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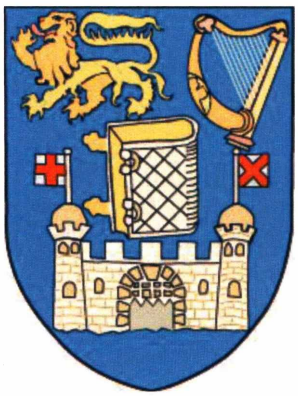
An Investigation into the Catalytic Versatility of Low Toxicity Azolium Ions



Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

Lauren Myles

Under the supervision of Prof. Stephen Connon

January 2013

Declaration

submitted as an exercise for a degree at this or any other
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rary may lend or copy the thesis upon request.

B. Procuranti, L. Myles, N. Gathergood and S. J. Connon, *Synthesis*, 2009, 4082.

L. Myles, R. Gore, M. Spulak, N. Gathergood, S. J. Connon, *Green Chem.*, 2010, 12, 1157.

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Acknowledgements

First and foremost, I would like to acknowledge my family, in particular my Mum and Dad, for their continued support and belief in me, for which I am eternally grateful. A huge thanks to my boyfriend Peter for always being there to support, listen to and encourage me throughout this process.

Thanks to my supervisor Prof. Stephen Connon for allowing me the wonderful opportunity to pursue this research. Thank you for all of your guidance, patience and support it is greatly appreciated.

Thank you to all of the incredible people I have had the privilege of meeting and working with over the course of my PhD. Thanks especially to the past and present members of the Connon group, Southern group and Scanlan group- to Claire-Louise, Claire, Neasa, Michelle, Linda, Sivaji, Cormac, Eoghan and the others I have spent time working with over the years. A special mention to the boys of the B-lab Seán, Francesco, Emiliano and Simon, thank you for making the lab such an enjoyable place I could not have picked better people to work with every day. A thank you to the Evans group; Rachel, Niamh, Judith and Adam, for listening to me and encouraging me during this process especially in the latter stages. Special thanks also to my dear friends Claudio and Sarah K, thank you both for your amazing support and friendship, I could not have done this without you.

Finally, I would like to extend my gratitude to the staff of the chemistry department, in particular to Dr. John O'Brien and Dr. Manuel Reuther.

Abstract

A somewhat unexpected observation made by our group that appropriately substituted pyridinium ions were capable of acting as Brønsted acid catalysts in the presence of protic additives (*i.e.* methanol) caught our attention. It is postulated that the addition of nucleophiles to these aprotic materials generate catalytically active acidic species *in situ*. This strategy was reasoned to be applicable to the design of catalysts based on the imidazolium ions with potential advantages over the pyridinium based molecules. These advantageous properties allowed for the design of additive controlled acidic molecules for use as catalysts which can be turned "on and off" in the presence of protic media, with the environmental impact of this novel catalyst also taken into account when designing the molecule.

Initial screening of a first generation of these imidazolium ion-based catalysts was carried out in the acetalisation of benzaldehyde with methanol. The preliminary screening was carried out using various catalysts incorporating both ester and amide side chains. The effect of the counterion was investigated and it was determined that there was a relationship between the catalytic activity of the salt and the choice of counterion; with the tetrafluoroborate salt proving to be significantly superior to the other salts evaluated. The most active catalyst developed can promote the acetalisation and thioacetalisation reactions of a range of aldehydes at relatively low catalyst loadings (5 mol%). The design of more efficient second generation catalysts was then undertaken, with the addition of electron withdrawing groups to the C-2, C-4 and C-4/5 positions of the imidazolium ion. The second generation catalysts proved to be highly active; converting benzaldehyde to the dimethyl acetal in 95% yield at 0.1 mol % loading, a considerable improvement on the efficacy of the first generation catalysts. The new generation catalysts tolerated all substrates compatible with the first generation with much lower loadings (5-50 times) being employed. In addition it was also found that the acetalisation of ketones could be carried out. Recycling of the both generations of catalysts was also carried out with the compound being recovered by precipitation; the 1st generation being reused in 15 iterative cycles while the 2nd generation catalysts could be recycled 5 times.

These 2nd generation imidazolium ion-based catalysts also demonstrated an affinity for thiol-derived compounds which was not observed with conventional Brønsted acidic catalysts. It was determined that the highly active 4,5- substituted imidazolium ion-based catalysts could

not only carry out an intramolecular transacetalisation to afford various 5-membered tetrahydrofuran ring systems, it also generated tetrahydrothiophene derived 5-membered rings through the novel intramolecular transthioacetalisation of various thiol derived substrates. This catalysis was particularly satisfactory, as it is not observed in the presence of conventional acids, such as *p*TSA. Furthermore, the predilection of thiols to react in the presence of these catalysts, led to the development of an organocatalytic procedure through which various highly synthetically useful cyclic dithiane-protected aldehydes and ketones could be cleaved in the presence of water. An equally effective anhydrous procedure for dithiane cleavage was also developed using these imidazolium ion-based catalysts. These represent novel mild and efficient catalytic hydrolysis procedures for a conventionally arduous deprotection reaction, which generally requires the employment of harsh reagents such as mercury-based compounds or stoichiometric amounts of reagents to cleave the synthetically useful dithiane.

It was also demonstrated that easily accessible, low toxicity 1,2,4-triazolium salts could operate through the same mode of action as these imidazolium ion-based compounds in the presence of protic media, generating an acidic moiety *in situ* which could efficiently catalyse the acetalisation of various aldehydes. At the same time, the ability of the same compounds to act as highly effective precatalysts in the NHC catalysed benzoin condensation of various aldehydes was also demonstrated. This led to the development of a highly novel 'bifunctional' catalyst system through which the practitioner can exploit the triazolium salt in a unique *in situ* catalyst modification strategy. The role played by the triazolium salt is sequentially controlled in an 'on-off' fashion: initially acting as a promoter of the acid-catalysed acetalisation reaction, then on addition of base, deprotonation to the corresponding carbene allows for subsequent NHC-mediated reactions *i.e.* the benzoin condensation (which under normal circumstances would be incompatible with acid catalysis) to occur.

Abbreviations

Å	Angstrom
Ac	Acetyl
Ad	Adamantyl
Adoc	Adamantyloxycarbonyl
ARC	Anion-relay chemistry
ATCC	American Type Culture Collection
atm	Atmosphere
BA	Brønsted acid
BAIL	Brønsted acidic ionic liquid
BCF	Bioconcentration factor
Biodeg.	Biodegradability
BINAP	2,2'-Diamino-1,1'-binapthalene
[bmim]	1-Butyl-3-methylimidazolium
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
BOD	Biochemical oxygen demand
BOM	Benzylmethyoxymethyl
Bu	Butyl
CAN	Ceric ammonium nitrate
cat.	Catalyst
Cbz.	Benzyloxycarbonyl
COD	Chemical oxygen demand
conv.	Conversion
Cys.	Cysteine
DABCO	1,4-diazobicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodimide
ee	Enantiomeric excess
[emim]	1-Ethyl-3-methylimidazolium
equiv.	Equivalent
er	enantiomeric ratio
Et	Ethyl
EWG	Electron withdrawing group
[hmim]	3-Methylimidazolium
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectroscopy
IBX	*o*-Iodobenzoic acid
IL	Ionic liquid
im	Imidazolium
*i*Pr	Isopropyl
IR	Infra red
LA	Lewis acid

m	*meta*
Me	Methyl
MeCN	Acetonitrile
MEM	Methoxyethoxymethyl
MIC	Minimum inhibitory concentration
MOM	Methoxymethyl
MOZ	*p*-methoxybenzyloxycarbonyl
MW	Microwave
nbd	norbornadiene
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NTf_2	Bis(trifluoromethylsulfonyl)imide
o	*ortho*
OTf	Trifluoromethanesulfonate
p	*para*
PG	Protecting group
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulfonate
*p*TSA	*p*-Toluenesulfonic acid
Pyr	Pyridinium
Rt	Room temperature
RTIL	Room temperature ionic liquid
SAR	Structure activity relationship
SDS	Sodium dodecyl sulfate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
ThOD	Theoretical oxygen demand
THP	Tetrahydropyran
TIC	Theoretical inorganic carbon
TMS	Trimethylsilyl
TOC	Total organic carbon
TON	Turnover number
TSIL	Task specific ionic liquid

1.1 Ionic liquids

Ionic liquids are low melting organic salts that consist solely of ions. They have a number of advantages as both solvent and catalyst candidates, these include negligible vapour pressures, good thermal stabilities, broad liquid temperature ranges and high solvation interactions with polar and non-polar solvents.[1] Due to these interesting properties, they have attracted great attention in both industrial and academic research groups. Although the first ionic liquid $[EtNH_2][NO_3]$, with a melting point of 12 °C, was discovered in 1914 by Walden,[2] the first functional ionic liquids or low temperature molten solids were discovered by Major Lowell King in 1963 whilst exploring replacements for LiCl/KCl molten salt electrolytes used in thermal batteries.[3]

Further progression was made by Wilkes *et al.* who, in 1982, developed binary ionic liquids made from aluminium (III) chloride and a 1,3-dialkylimidazolium chloride.[4] These binary salts allowed for the tuning of the melting point by variation of the mole fractions of the aluminium(III)chloride and 1,3-dialkylimidazolium chloride present,[5] which was not possible using the earlier simple salts *e.g.* $[EtNH_2][NO_3]$ which exhibit a more simple melting behaviour. In 1986, the same group introduced the first generation of Lewis acidic ionic liquids based on simple salt structures *e.g.* 1-butyl-3-methyl imidazolium chloroaluminate salts such as **1** (Figure 1.1).[6] Second generation ionic liquids, synthesised by Wilkes and Zaworotko, then emerged in 1992 in which the anion was changed from the moisture sensitive chloroaluminate to tetrafluoroborate *i.e.* **2** (Figure 1.1) and other anions; thereby rendering the moieties much more air and moisture stable.[7]

Further advancements ten years later by Davis *et al.* led to the development of task specific ionic liquids (TSILs) such as **3** (Figure 1.1). This development resulted in augmented interest in these molecules due to the "designability" of the moieties by changing either the cation, anion or both to produce a compound with particular physical or chemical properties as part of the ionic structure.[8] This allowed for the design of compounds meeting the requirements of the chemical reaction under scrutiny, meaning there could be vast applications for these simple salts in organic synthesis, electrochemistry,[9] dye sensitised solar cells,[10] fuel cells and separation sciences.[11]

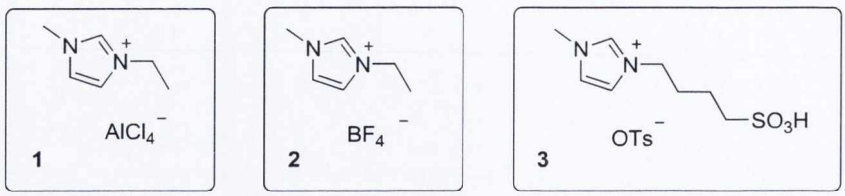


Figure 1.1 Three different classes of ionic liquids.

