206)-N(201)	131.6(3)
N(2)-C(8)-C(9)	112.5(3)	C(205)-C(206)-C(207)	121.5(3)
N(2)-C(8)-C(9A)	111.7(4)	N(201)-C(206)-C(207)	106.9(3)
C(9)-C(8)-C(9A)	32.8(4)	C(202)-C(207)-N(202)	131.2(3)
C(8)-C(9)-C(10)	109.9(5)	C(202)-C(207)-C(206)	121.7(3)
C(9)-C(10)-C(11)	112.1(5)	N(202)-C(207)-C(206)	107.1(3)
C(10A)-C(9A)-C(8)	112.3(8)	N(202)-C(208)-C(209)	113.3(2)
C(11A)-C(10A)-C(9A)	110.5(9)	C(210)-C(209)-C(208)	113.7(3)
C(13)-C(12)-C(17)	120.3(3)	C(209)-C(210)-C(211)	111.7(3)
C(13)-C(12)-C(1)	117.8(3)	C(213)-C(212)-C(217)	122.7(3)
C(17)-C(12)-C(1)	121.9(3)	C(213)-C(212)-C(201)	129.8(3)
C(14)-C(13)-C(12)	121.1(3)	C(217)-C(212)-C(201)	107.4(3)
C(15)-C(14)-C(13)	119.6(3)	C(214)-C(213)-C(212)	117.6(3)
C(14)-C(15)-C(16)	119.1(3)	C(215)-C(214)-C(213)	120.7(3)
C(15)-C(16)-C(17)	122.6(3)	C(214)-C(215)-C(216)	120.8(3)
C(12)-C(17)-C(16)	117.3(3)	C(217)-C(216)-C(215)	121.0(3)
C(12)-C(17)-B(1)	125.0(3)	C(216)-C(217)-C(212)	117.2(3)
C(16)-C(17)-B(1)	117.7(3)	C(216)-C(217)-B(3)	130.0(3)
C(101)-N(101)-C(106)	107.4(2)	C(212)-C(217)-B(3)	112.7(3)

Appendix 5: X-ray diffraction data for compound 147.

Table 28: Crystal data and structure refinement for **147**.

Empirical formula	C_{21} H_{28} N_2 O_2 Si	
Formula weight	368.54	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.9301(2) Å	α= 90°.
	b = 18.2706(6) Å	β= 96.2190(10)°.
	c = 16.8702(6) Å	γ = 90°.
Volume	2123.49(12) $Å^3$	
Z	4	
Density (calculated)	1.153 Mg/m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	792	
Crystal size	0.5 x 0.4 x 0.3 mm^3	
Theta range for data collection	1.65 to 27.50°.	
Index ranges	-8<=h<=8, -23<=k<=23, -21<=l<=20	
Reflections collected	18932	
Independent reflections	5000 [R(int) = 0.0271]	
Completeness to theta = 27.50°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.959 and 0.940	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5000 / 1 / 469	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0832	
R indices (all data)	R1 = 0.0364, wR2 = 0.0858	

Absolute structure parameter	0
Extinction coefficient	0
Largest diff. peak and hole	0.368 and -0.201 e.Å^{-3}

Table 29: Bond lengths [Å] and angles [°] for **137**.

Si(1)-C(2)	1.863(2)	C(10)-N(2)	1.379(3)
Si(1)-C(3)	1.872(2)	N(1)-C(11)	1.394(3)
Si(1)-C(1)	1.879(3)	C(11)-C(12)	1.402(3)
Si(1)-C(4)	1.902(2)	C(11)-C(16)	1.413(3)
C(1)-H(1B)	0.9800	C(12)-C(13)	1.388(3)
C(1)-H(1C)	0.9800	C(12)-H(12A)	0.9500
C(1)-H(1D)	0.9800	C(13)-C(14)	1.398(4)
C(2)-H(2A)	0.9800	C(13)-H(13A)	0.9500
C(2)-H(2B)	0.9800	C(14)-C(15)	1.391(3)
C(2)-H(2C)	0.9800	C(14)-H(14A)	0.9500
C(3)-H(3A)	0.9800	C(15)-C(16)	1.392(3)
C(3)-H(3B)	0.9800	C(15)-H(15A)	0.9500
C(3)-H(3C)	0.9800	C(16)-N(2)	1.392(3)
C(4)-C(5)	1.412(3)	N(2)-C(17)	1.464(3)
C(4)-C(9)	1.414(3)	C(17)-C(18)	1.522(3)
C(5)-C(6)	1.391(3)	C(17)-H(17A)	0.9900
C(5)-H(5A)	0.9500	C(17)-H(17B)	0.9900
C(6)-C(7)	1.380(3)	C(18)-O(1)	1.422(3)
C(6)-H(6A)	0.9500	C(18)-H(18A)	0.9900
C(7)-C(8)	1.396(3)	C(18)-H(18B)	0.9900
C(7)-H(7A)	0.9500	O(1)-C(19)	1.426(3)
C(8)-C(9)	1.402(3)	C(19)-C(20)	1.502(4)
C(8)-H(8A)	0.9500	C(19)-H(19A)	0.9900
C(9)-C(10)	1.485(3)	C(19)-H(19B)	0.9900
C(10)-N(1)	1.320(3)	C(20)-O(2)	1.406(3)