1.1.1 Room temperature ionic liquids

Recent years have seen a significant increase in the number of publications on the subject of room temperature ionic liquids (RTILs). Their uses include that of both co-solvents and reagents,[12,13] along with applications in biotransformations[14-16] and in organocatalysis.[17] RTILs have a somewhat simple composition- they generally consist of uncomplicated functionalised heterocycles (*e.g.* pyridinium **4**, imidazolium **5**), ammonium **6** or phosphonium **7** cationic moieties with organic (**8-10**) and inorganic(**11-14**) anions (Figure 2). This along with the fact that one or both of the ions are relatively large, when compared to typical inorganic salts such as NaCl (which consist of tightly packed ions), leads to the cation/anion pairing having a low degree of symmetry. This phenomenon contributes to a reduction in the lattice energy of the crystalline form of the salt *i.e.* the cations and anions do not pack effectively, hence preventing crystallisation and giving rise to them remaining liquids at low temeperature.[18] As stated, although the main cations employed today include compounds **4-8** (Figure 1.2) however there are also some derived from natural products[19] and some more obscure compounds.[20]

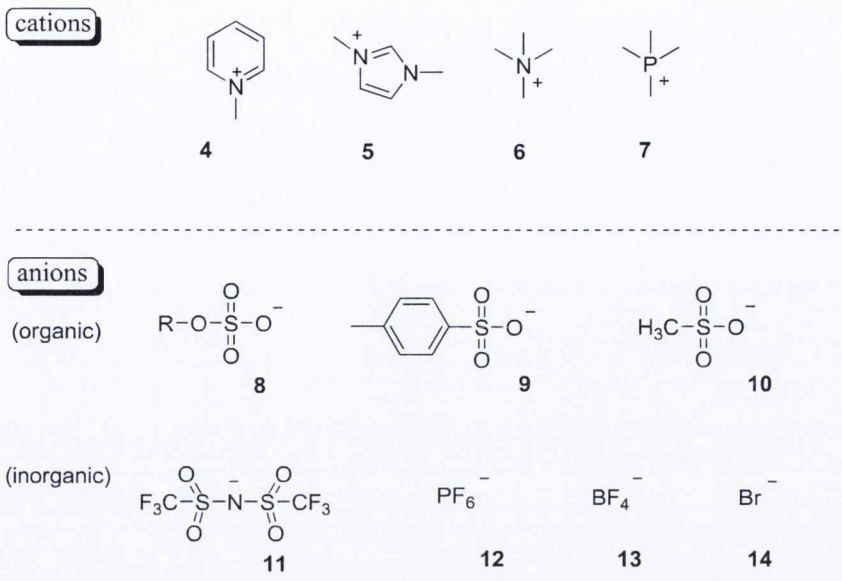


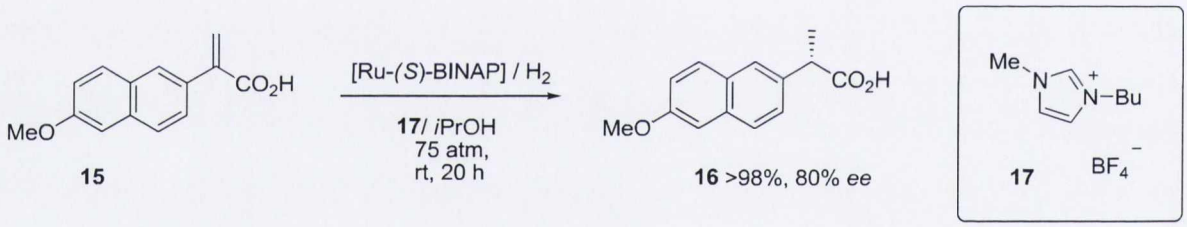
Figure 1.2 Commonly employed cations and anions for RTILs.

The variation in cation and anion choice allows for the fine tuning of these liquids for specific chemical applications, in addition to altering the physical properties of the compounds.[21] Bulky, asymmetric cationic moieties result in low melting points, while the anion choice generally determines the air and moisture stability of the ionic liquid.[21] The polarity of the molecule can also be altered, again through the modification of the cationic/anionic component, the variability of which allows for the dissolution of various compounds, including gases, in the ionic media.[21] Due to their non-volatile nature, easy recovery from reaction media and other chemical properties these neoteric solvents can be regarded as green.[22]

1.1.1.1 Room temperature ionic liquids as solvents: transition metal catalysis

Ionic liquids as solvents for transition metal catalysis have been investigated since the work of Chauvin *et al.* in 1990, in which they dissolved nickel catalysts in weakly acidic chloroaluminate melts and explored the use of the resulting ionic liquid solution in the olefin dimerisation of propene.[23] Since these initial studies, it has been found that RTILs can be used to dissolve many organometallic species, and depending on the properties of the anion, can be used as either inert solvents or co-catalysts.

The presence of a hexafluorophosphate, tetrafluoroborate or similar counterion usually renders the ionic liquid an inert solvent which provides a weakly coordinating medium for the transition metal catalysis to take place.[24] Hydrogenations are common reactions carried out in biphasic ionic liquid/solvent media. Seminal work by Chauvin *et al.* in 1995 showed that the hydrogenation of cyclohexa-1,3-diene by $[Rh(nbd)PPh_3][PF_6]$ (nbd = norbornadiene) in $[emim][SbF_6]$ (where [emim] = 1-ethyl-3-methylimidazolium) afforded cyclohexene with 98% selectivity and 96% conversion.[25] This led to the first asymmetric hydrogenation being performed by Dupont in which the chiral catalyst $[RuCl_2$-(*S*)-BINAP$]_2 \cdot NEt_3$ was used to hydrogenate 2-(6-methoxy-2-naphtyl)acrylic acid (**15**) to the natural product (*S*)-Naproxene (**16**) quantitatively with 80% *ee* using $[bmim][BF_4]$ **17** (where [bmim] = 1-butyl-3-methylimidazolium) as a co-solvent (Scheme 1.1).[26] Many other transition metal catalysed reactions can be carried out using these types of imidazolium based cationic liquids as solvents including hydroformylations,[27] Trost-Tsuji couplings,[28] Negishi cross-couplings,[29] oligimerisations[30] and Heck reactions.[31]



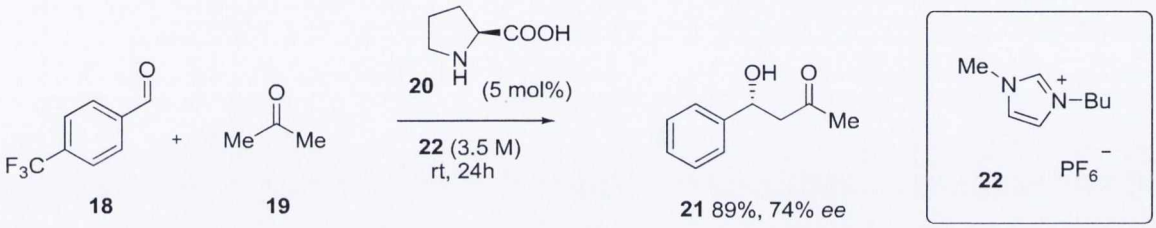
Scheme 1.1 The asymmetric hydrogenation of 2-(6-methoxy-2-naphthyl) acrylic acid (**15**) in $[bmim]^+[BF_4]^-$ / *i*PrOH.

When a halide-based counterion is present *e.g.* chloroaluminate, the ionic liquid can then act as a co-catalyst with the Lewis acidity/basicity present interacting with the catalyst; in some cases converting the neutral catalyst precursor into the active form. An example of the use of chloroaluminate ionic liquids in transition metal catalysis can be seen in olefin dimerisations, olefin polymerisation and olefin hydrogenation.[17]

1.1.1.2 Room temperature ionic liquids as solvents: organocatalysis

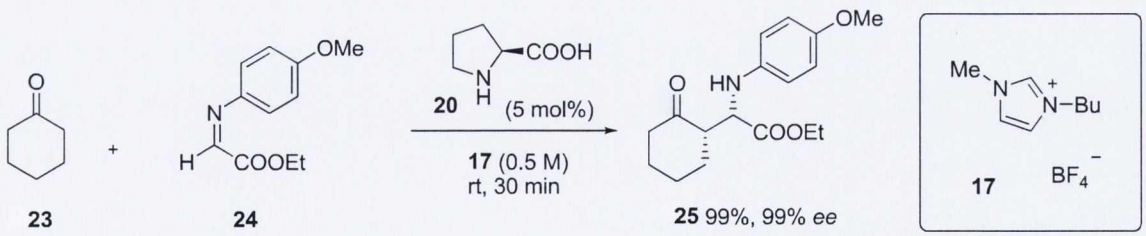
In more recent years the use of room temperature ionic liquids as solvents has not only been limited to transition metal catalysis but has also found a niche in the area of organocatalysis.

In general, imidazolium ions are the most common and synthetically useful cations employed as RTIL solvents. Kotrusz *et al.* used [bmim][PF_6] **22** as a solvent in the L-proline (**20**) catalysed aldol reaction of various aldehydes and ketones. The findings of this investigation inferred that catalyst loadings could be decreased from a conventional amount (in the absence of ionic liquid) of 30 mol% to just 5 mol% using the ionic liquid as a stand-alone solvent. The reaction between the aldol *p*-trifluoromethylbenzaldehyde **(18)** and acetone **(19)** afforded **21** in 89% yield and 74% *ee* (Scheme 1.2).[32]



Scheme 1.2 The L-Proline catalysed aldol reaction in ionic liquid solvent.

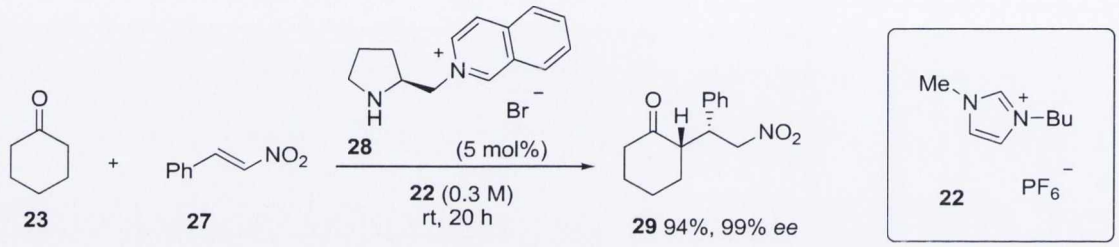
Barbas *et al.* have also demonstrated the employment of the same catalyst **20** in an asymmetric Mannich reaction of cyclohexanone (**23**) with **24** in [bmim][BF_4] **17**. This resulted in the reaction rate being amplified, with the formation of the product **25** occurring up to 50 times faster than reactions performed in traditional organic solvents. In addition, the reaction proceeded with both excellent product enantioselectivity (99% *ee*) and diastereoselectivity (*dr* 10:1) (Scheme 1.3).[33]



Scheme 1.3 L-Proline catalysed Mannich reaction in ionic liquid medium.

Organocatalytic Michael-type additions carried out in ionic liquid solvents is another area which has received considerable attention. Xu *et al.* used the functionalised ionic liquid **28** as a catalyst in the addition of cyclohexanone (**23**) to (*E*)-β-nitrostyrene (**27**) in [bmim][PF_6] **22**,

which produced high yields (94%). This is a result comparable to that obtained in more conventional solvents such as MeOH and CH_2Cl_2, whilst use of this catalyst also led to the promotion of the reaction with higher enantioselectivity (99% *ee*) than that obtained in the conventional solvents above. The reaction also required a much lower catalyst loading of 5 mol% when employed in the ionic liquid medium when compared to that in MeOH or CH_2Cl_2, which required 20 mol% loading (Scheme 1.4).[34]



Scheme 1.4 Michael addition using the functionalised IL organocatalyst **28** in an IL solvent **22**.

1.1.2 Brønsted acidic ionic liquids (BAILs)

Generally speaking Brønsted-acid catalysed reactions require the use of corrosive liquid acids (*e.g.* H_2SO_4, HCl, AcOH) which are environmentally unfriendly, hazardous and difficult to reuse. Although solid acids overcome the drawbacks of the use of liquid acids the use of these materials can too be problematic with: a) restriction of access to the matrix bound acid sites and b) deactivation through coking.[17] Many reactions also require the use of organic solvents which, again, can be environmentally impacting. Therefore, the development of more benign alternatives to these acids is desirable. Brønsted acidic ionic liquids are a type of task specific ionic liquid which partially overcome this problem: they possess the advantages of solid acids in terms of operational convenience, however, they are non-volatile and they are not vulnerable to deactivation. In addition, as homogenous catalysts, they do not suffer from the surface-area related slow-reaction rates which often bedevil heterogeneous catalysis. To date, the Brønsted acidity of the ionic liquid has been introduced *via* either the cation, anion or both.

1.1.2.1 BAILs (Type 1): ionic liquids with a covalently bound acidic site

The first reported synthesis of BAILs in 2002 by Davis *et al.* involved imidazolium and phosphonium-based compounds used as dual solvent catalysts.[8] These Brønsted acidic molecules were also, as mentioned previously, the first task specific ionic liquids. The imidazolium **30** and phosphonium **31** cation-based structures were functionalised with a covalently strong alkane sulfonic acid group, which acted as the Brønsted acidic site (Figure 1.3).

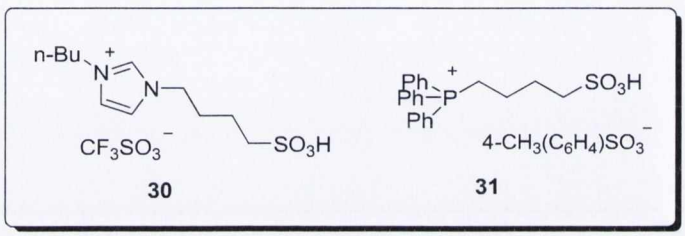
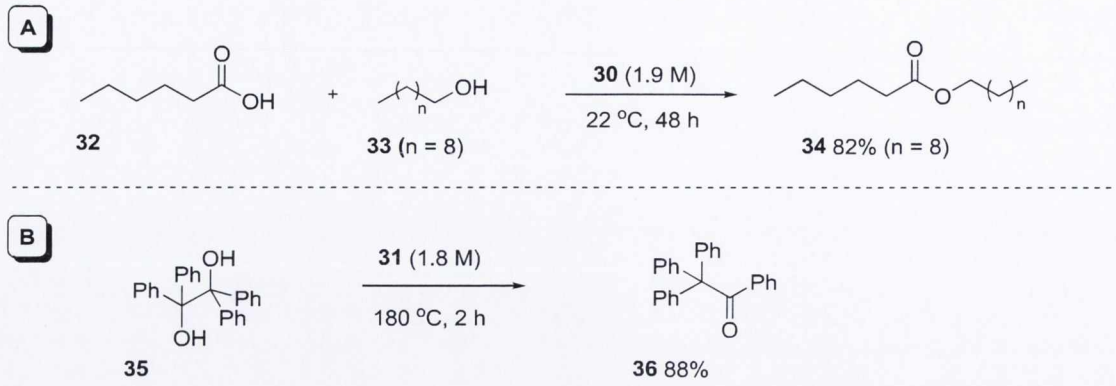


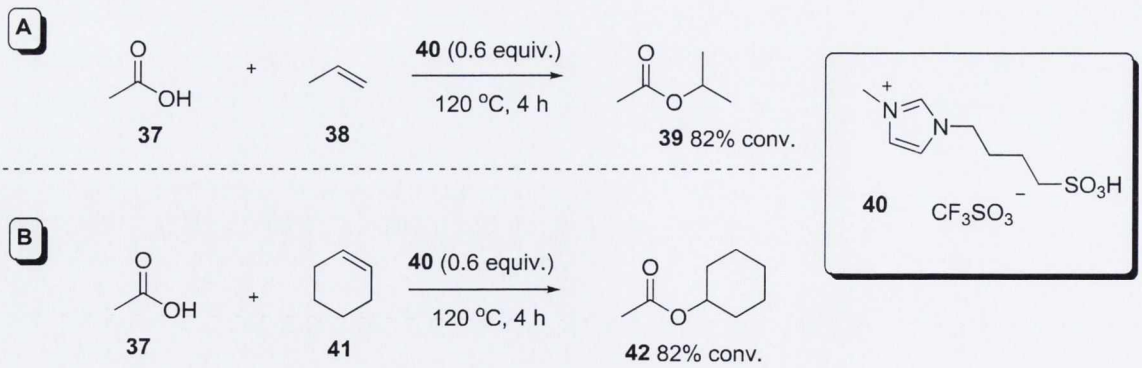
Figure 1.3 The first Brønsted acid ionic liquids (BAILs).

These catalysts represented a significant departure from the Lewis acidic ionic liquids used previously (Section 1.1) with the obvious advantage of being more air and moisture stable. Furthermore, the product could also be easily extracted, as the salts are immiscible with non-polar solvent. Both catalysts **30** and **31** were evaluated in a Fischer esterification reaction, for example the reaction of carboxylic acid **32** and alcohol **33** took place in 48 h using **30** as the acid catalyst/solvent affording the ester **34** in 82% yield (Reaction A, Scheme 1.5). While phosphonium salt **31** also catalysed an alcohol dehydrodimerisation and the pinacol/benzopinacol rearrangement, a representative example outlined below includes the benzopinacol rearrangement of **35** to yield 88% of **36** after 2 h (Reaction B, Scheme 1.5).[8]



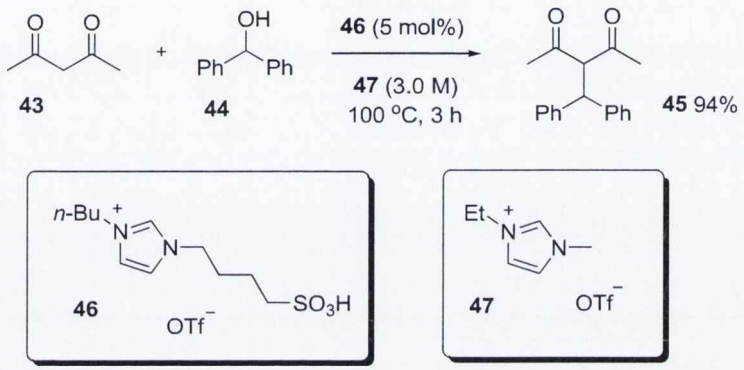
Scheme 1.5 Representative examples of employment of **30** and **31** as BAILs.

In 2005, Deng *et al.* developed a method for esterification in ionic liquids using aliphatic acids and olefins to overcome the problems experienced both with the use of expensive alcohols and the removal of water produced in esterifications involving alcohols.[35] They found that an imidazolium ionic liquid with a tethered sulfonic acid group **40**, used in stoichiometric amounts, promoted reactions between acetic acid and linear olefins, resulting in 78-99% conversion and selectivities of 100% for ethylene, propylene and butene. A representative example of this, is the reaction of acetic acid (**37**) and propylene (**38**) taking place in the presence of **40** to afford the ester **39** with 82% conversion and 100% selectivity (Reaction A, Scheme 1.6) Cycloolefin substrates gave similar conversion and selectivity, such as the reaction of **41** with **37** producing **42** with 82% conversion (Reaction B, Scheme 1.6), while the use of different aliphatic acids such as α,β-unsaturated acids also resulted in conversions of 77-89% and 100% selectivity for the ester product.[35]



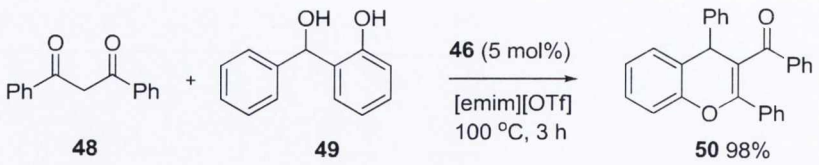
Scheme 1.6 Representative examples of esterifications carried out by Deng and co-workers using BAIL **40**.

A third example of the use of this type of sulfonic acid bound ionic liquids can be observed in the work of Matsui *et al.* in 2009. They carried out a number of direct benzylation and allylation reactions on various diketones and esters with alcohols using the Brønsted acidic catalyst **46** with good to excellent yields. An example of this includes the reaction of the diketone **43** and diphenyl methanol (**44**) in the presence of the catalyst **46** and IL-based solvent **47** affording **45** in 94% yield (Scheme 1.7).[40]



Scheme 1.7 BAIL catalysed reaction of diketone **43** and alcohol **44**.

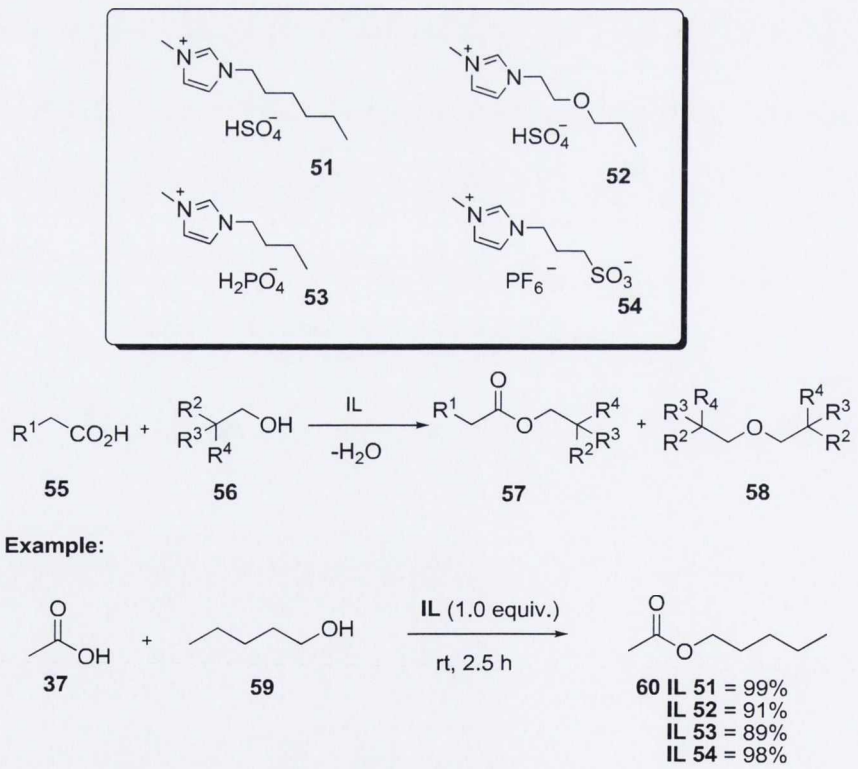
Although there had been many previous examples of catalysts for these direct C-C bond forming reactions in activated methylene compounds using alcohols as alkylating agents including trifluoromethanesulfonic acid,[36] *p*TSA,[37] methyl triflate[38] and iron (III)chloride[39] each of these possess their own hazards and also require the use of volatile organic solvents. The group led by Matsui however overcame these by carrying out the reaction in an ionic liquid medium $[emim]^+[OTf]^-$. A method was also developed for the conversion of 1,3-dicarbonyl compounds to functionalised 4*H*-chromenes in an ionic liquid system. An example of which is the catalysis of the reaction of the diketone **48** and phenol **49** to produce (2,4,-diphenyl-4*H*-chrome-3-yl)methanone **50** in 98% yield (Scheme 1.8).[40]



Scheme 1.8 Synthesis of a functionalised 4*H*-chromene using a BAIL catalyst in an ionic liquid medium.