C(20)-H(20A)	0.9900	C(32)-C(37)	1.402(3)
C(20)-H(20B)	0.9900	C(32)-C(33)	1.403(3)
O(2)-C(21)	1.415(3)	C(33)-C(34)	1.387(3)
C(21)-H(21A)	0.9800	C(33)-H(33A)	0.9500
C(21)-H(21B)	0.9800	C(34)-C(35)	1.401(4)
C(21)-H(21C)	0.9800	C(34)-H(34A)	0.9500
Si(2)-C(24)	1.866(2)	C(35)-C(36)	1.392(3)
Si(2)-C(23)	1.872(2)	C(35)-H(35A)	0.9500
Si(2)-C(22)	1.878(3)	C(36)-C(37)	1.398(3)
Si(2)-C(25)	1.897(2)	C(36)-H(36A)	0.9500
C(22)-H(22A)	0.9800	C(37)-N(4)	1.392(3)
C(22)-H(22B)	0.9800	N(4)-C(38)	1.469(3)
C(22)-H(22C)	0.9800	C(38)-C(39)	1.524(3)
C(23)-H(23A)	0.9800	C(38)-H(38A)	0.9900
C(23)-H(23B)	0.9800	C(38)-H(38B)	0.9900
C(23)-H(23C)	0.9800	C(39)-O(3)	1.418(3)
C(24)-H(24A)	0.9800	C(39)-H(39A)	0.9900
C(24)-H(24B)	0.9800	C(39)-H(39B)	0.9900
C(24)-H(24C)	0.9800	O(3)-C(40)	1.416(3)
C(25)-C(26)	1.408(3)	C(40)-C(41)	1.504(4)
C(25)-C(30)	1.421(3)	C(40)-H(40A)	0.9900
C(26)-C(27)	1.393(3)	C(40)-H(40B)	0.9900
C(26)-H(26A)	0.9500	C(41)-O(4)	1.418(3)
C(27)-C(28)	1.382(3)	C(41)-H(41A)	0.9900
C(27)-H(27A)	0.9500	C(41)-H(41B)	0.9900
C(28)-C(29)	1.393(3)	O(4)-C(42)	1.415(3)
C(28)-H(28A)	0.9500	C(42)-H(42A)	0.9800
C(29)-C(30)	1.400(3)	C(42)-H(42B)	0.9800
C(29)-H(29A)	0.9500	C(42)-H(42C)	0.9800
C(30)-C(31)	1.487(3)		
C(31)-N(3)	1.320(3)	C(2)-Si(1)-C(3)	110.86(12)
C(31)-N(4)	1.381(3)	C(2)-Si(1)-C(1)	107.60(12)
N(3)-C(32)	1.393(3)	C(3)-Si(1)-C(1)	107.83(13)