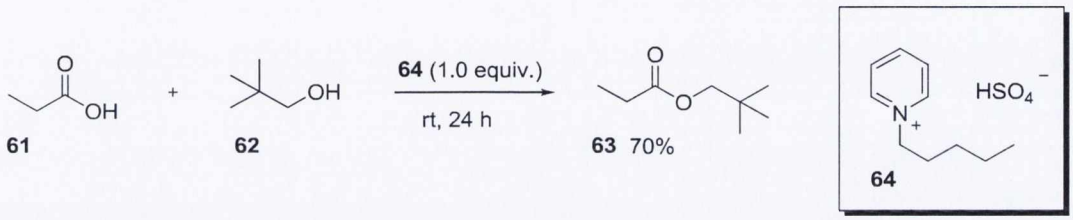
1.1.2.2 BAILs (Type 2): ionic liquids with Brønsted acidic counterion

Simultaneously to the seminal work by Davis *i.e.* concerning the sulfonic acid tethered ionic liquids, Hamelin *et al.* reported the synthesis of various imidazolium cationic liquids containing Brønsted acidic anions which were used as stoichiometric acids (**51-54**) in homogeneous esterifications (**55-58**) with good to excellent yields of 86-99%. An example of the use of these ILs and their relative activity can be observed in the reaction of **37** with alcohol **59** forming the ester **60** (Scheme 1.9).[41]



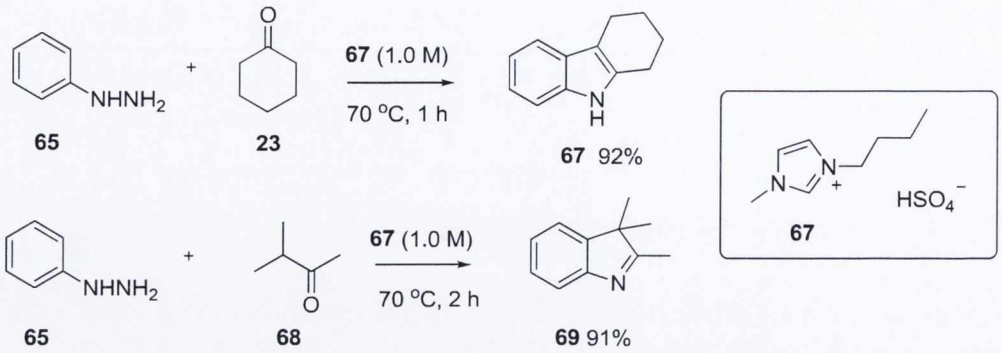
Scheme 1.9 Brønsted acidic ionic liquids type 2: anionic acids.

In 2005, Bazureau *et al.* carried out similar esterification reactions involving pyridinium ion-based compound **64** with excellent yields and catalyst recyclability, such as the formation of the ester **63** from alcohol **62** and the carboxylic acid **61** in the presence of 1 equiv. of **64** (Scheme 1.10).[42] In the same year, the application of the [bmim][HSO_4] catalyst in the protection of alcohols with tetrahydropyran (THP) ethers under solvent free conditions was also discovered.[43]



Scheme 1.10 Esterification of acid **61** with alcohol **62** catalysed by pyridinium ion-based BAIL **64**.

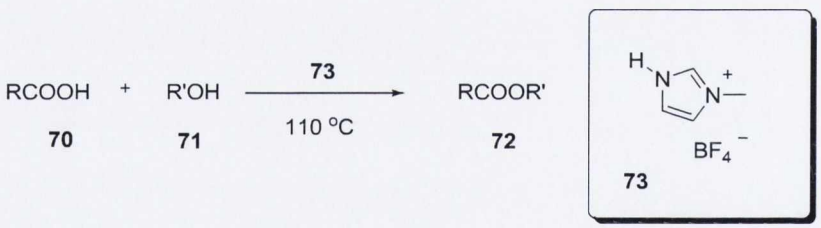
Indole rings are common heterocycles used as building blocks for many drug molecules. The Fischer indole synthesis is one of the most widespread methods used for the preparation of this ring system. Xu *et al.* carried out a one-pot Fischer indole synthesis using imidazolium cation based Brønsted acid ionic liquids containing acidic anions as dual solvent-catalysts.[44] The most active catalyst/solvent was found to be a 1-butyl-3-methylimdazolium cation with a hydrogen sulfate counterion (*i.e.* [bmim][HSO_4], (**67**)) which allowed for the formation of 1,2,3,4-tetrahydrocarbazole (**67**) through the reaction of cyclohexanone (**23**) and phenylhydrazine (**65**) in 92% yield (Scheme 1.11). Use of this compound also resulted in the selective formation of 2,3-disubstituted indoles, such as **69** in reactions involving unsymmetrical ketones *e.g.* **68** and phenyhydrazine (**65**) (Scheme 1.11). This selectivity arose due to the weakly acidic nature of the ionic liquid catalyst which leads to the formation of the more branched product.[45,46]



Scheme 1.11 Fischer indole synthesis: Brønsted acidic anion containing IL.

1.1.2.3 BAILs (Type 3): ionic liquids containing a protic ion

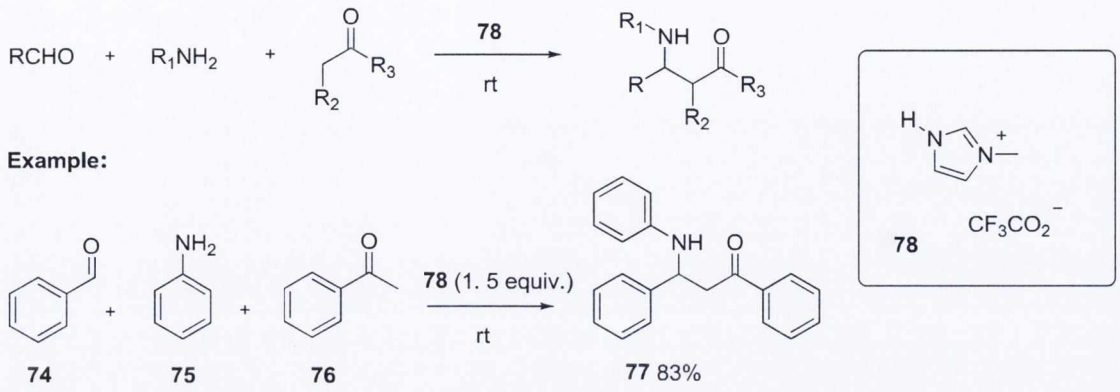
A third general strategy has also emerged in which the Brønsted acidity of the catalyst is induced through the presence of a protic imidazolium ion. This strategy was first employed by He *et al.* in 2003. He demonstrated the use of the imidazolium ionic liquid [hmim][BF_4] **73** in the esterification of various carboxylic acids **70** with alcohol **71**, resulting in the generation of esters (**72**) with excellent conversions of 83-99% at stoichiometric loading.[47] The catalyst was recycled through the decantation of the insoluble ester product and reused in 8 runs without exhibiting any loss in activity (Scheme 1.12).



Scheme 1.12 Brønsted acid ionic liquids type 3: protic imidazolium ions.

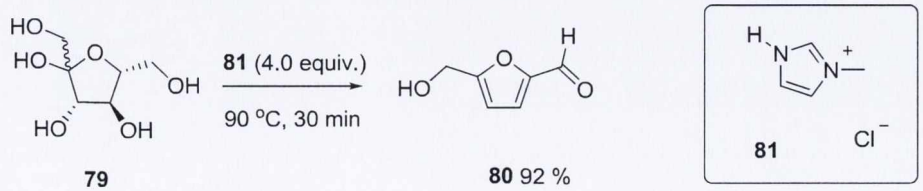
The production of β-amino carbonyl compounds *via* the Mannich reaction is one of the most useful methods for the synthesis of nitrogenous molecules used in natural product synthesis and pharamceuticals.[48,49] In 2004, Sun *et al.* demonstrated the activity of the imidazolium ionic liquid [hmim][TFA] **78** in a three-component Mannich reaction. An example of which involves the reaction of benzaldehyde (**74**), aniline (**75**) and acetophenone (**76**) yielding 83% of the β-amino carbonyl product **77** (Scheme 1.13).[50] This IL was also found to catalyse the

reaction utilising other aldehydes, ketones and amines with desirable yields and was reused 5 times with little loss in activity.



Scheme 1.13 Catalysis of Mannich reaction by **78**.

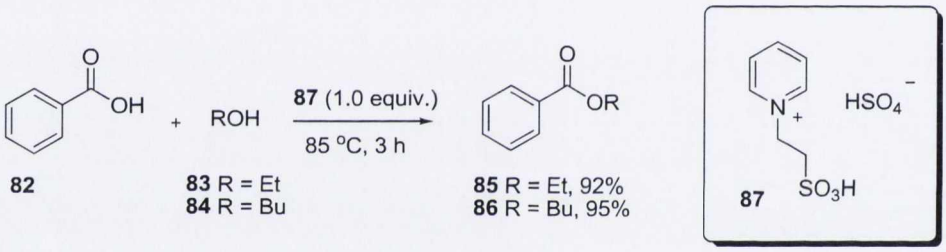
The dehydration of alcohols, in particular sugars, is a reaction in which ionic liquid catalysts have been widely investigated.[51] The dehydration of fructose to 5-(hydroxymethyl)furfural (HMF) (**79**) (Scheme 1.14) was carried out previously using Amberlyst-15 sulfonic ion-exchange resin as a catalyst in the ionic liquid solvent [bmim][BF_4]. The yields of HMF product formed under these conditions was 40-50% in 3 h, after which time the product was extracted to prevent further acid catalysed decomposition.[52] However, the same group counteracted this selectivity problem by employing 4 equiv. of the ionic liquid with a covalently bound acidic proton [hmim][Cl] **81** which promoted the dehydration of fructose (**79**) in 30 minutes with a 92% yield of **80** (Scheme 1.14). More importantly no decomposition products *e.g.* leuvilinic acid were observed. The absence of decomposition products may have been due to the lower free energy of activation in the presence of the ionic liquid used compared to the more conventional acid catalysts, thus almost quantitatively producing HMF.[53]



Scheme 1.14 The dehydration of fructose to HMF in an acidic IL containing a protic ion.

1.1.2.4 BAILs (Type 4): ionic liquids containing a covalently tethered sulfonic acid group and an acidic counterion

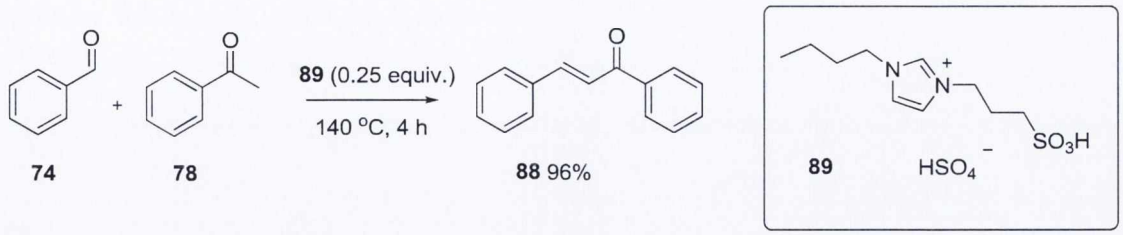
A fourth and final approach to the design of BAILs is through the generation of acidity by virtue of the presence of both a cation tethered with a sulfonic acid group and an acidic anionic species. An example of the use of these ionic liquids was reported in 2005 when Xing *et al.* employed stoichiometric amounts of a pyridinium ion-based ionic liquid $[(HO_3S)^3C_3Pyr][HSO_4]$ **87** in the esterification of benzoic acid (**82**) with simple alcohols, such as ethanol (**83**), to produce **85** in 92% yield and butanol (**84**) to produce **86** in 95% yield (Scheme 1.15). It was found that the activity of the ionic liquid containing the HSO_4^- counterion was much higher than that previously obtained using anions such as BF_4 and *p*TSA.[54]



Scheme 1.15 Esterification of benzoic acid (**82**) in the presence of the pyridinium ion-based ionic liquid **87**.

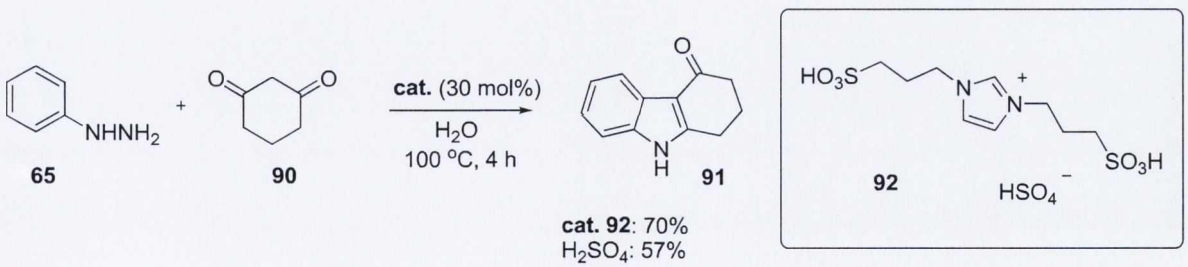
An imidazolium ion-based ionic catalyst containing both cationic and anionic acidic functionalities was exploited in 2008 in an aldol condensation. These reactions are traditionally carried out in basic/acidic media employing conventional homogenous catalysis which again posed problems with respect to recovery of the catalyst, in addition to the necessity of the use volatile organic compounds (VOCs) as solvents. Liu *et al.* reported the use of these BAILs as efficient and environmentally friendly dual catalysts and solvents.[55] The reaction of benzaldehyde (**74**) and acetophenone (**78**) was carried out furnishing the chalcone product **88** in 96% yield in 4 h using the catalyst/solvent **89** (Scheme 1.16). The ionic liquid again proved more active when incorporating a HSO_4 anion than a PF_6^- counterion. The recyclability of **89** was also determined through the recovery of the catalyst

by decantation of the organic layer followed by the simple extraction of the ionic liquid and was found to be effective with no loss in activity after 3 recycles.



Scheme 1.16 BAIL catalysed aldol condensation.

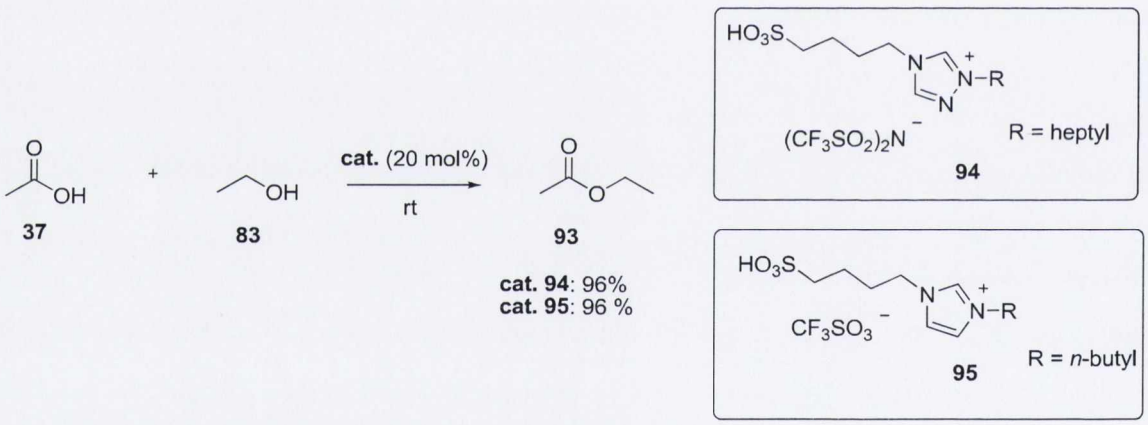
In 2009, a novel 'environmentally benign' catalyst system was designed by Xu *et al.* for a one-pot Fischer indole synthesis in which a $-SO_3H$ functionalised ionic liquid with 2 alkyl sulfonic acid groups on the imidazolium cation and a Brønsted acidic HSO_4 anion was employed in an aqueous medium.[56] This new catalytic system was applied to indole synthesis with both single-carbonyl ketones and cyclohexanediones with good to excellent yields. The optimum catalyst, imidazolium **92** (Scheme 1.17), proved to be more effective than H_2SO_4 at 30 mol% loading in the reaction of cyclohexanone and phenylhydrazine producing 1,2,3,4-tetrahydrocarbazole in 90% yield, compared to the 42% yield obtained using the H_2SO_4 catalyst under the same conditions. The catalyst also proved superior to its conventional acidic peer in the indole synthesis involving phenylhydrazine **(65)** and 1,3-cyclohexanedione **90**, affording **91** in 70% yield, while the use of H_2SO_4 produced 57% of **91** (Scheme 1.17).



Scheme 1.17 Fischer indole synthesis employing a BAIL with two covalently bound sulfonic acid groups and an acidic counterion.

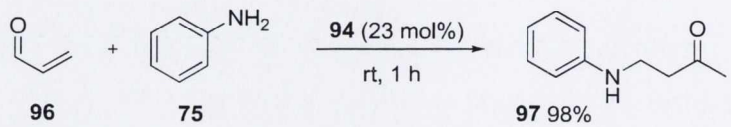
1.1.2.5 Triazolium salts as BAILs

Triazolium ion-based Brønsted acidic ionic liquid catalysts are not as widely investigated as their imidazolium ion and pyridinium ion-derived counterparts, however some examples exist. The first triazole ionic liquid designed for this purpose was introduced by Mirzaei *et al.* in 2004. This group designed a 1,2,4-triazole based ionic liquid, with a covalently bound sulfonic acid group tethered to the triazole core and an NTf_2 counterion **95** (Scheme 1.18). The employment of this solvent/catalyst in the esterification of various carboxylic acids with different alcohols proved to be successful with yields greater than 90% for each reaction. The esterification of acetic acid (**37**) with ethanol (**83**) was carried out using both the triazolium salt **94** and the imidazolium ionic liquid **95** with each producing ethyl acetate (**93**) in 96% yield, hence portraying the comparable activities of both compounds in this acid catalysed reaction (Scheme 1.18).[56]



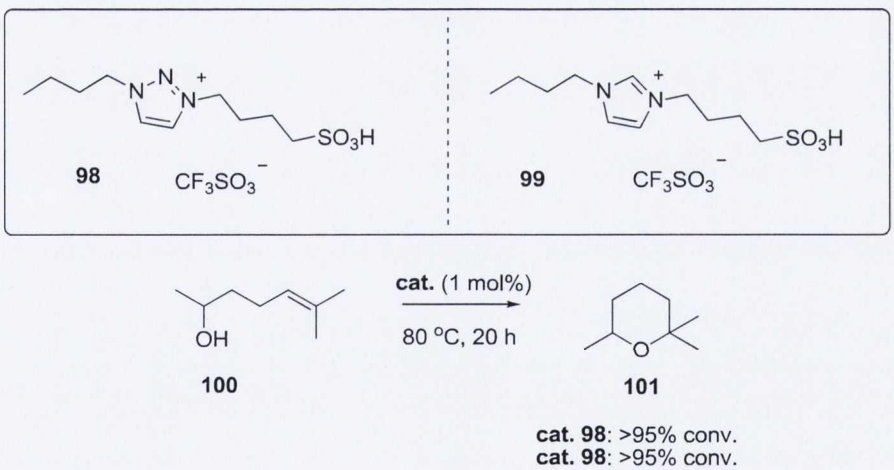
Scheme 1.18 Synthesis of ethyl acetate (**93**) using triazolium ion **94** and imidazolium ion **95**.

Furthermore, the hetero-Michael addition of aniline (**75**) to methyl vinyl ketone (**96**) also took place using **94** as a catalyst/solvent to yield 98% of **97** in 1 h at room temperature (Scheme 1.19).[56]



Scheme 1.19 The hetero-Michael addition of aniline (**75**) to methyl vinyl ketone (**96**) in a 1,2,4-triazolium ion-based ionic liquid **94** catalyst/solvent system.