C(2)-Si(1)-C(4)	112.45(10)	C(7)-C(8)-C(9)	120.3(2)
C(3)-Si(1)-C(4)	110.24(10)	C(7)-C(8)-H(8A)	119.8
C(1)-Si(1)-C(4)	107.66(11)	C(9)-C(8)-H(8A)	119.8
Si(1)-C(1)-H(1B)	109.5	C(8)-C(9)-C(4)	121.25(19)
Si(1)-C(1)-H(1C)	109.5	C(8)-C(9)-C(10)	118.89(19)
H(1B)-C(1)-H(1C)	109.5	C(4)-C(9)-C(10)	119.79(19)
Si(1)-C(1)-H(1D)	109.5	N(1)-C(10)-N(2)	113.51(18)
H(1B)-C(1)-H(1D)	109.5	N(1)-C(10)-C(9)	122.80(19)
H(1C)-C(1)-H(1D)	109.5	N(2)-C(10)-C(9)	123.66(18)
Si(1)-C(2)-H(2A)	109.5	C(10)-N(1)-C(11)	104.71(17)
Si(1)-C(2)-H(2B)	109.5	N(1)-C(11)-C(12)	129.9(2)
H(2A)-C(2)-H(2B)	109.5	N(1)-C(11)-C(16)	110.28(18)
Si(1)-C(2)-H(2C)	109.5	C(12)-C(11)-C(16)	119.8(2)
H(2A)-C(2)-H(2C)	109.5	C(13)-C(12)-C(11)	117.6(2)
H(2B)-C(2)-H(2C)	109.5	C(13)-C(12)-H(12A)	121.2
Si(1)-C(3)-H(3A)	109.5	C(11)-C(12)-H(12A)	121.2
Si(1)-C(3)-H(3B)	109.5	C(12)-C(13)-C(14)	121.7(2)
H(3A)-C(3)-H(3B)	109.5	C(12)-C(13)-H(13A)	119.2
Si(1)-C(3)-H(3C)	109.5	C(14)-C(13)-H(13A)	119.2
H(3A)-C(3)-H(3C)	109.5	C(15)-C(14)-C(13)	122.0(2)
H(3B)-C(3)-H(3C)	109.5	C(15)-C(14)-H(14A)	119.0
C(5)-C(4)-C(9)	116.40(19)	C(13)-C(14)-H(14A)	119.0
C(5)-C(4)-Si(1)	118.34(16)	C(14)-C(15)-C(16)	116.1(2)
C(9)-C(4)-Si(1)	125.22(15)	C(14)-C(15)-H(15A)	121.9
C(6)-C(5)-C(4)	122.2(2)	C(16)-C(15)-H(15A)	121.9
C(6)-C(5)-H(5A)	118.9	N(2)-C(16)-C(15)	132.2(2)
C(4)-C(5)-H(5A)	118.9	N(2)-C(16)-C(11)	105.01(18)
C(7)-C(6)-C(5)	120.4(2)	C(15)-C(16)-C(11)	122.8(2)
C(7)-C(6)-H(6A)	119.8	C(10)-N(2)-C(16)	106.47(17)
C(5)-C(6)-H(6A)	119.8	C(10)-N(2)-C(17)	128.95(18)
C(6)-C(7)-C(8)	119.5(2)	C(16)-N(2)-C(17)	124.50(18)
C(6)-C(7)-H(7A)	120.3	N(2)-C(17)-C(18)	113.30(18)
C(8)-C(7)-H(7A)	120.3	N(2)-C(17)-H(17A)	108.9