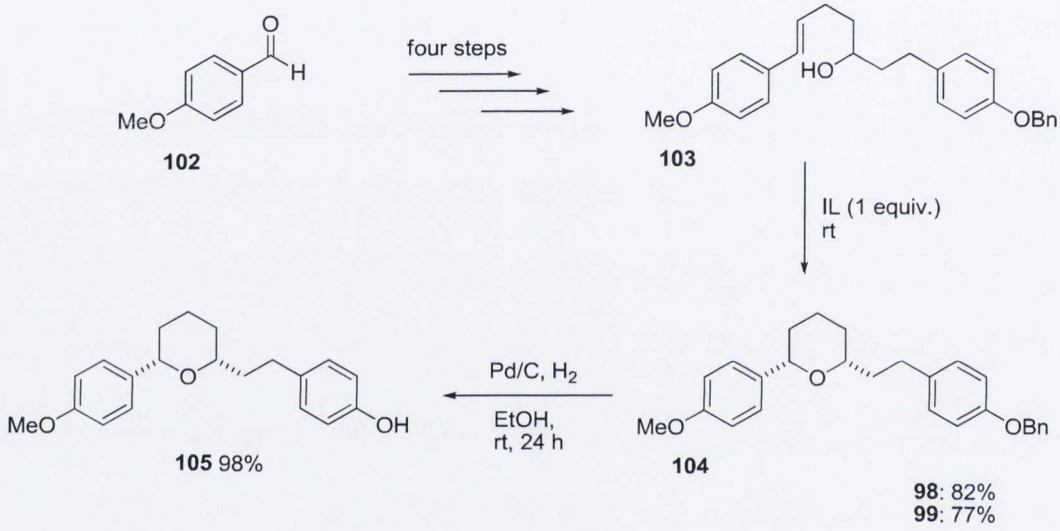
In 2011, Jeong *et al.* used SO_3H tethered 1,2,3-triazolium ion-based ionic liquids in the intramolecular hydroalkoxylation of olefins.[57] Substituted tetrahydrofurans (THF) and tetrahydropyrans (THP) are frequently found in biologically active natural products; including cyclic ether antibiotics.[58] A straightforward approach for the synthesis of these heterocycles is through the intramolecular hydroalkoxylation of unsaturated alcohols,[59] as the intramolecular insertion of O-H bonds across carbon-carbon double bonds has gained much attention due to its high atom economy and synthetic efficency.[57] The use of various metal catalysts have been reported to carry out this reaction including lanthanide,[60] palladium,[61] platinum,[62] aluminium[63] and copper[64]-based systems, each of which have been successful to varying degrees. Brønsted acids including triflic acid[65] and chlorosulfonic acid[66] have also been utilised to promote this reaction. However, each of these required the use of stoichiometric amounts of 'catalyst' and also suffer from the disadvantages outlined previously in relation to conventional Brønsted acids. The BAIL **98** was therefore synthesised and evaluated as a catalyst in the reaction of (±)-6-methyl-5-hepten-2-ol (**100**) to form **102,** with >95% conversion at 1 mol% loading after 20 h (Scheme 1.20).[57] This conversion was again comparable to that obtained using the sulfonic acid-tethered imidazolium ionic liquid **99**.



Scheme 1.20 The intramolecular hydroalkoxylation of **100** with triazolium ion-based **98** and imidazolium ion-based **99** BAIL catalysts.

This protocol was then employed in the total syntheis of (±)-centrolobine (**105**, Scheme 1.21). (-)-Centrolobine is an anti-protozoal natural product isolated from the stem of *Brosinilium Yobustum* in the Amazon rainforest.[58] Several total syntheses had previously been

reported,[59,60,61] however, none involving the use of an intramolecular hydroalkoxylation as a key step in the THP ring construction through the cyclisation of the alkenyl alcohol **103**. Starting with the 4-methoxybenzaldehyde (**102**) a four step process was carried out to obtain **103**. Both the imidazolium **98** and triazolium **99** ionic liquids (1 equiv.) were employed to cyclise **103,** producing the *cis*-disubstituted THP **104** in 77% and 82% yields respectively at rt, after which the Bn protecting group was removed by catalytic hydrogenation to give **105** in 98% yield (Scheme 1.21). Here it was observed that the triazolium salt was slightly more active than its imidazolium counterpart in this reaction.



Scheme 1.21 Cyclisation of alcohol **103** to THP **104** using BAILs in the total synthesis of (±)-centrolobine (**105**).

1.1.3 Conclusions: Brønsted acidic ionic liquids

From this discussion it can be noted that many advances have been made in the last 20 years in the area of ionic liquid research. From the original salt melts used in electrochemistry, to their evolution from solvents for transition metal catalysis and organocatalysis, to their use as Lewis acids and finally protic Brønsted acids, knowledge of this area has advanced remarkably. The area of Brønsted acidic ionic liquid catalysis has grown rapidly, particularly in the last decade, alleviating various problems encountered with both conventional catalytic methods and also the preceding Lewis acidic-based ionic liquids, hence allowing for more novel, sustainable ways to carry out each of the reactions outlined above. However, it should

be noted that each of the examples mentioned, whether they contain a covalently bound acidic moiety, protic cation or acidic anion, are all inherently acids. Thus they still possess the disadvantages, although admittedly not as substantial, that accompany the handling and use of acid catalysts including corrosion. In addition, many of these compounds are also employed in stoichiometric amounts or at relatively high catalytic loadings. Therefore, there is still scope to develop this area further and design effective yet even more environmentally benign, safer ionic liquid catalysts.

1.2 Pyridinium salt-based catalysis

The enzyme catalysed interconversion of pyridinium ions to their corresponding dihydropyridine compounds (*i.e.* NAD^+ (**62**) to NADH (**61**) and *vice versa*) is an essential reaction in cellular processes with several important roles in a wide range of biochemical processes.[67] The primary role of these species in biological systems is that of a stoichiometric cofactor, wherein they participate in redox processes being oxidised or reduced by the substrate as required. The structure of these enzymes includes two ribose rings linked by a pair of phosphate groups, attached to the C-1 position of one ribose is adenine, while at the same position of the second ribose ring is the nicotinamide unit which forms $NADP^+$/NADPH (**106**, Figure 1.4).

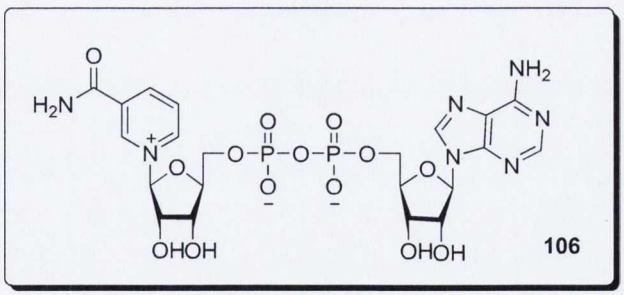
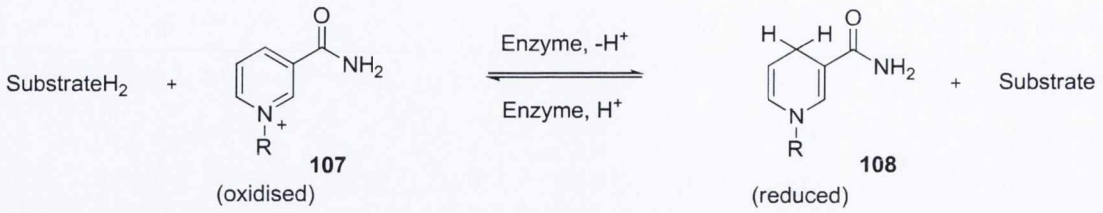


Figure 1.6 Structure of nicotinamide adenine dinucleotide (**106**).

This nicotinamide structure is the reactive site of the co-enzyme which can be reversibly oxidised to the pyridinium ion **107** or reduced to the dihydropyridine **108** (Scheme 1.22).[68]

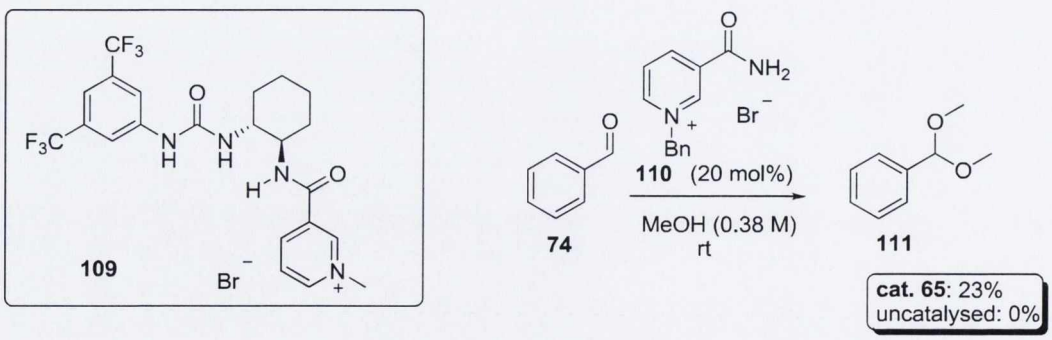


Scheme 1.22 General reaction scheme for reduction mediated by NADH/NAD$^+$.

The role of synthetic dihydropyridines (DHP) is not limited to that of catalysts in redox processes in conjunction with stoichiometric co-reductants,[69] as *N*-alkyl pyridinium ions have also been used as catalysts in electrochemical and photoinduced polymerisation[70] reactions involving redox *in situ*. There have also been catalysts incorporating *N*-alkyl pyridinium ions for which no specific catalytic role other than as a polar or an electron deficient group reported. Also, as mentioned previously, there are various ionic liquid catalysts and solvents derived from the pyridinium ion.

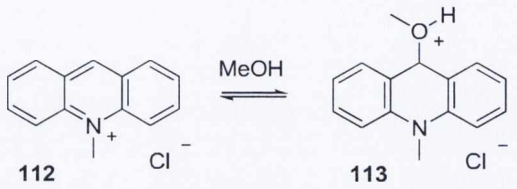
1.2.1 Pyridinium salt based catalysis: an aprotic Brønsted acid catalyst

In 2008, Procuranti and Connon observed an unusual phenomenon during the investigation of the design of artificial ketoreductase enzymes,[71] *e.g.* **109**, in that a simple nicotinamide derived pyridinium ion **110** catalysed the conversion of benzaldehyde (**74**) to its dimethyl acetal **111** in a methanolic solution in the absence of any discernible uncatalysed process (Scheme 1.23).[72]



Scheme 1.23 Initial acetalisation of benzaldehyde (**74**) catalysed by nicotinamide derived moiety **110**.

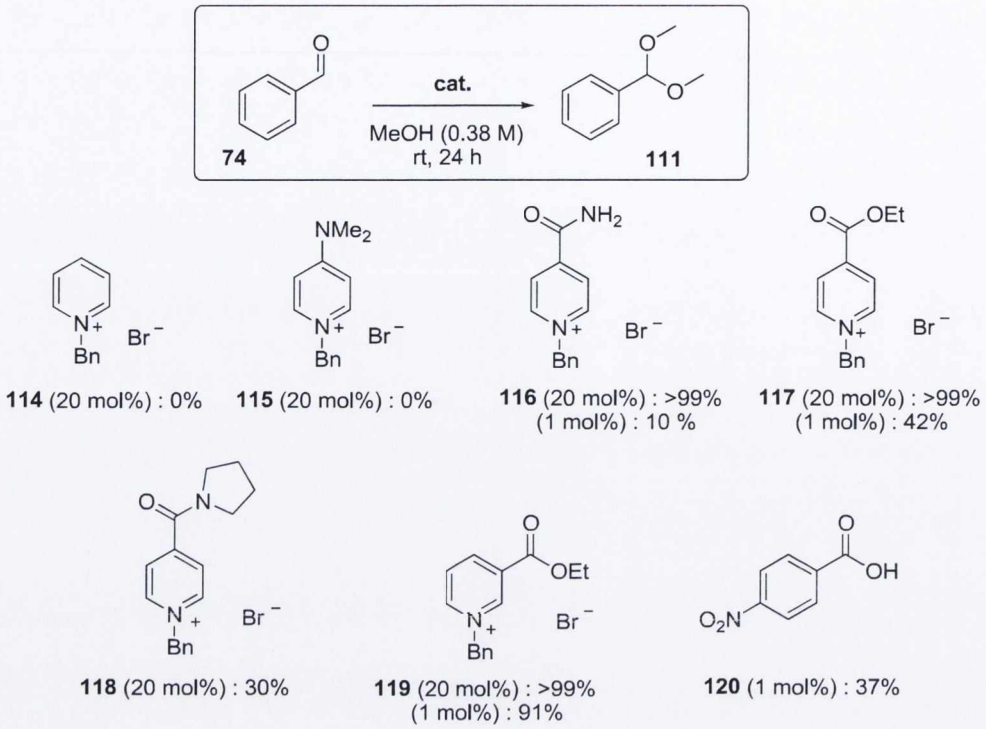
This highly unusual, though inefficient, catalyst activity led to the further investigation of the catalyst pathway. The proposed mode of action for this unexpected catalysis was based on a variant of Brønsted acid catalysis, introduced by Kano *et al.* in 1985.[73,74] They reported that the reversible conversion of the *N*-methyl acrdinium ion **112** to the acidic moiety **113** took place in the presence of methanol, through the addition of the alcohol to the **112** (Scheme 1.24).