C(18)-C(17)-H(17A)	108.9	C(24)-Si(2)-C(25)	114.84(10)
N(2)-C(17)-H(17B)	108.9	C(23)-Si(2)-C(25)	109.58(10)
C(18)-C(17)-H(17B)	108.9	C(22)-Si(2)-C(25)	106.37(10)
H(17A)-C(17)-H(17B)	107.7	Si(2)-C(22)-H(22A)	109.5
O(1)-C(18)-C(17)	108.67(18)	Si(2)-C(22)-H(22B)	109.5
O(1)-C(18)-H(18A)	110.0	H(22A)-C(22)-H(22B)	109.5
C(17)-C(18)-H(18A)	110.0	Si(2)-C(22)-H(22C)	109.5
O(1)-C(18)-H(18B)	110.0	H(22A)-C(22)-H(22C)	109.5
C(17)-C(18)-H(18B)	110.0	H(22B)-C(22)-H(22C)	109.5
H(18A)-C(18)-H(18B)	108.3	Si(2)-C(23)-H(23A)	109.5
C(18)-O(1)-C(19)	112.80(17)	Si(2)-C(23)-H(23B)	109.5
O(1)-C(19)-C(20)	108.7(2)	H(23A)-C(23)-H(23B)	109.5
O(1)-C(19)-H(19A)	110.0	Si(2)-C(23)-H(23C)	109.5
C(20)-C(19)-H(19A)	110.0	H(23A)-C(23)-H(23C)	109.5
O(1)-C(19)-H(19B)	110.0	H(23B)-C(23)-H(23C)	109.5
C(20)-C(19)-H(19B)	110.0	Si(2)-C(24)-H(24A)	109.5
H(19A)-C(19)-H(19B)	108.3	Si(2)-C(24)-H(24B)	109.5
O(2)-C(20)-C(19)	108.6(2)	H(24A)-C(24)-H(24B)	109.5
O(2)-C(20)-H(20A)	110.0	Si(2)-C(24)-H(24C)	109.5
C(19)-C(20)-H(20A)	110.0	H(24A)-C(24)-H(24C)	109.5
O(2)-C(20)-H(20B)	110.0	H(24B)-C(24)-H(24C)	109.5
C(19)-C(20)-H(20B)	110.0	C(26)-C(25)-C(30)	116.07(19)
H(20A)-C(20)-H(20B)	108.3	C(26)-C(25)-Si(2)	117.96(16)
C(20)-O(2)-C(21)	113.4(2)	C(30)-C(25)-Si(2)	125.53(15)
O(2)-C(21)-H(21A)	109.5	C(27)-C(26)-C(25)	122.6(2)
O(2)-C(21)-H(21B)	109.5	C(27)-C(26)-H(26A)	118.7
H(21A)-C(21)-H(21B)	109.5	C(25)-C(26)-H(26A)	118.7
O(2)-C(21)-H(21C)	109.5	C(28)-C(27)-C(26)	119.9(2)
H(21A)-C(21)-H(21C)	109.5	C(28)-C(27)-H(27A)	120.1
H(21B)-C(21)-H(21C)	109.5	C(26)-C(27)-H(27A)	120.1
C(24)-Si(2)-C(23)	110.07(11)	C(27)-C(28)-C(29)	119.8(2)
C(24)-Si(2)-C(22)	106.86(12)	C(27)-C(28)-H(28A)	120.1
C(23)-Si(2)-C(22)	108.89(12)	C(29)-C(28)-H(28A)	120.1

C(28)-C(29)-C(30)	120.3(2)	N(4)-C(38)-H(38A)	108.8
C(28)-C(29)-H(29A)	119.8	C(39)-C(38)-H(38A)	108.8
C(30)-C(29)-H(29A)	119.8	N(4)-C(38)-H(38B)	108.8
C(29)-C(30)-C(25)	121.30(19)	C(39)-C(38)-H(38B)	108.8
C(29)-C(30)-C(31)	119.19(18)	H(38A)-C(38)-H(38B)	107.6
C(25)-C(30)-C(31)	119.50(18)	O(3)-C(39)-C(38)	109.38(18)
N(3)-C(31)-N(4)	113.39(18)	O(3)-C(39)-H(39A)	109.8
N(3)-C(31)-C(30)	123.14(18)	C(38)-C(39)-H(39A)	109.8
N(4)-C(31)-C(30)	123.46(18)	O(3)-C(39)-H(39B)	109.8
C(31)-N(3)-C(32)	104.62(17)	C(38)-C(39)-H(39B)	109.8
N(3)-C(32)-C(37)	110.48(18)	H(39A)-C(39)-H(39B)	108.2
N(3)-C(32)-C(33)	129.8(2)	C(40)-O(3)-C(39)	114.08(17)
C(37)-C(32)-C(33)	119.7(2)	O(3)-C(40)-C(41)	109.1(2)
C(34)-C(33)-C(32)	117.5(2)	O(3)-C(40)-H(40A)	109.9
C(34)-C(33)-H(33A)	121.3	C(41)-C(40)-H(40A)	109.9
C(32)-C(33)-H(33A)	121.3	O(3)-C(40)-H(40B)	109.9
C(33)-C(34)-C(35)	121.9(2)	C(41)-C(40)-H(40B)	109.9
C(33)-C(34)-H(34A)	119.0	H(40A)-C(40)-H(40B)	108.3
C(35)-C(34)-H(34A)	119.0	O(4)-C(41)-C(40)	109.0(2)
C(36)-C(35)-C(34)	121.8(2)	O(4)-C(41)-H(41A)	109.9
C(36)-C(35)-H(35A)	119.1	C(40)-C(41)-H(41A)	109.9
C(34)-C(35)-H(35A)	119.1	O(4)-C(41)-H(41B)	109.9
C(35)-C(36)-C(37)	115.7(2)	C(40)-C(41)-H(41B)	109.9
C(35)-C(36)-H(36A)	122.1	H(41A)-C(41)-H(41B)	108.3
C(37)-C(36)-H(36A)	122.1	C(42)-O(4)-C(41)	111.5(2)
N(4)-C(37)-C(36)	131.3(2)	O(4)-C(42)-H(42A)	109.5
N(4)-C(37)-C(32)	105.34(18)	O(4)-C(42)-H(42B)	109.5
C(36)-C(37)-C(32)	123.4(2)	H(42A)-C(42)-H(42B)	109.5
C(31)-N(4)-C(37)	106.14(17)	O(4)-C(42)-H(42C)	109.5
C(31)-N(4)-C(38)	129.76(18)	H(42A)-C(42)-H(42C)	109.5
C(37)-N(4)-C(38)	123.84(18)	H(42B)-C(42)-H(42C)	109.5
N(4)-C(38)-C(39)	114.01(18)		

Conferences and Colloquia

Colloquia

October, 2001	Dr Colin Raston (Univ of Leeds): Towards benign supramolecular chemistry: synthesis - self organisation
November, 2001	Dr Jeremy Kilburn (University of Southampton): Synthetic Receptors for Peptides – Rational and Combinatorial Approaches.
December, 2001	Dr Mike Eaton (Celltech): Drugs of the Future.
February, 2002	Dr Elizabeth Hall (Institute of Biotechnology, Cambridge University): The Heart of the Matter.
February, 2002	Ezat Khosdel (Unilever): Industrial aspects of research.
October, 2002	Professor Gideon Davies (University of York): Structural Enzymology of Glycosyl Transfer: How Enzymes Make and Degrade Polysaccharides.
October, 2002	Professor Marcetta Darensbourg, (Texas A&M University): Functioning Catalysts Inspired by Active Sites in Bio-Organometallic Chemistry: The Hydrogenases.
November, 2002	Dr Dave Alker (Pfizer): The Discovery of a New Medicine.
December, 2002	Professor Carsten Bolm (Institut für Organische Chemie der RWTH, Aachen): Asymmetric catalysis for enantioselective C-C-bond formation (*Degussa lecture*).
January, 2003	Professor Pat Bailey (UMIST): Planned and unplanned routes to bio-active target molecules.
January, 2003	Dr David Procter (University of Glasgow): New Strategies and Methods for Organic Synthesis.
February, 2003	Dr John Emsley (University of Cambridge): False Alarms: Chemistry and the Media.
March, 2003	Professor Richard Taylor (University of York): Adventures in Natural Product Synthesis.

October, 2003	Professor Huw Davies (University at Buffalo, USA): Applications of Catalytic Asymmetric C-H Activation to Organic Synthesis.
October, 2003	Dr Roger Newton (Maybridge plc): The Pharmaceutical Industry - Does it have a Future?
October, 2003	Professor Matthias Beller (Inst. für Organische Katalyseforschung an der Universität Rostock, Germany): Homogeneous Catalysis a Key Technology for Environmentally Benign Synthesis of Fine Chemicals and Pharmaceuticals (The Degussa Lecture).
January, 2004	Professor Mark Bradley (University of Southampton): Arrays and Combinatorial Chemistry.
February, 2004	Dr Andrew Burgess (ICI): Human Skin - Barrier Function and Material Properties.
February, 2004	Professor A P De Silva, (Queens University of Belfast): Designer Molecules for Photonic Signalling.
March, 2004	Dr D.N. Woolfson (Department of Biochemistry, University of Sussex): Bottom-up assembly of peptide-based supramolecular and nanoscale structures.
July, 2004	Professor Sir Harry Kroto, Nobel Laureate in Chemistry (1996) 2010: a NanoSpace Odyssey

Symposia and Conferences

December 2001	Sheffield Stereochemistry, University of Sheffield.
April 2002	Perkin North East Meeting, University of York.
September 2002	The Merck Lectureship Reunion, University of Cambridge.
December2002	Sheffield Stereochemistry, University of Sheffield.
March 2003	Perkin Division North East Meeting, University of Newcastle.
December 2003	Sheffield Stereochemistry, University of Sheffield.
March 2004	15th SCI Post-graduate Organic Chemistry Symposium (North), University of York.
May 2004	Boronate Symposium, University of Durham.
September 2004	The 3rd European Meeting on Boron Chemistry (Euroboron 3), Prague, Czech Republic.

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