Scheme 1.24 Proposed addition of methanol to acridinium ion **112**.

The formation of the Brønsted acid has been implied in other studies involving rotaxane/calixarene design[75,76] and aldehyde oxidation.[77] The addition of hydroxide to the C-4 position has been observed in *N*-alkylpyridinium ions derived from nicotinamide under alkaline conditions.[78] Similarly, under these conditions the reversible addition of thiolates and enolates to pyridinium ions occur.[79,80] However, prior to the investigation by Connon and Procuranti, no examples of the base-free alcoholysis of pyridinium ions was reported.

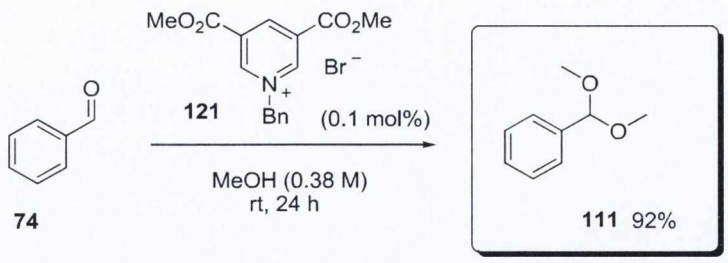
The catalysis of the acetalisation of benzaldehyde (**74**) in MeOH at room temperature by pyridinium ion-based materials (at 20 mol% loading) was investigated.[72] A representative sample of the various catalysts evaluated is shown in Scheme 1.25. The *N*-benzyl pyridinium bromide moiety (**114**) as well as compounds with electron donating groups at C-4 (for example **115**) proved ineffective. The introduction of an electron withdrawing group at C-4 however proved effective, with the use of **116** and **117** producing the acetal in near quantitative yield, except in the case of pyrrolidinamide catalyst **118**. The presence of an EWG at C-3 **119** also promoted the reaction efficiently at 20 mol% loading (Scheme 1.25).



Scheme 1.25 Catalyst screening for pyridinium catalysed acetalisation of benzaldehyde.

The electron deficient pyridinium ionic compounds **116**, **117** and **119** were then evaluated at 1 mol% loadings: it was found that ester **119** was the most effective, with yields of 92% of acetal **111** obtainable. This result was surprising in that **119** proved to be a better catalyst than 3-nitrobenzoic acid (**120**) (pK_a H_2O, 25 °C: 3.46) which yielded 37% acetal under the same conditions. The inactivity of **119** in the presence of an equimolar amount of an amine base (DABCO) also suggested that the catalysts operated *via* proton donation (Scheme 1.25).

These observations led to the synthesis of a compound containing two electron-withdrawing groups; the 3,5-diester **121**. This catalyst proved highly active, promoting the formation of acetal **111** in excellent yields (92%) at just 0.1 mol% loading. This new catalyst was more active than 2-nitrobenzoic acid (pK_a H_2O, 25 °C : 2.19) which acetalised benzaldehyde with 80% yield at the same loading (Scheme 1.26).



Scheme 1.26 Optimised pyridinium ion-based catalyst **121** for acetalisation of benzaldehyde.

The fact that this catalyst was capable of promoting this Brønsted acid catalysed reaction more effectively than acids like 2-nitrobenzoic acid, while possessing no obvious Brønsted acidic characteristics, led to the proposal of a mode of action based on the work by Kano *et al.* above. Wherein, the addition of the alcohol nucleophile occurs at the C-4 position of the pyridinium moiety **121,** generating the equilibrating species **121a** and **121b** which then act as the proton donating catalytically active molecules in methanolic solution (Scheme 1.27).

Scheme 1.27 Proposed mode of action for pyridinium ion catalysis of acetalisation reaction.

This mechanistic rationale is supported by the fact that **121** was superior to the less electrophilic compounds evaluated. The absence of any activity in the presence of a base and also the failure of the expected activity of ethylene glycol as a nucleophile (the nucleophilicity of which was reduced due to the mutual inductive withdrawal within proximinal oxygen atoms) also lend weight to this hypothesis. This novel aprotic ionic liquid compound could therefore exhibit acidic characteristics only in the presence of protic additives hence acting as a Brønsted acid in a controllable 'on-off' fashion.[72]

1.3 Green Chemistry

The definition of 'green chemistry' is chemistry that efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products. Anastas and Warner introduced this definition along with the 12 principles of green chemistry in 1998.[81] These principles are guidelines to address the environmental impact of both chemical products and the processes through which they are generated. The 12 principles are as follows:

1) Waste prevention rather than remediation.
2) Atom efficiency *i.e.* synthetic methods should be developed to maximise the incorporation of all materials used in the process into the final product.
3) Less hazardous/toxic chemicals; where possible synthetic methods should be designed to use substances with little or no effect on the environment and human health.
4) Safer products by design *i.e.* chemical products should be designed to not only be suitably effective for their desired purpose but also to have minimal toxicity.
5) Innocuous solvents and auxiliaries should be used where necessary, however processes should be designed by which they are not obligatory.
6) Energy efficient by design *i.e.* energy requirements should be taking into account regarding both the environmental and economical impact. The design of reactions carried out at ambient temperature and pressure, where possible, are superlative.
7) Renewable raw materials are preferable where it is technically and economically practicable.
8) Shorter syntheses *i.e.* avoid unnecessary derivatisation by protection/deprotection, use of blocking groups or temporary modification of physical/chemical processes.
9) Catalytic (as selective as possible) rather than stoichiometric reagents.
10) Design products for degradation so that at the end of a chemical products function they become innocuous compounds and do not persist in the environment.
11) Development of analytical methodologies for pollution prevention by analysing and controlling the production of hazardous materials in real-time.
12) Inherently safer processes in which the substances and their form are chosen to minimise the potential for chemical accidents.

1.3.1 Green chemistry and ionic liquids

The link between ionic liquids and green chemistry have already been highlighted above in the detailed discussion of the evolution of ionic liquids. The low vapour pressure and non-volatility of the salts, rendering them non-flammable are advantages over volatile organic compounds for use as solvents in various reactions.[16] The ability to solubilise inorganic, organic and polymeric material along with the capacity for the design of air/water stable ionic liquids also strengthens the idea that these molecules could make greener alternatives for more conventional catalysts and solvents.[17] It has also been illustrated that they allow for easier product extraction/separation and catalyst recovery by simple distillation or decantation, hence negating the need for hazardous solvents to carry out extractions.[22] The facile recovery of these compounds also led to ease of reusability of the ionic liquid catalysts and solvents. However, as this potential of IL as solvents and catalysts as a greener alternative has developed questions have been raised with respect to other environmentally impacting factors. The stability of these ionic liquids has led to negative claims regarding their environmental persistance.[82]

Jastorff *et al.* highlighted this when they reported a theoretical environmental risk analysis on a set of dialkylimidazolium ionic liquids.[82] The analysis was based on five key ecotoxicological indicators:

1) Release: The release of a chemical is usually more application-specific than chemical-specific, however a chemical will possess properties which will make it less likely to be released into the environment. An example is the low vapour pressure of ionic liquids which make them theoretically less likely to be released into the environment than conventional VOC's.[83]
2) Spatiotemporal range: The spatiotemporal range is defined as the tendency of a potentially released substance and its transformation products to spread in the environment over time. This indicator is one of the most difficult to predict and is generally done by investigating the compound of interests ability to persist over a set period of time in a specific, controlled environment.[83,84]
3) Bioaccumulation: is the tendency of a compound to accumulate in the biological membranes of micro-organisms generally leading to toxicological effects. The bioaccumulation potential of a substance is usually investigated by determining a

substances partitioning constant in 1-octanol and water ($\log K_{OW}$) or its bioconcentration factor (BCF) in fish tissue.[83]

4) Biological activity: is determined using the critical dilution factor, this means that the biomass must dilute a defined amount of the chemical substance to a level not producing any observable chronic effect.[83]
5) Uncertainty: The uncertainty indicator *U* is determined through the combination of the resulting uncertainties from the evaluation of the four previous indicators and dividing by the mean of these uncertainties.[85]

The lack of biodegradability data on ILs complicated many of these predictions (particularly bioaccumulation and spatiotemporal range), due to a high level of uncertainty despite theoretically low risk for some ionic liquid species with respect to the above indicators.

This has led to the recent developments in determining the full environmental impact of these solvents/catalysts prior to labelling them entirely green. This impact was determined, not only by taking into account the factors outlined above, which many ionic liquids already possess, but also the biodegradability and toxicity of the molecules *i.e.* for an IL to be considered green it must be readily biodegradable and of low toxicity.[86] These two factors should therefore be taken into account when designing any new ionic liquid catalyst and solvent candidates.

1.3.2 Biodegradability: considerations with respect to the environment

Biodegradability can be defined as the susceptibility of a substance to chemical breakdown when attacked by micro-organisms.[87] There are a number of physical, chemical and biological factors which influence the biodegradation of a compound by micro-organisms. Physical factors include temperature (*e.g.* is the micro-organism mesophilic, psycrophilic or thermophilic) and mineral structure *i.e.* the structure of the terrestrial environment.[88] Biological factors include the diversity of the microbial population, more diverse communities will produce different enzymes which can catalyse the biodegradation pathway. The initial biodegradation of chemical compounds usually takes place extracellularly when exoenzymes are excreted to break down the compound into smaller compounds, which are then further degraded intracellularly.[88] The final set of factors are chemical factors including pH, optimum pH must be present for the micro-organism to survive (fungi prefer generally

acidic pH, while bacteria slightly basic). Optimised moisture content (optimum 50%) and nutrient content *i.e.* carbon: nitrogen ratio (20-40 C for each N) are paramount. Oxygen availability for aerobic and oxygen deficiency for anaerobic micro-organisms is also evidently important.[88] The production of CO_2 under aerobic conditions is the main way in which the complete breakdown of a chemical compound by the metabolism of micro-organisms is measured, while in anaerobic testing it is CO_2 and CH_4 production which is quantified. Each of these factors requires manipulation to set up the optimum parameters for biodegradability to occur while simulating a natural environment. Strict controls and regulations are therefore in place for biodegradability testing.[89]

1.3.2.1 Biodegradability test methods

There are various methods used for biodegradability testing, with each designed to determine if a chemical compound can be classed as readily biodegradable. 'Readily biodegradable' can be defined as 'an arbitrary classification of chemicals which have passed certain specified screening tests for ultimate biodegradability; the conditions in these tests are so stringent-relatively low density of non-acclimatized bacteria, relatively short duration, absence of other compounds-that such chemicals will rapidly and completely biodegrade in aquatic environments under aerobic conditions'.[87]

Testing methods can vary from simple visual testing (by comparing the microbial colonies with the naked eye and the compounds degradation using Scanning Electron Microscopy (SEM)), to the more complex and expensive semi-continuous activated sludge test. To discuss the wide variety of testing routines is beyond the scope of this thesis, however the three most popular methods used to test the biodegradability of ionic liquids are: 1) The modified Sturm test and 2) The 'CO_2 Headspace Test' and 3) the 'Closed Bottle Test'.[90]

The modified Sturm test ((OECD 310B) based on original tests carried out by Sturm)[91] is sanctioned by the Organisation for Economic Co-operation and Development (OECD) and consists of natural inoculums from activated sludge in solution, in which the test sample is the only source of carbon. The test system is incubated at ambient temperature for 28 days. The production of CO_2 is measured using a respirometer and used to calculate the total percentage of CO_2 produced. This percentage biodegradation is calculated using the following equation:

$$\% \text{ degradation} = \frac{\text{mg } CO_2 \text{ produced}}{ThCO_2 \text{ x mg test substance added}} \text{ X } 100$$

Where $ThCO_2$ is the theoretical CO_2 present in the test system. As the production of CO_2 will not reach 100% in such a short time-scale a compound can be called readily biodegradable if it reaches a total CO_2 percentage of 60% or more. This method is reproducible and fast, making it the ideal screening test. It is suitable for water soluble and insoluble compounds, however volatile and adsorbing compounds are less suited.[90]

The CO_2 headspace test is carried out under aerobic and aquatic conditions similar to the Sturm test, however it is a much simpler method. This system measures the extent to which an organic compound is mineralised *i.e.* the complete degradation of an organic molecule to smaller molecules for example CO_2 and water. The CO_2 evolution is measured without the use of a respirometer, instead a headspace bottle is fitted with a mineral medium, inoculums of sewage sludge and the test compound. The headspace bottle is stored at a variety of temperatures and once a week the percentage CO_2 is measured. The percentage biodegradation is expressed as a percentage of the Theoretical Inorganic Carbon (TIC) evolved based on the concentration of the test compound initially added. The following equation is used to determine the percentage degradation:

$$\% \text{ biodegradation} = \frac{(TIC_t - TIC_b)}{TOC} \text{ X } 100$$

Where TIC_t refers to the TIC in the sample bottle at time t, TIC_b is the TIC in the blank bottle at time t and TOC is the total organic carbon in solution and suspension. This method is simple, cheap, reasonably reproducible and many samples can be tested at one time. It allows for the testing of hydrophilic and hydrophobic substances, including organic solvents and surfactants.[90]

The 'Closed Bottle Test' (OECD 310D) involves the addition of an ionic liquid to an aerobic aqueous medium inoculated with wastewater micro-organisms and the depletion of molecular oxygen is measured over a defined period of time (usually 28 days) as a percentage of the

theoretical maximum. The percentage degradation is calculated by either of the following equations:

$$\% \text{ biodegradation} = \frac{\text{BOD (mg } O_2\text{/ mg test substance)}}{\text{ThOD (mg } O_2\text{/ mg test substance)}} \times 100$$

$$\% \text{ biodegradation} = \frac{\text{BOD (mg } O_2\text{/ mg test substance)}}{\text{COD (mg } O_2\text{/ mg test substance)}} \times 100$$

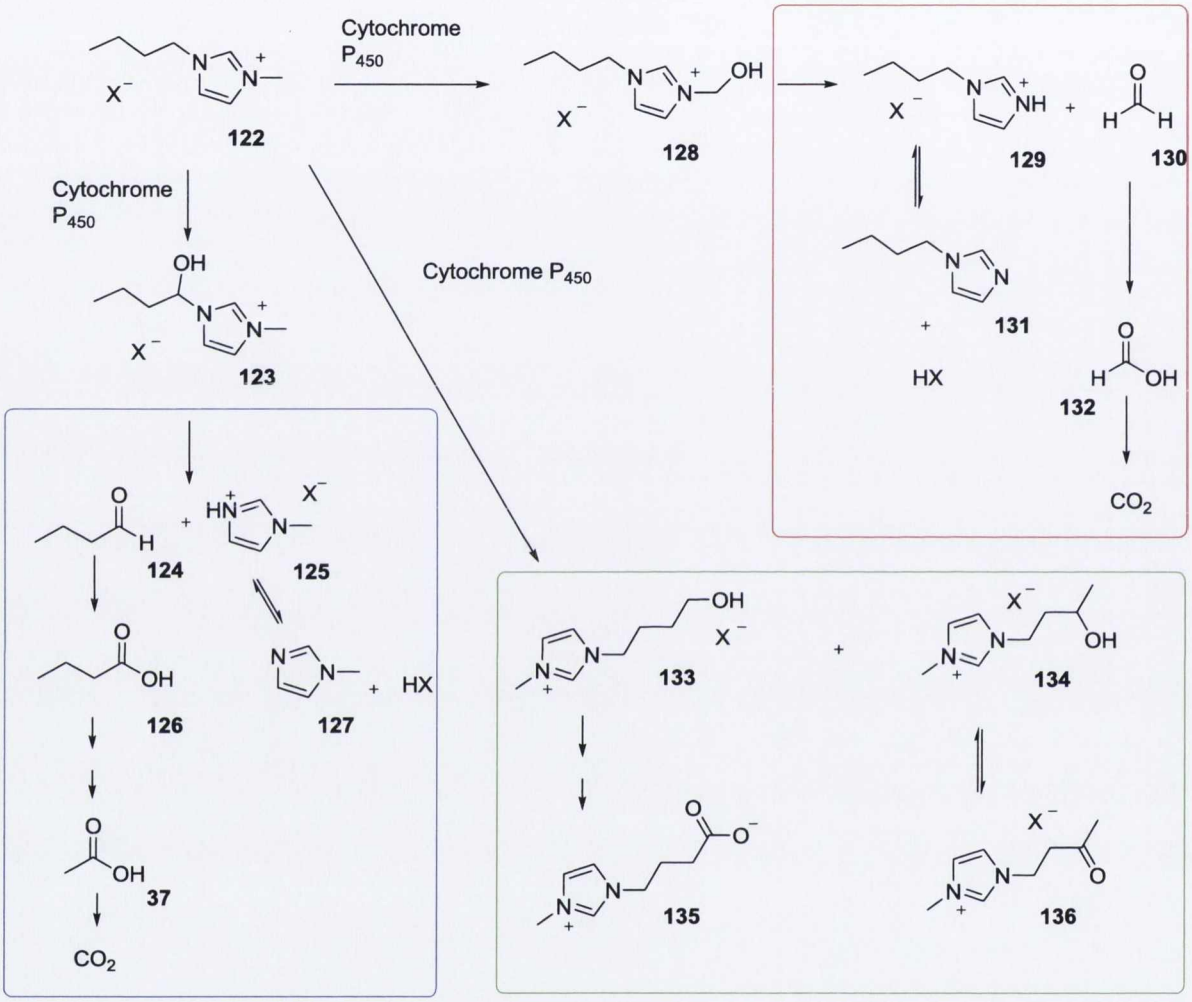
Where BOD is the biochemical oxygen demand, the amount of oxygen consumed by the micro-organism to metabolise the test substance, ThOD is theoretical oxygen demand and COD is the chemical oxygen demand, the amount of oxygen consumed during oxidation of a test compound with hot acidic dichromate. Again, compounds reaching above 60% oxygen depletion are characterised as readily biodegradable.[90] For each of the methods above sodium dodecyl sulfate (SDS) is used as a reference compound. This surfactant will reach 60% biodegradability within 5 days with each of these methods.

1.3.2.2 Biodegradability and ionic liquids

The design of biodegradable ionic liquids was initially based on the knowledge previously gained during the design of more biodegradable surfactants,[92] which have been developed since the 1940's to establish new environmentally benign ionic liquid moieties. In the design of biodegradable surfactants Boethling[93] identified three important factors which could be translated to the design of ionic liquid moieties: 1) the presence of potential sites for enzymatic hydrolysis *e.g.* ester or amide groups, 2) the presence of an oxygen in the form of a hydroxyl, aldehyde or carboxylic acid and 3) the presence of unsubstituted linear alkyl chains (≥4 carbons) and phenyl rings, these represent possible sites for enzymatic attack. Enzymatic oxidation is a common method through which living systems break down chemical compounds to more water soluble molecules by hydroxylation, or sometimes epoxidation. Oxidase enzymes can usually degrade inert species such as unsubstituted alkyl chains (≥ 4 carbons long) and aromatic rings, which act as possible sites for oxygenases.

An example of the last factor was reported by Jastorff *et al.*[82] in the metabolism of the $[bmim]^+$ cation **122** by Cytochrome P_{450}, which could oxidise the ionic liquid at various alkyl

positions allowing for further metabolic breakdown to biocompatible fatty acids and imidazoles (**123-136**). However, in naturally occurring environments this may not always occur (Scheme 1.28).



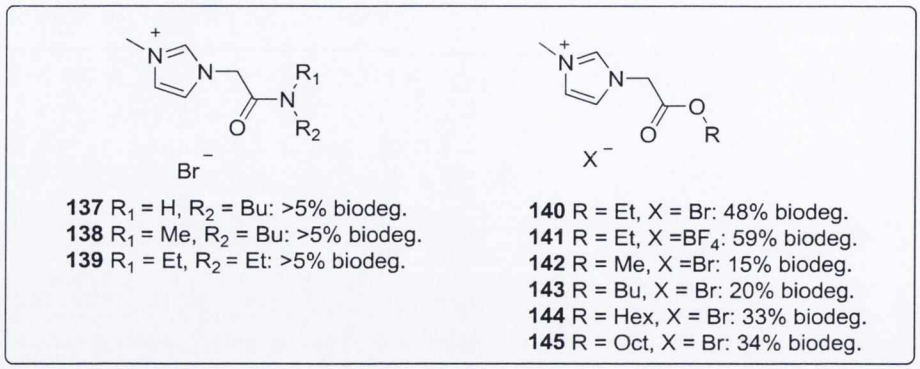
Scheme 1.28 Theoretically predicted metabolism of [bmim] cation by Cytochrome P_{450}.

Along with determining factors beneficial to biodegradation, Boethling also identified factors leading to an increase in resistance to biological decomposition,[93] which must also be taken into account when designing environmentally friendly ionic liquid moieties. These include the presence of halogens (*e.g.* chlorine and fluorine), chain branching, the presence of tertiary amine groups, quaternary carbons or highly branched chains; each of which leads to a decrease in the biological decomposition of a compound. The presence of nitro, nitroso, azo

and arylamino groups also contributes to resistance to the metabolism of the compound, while polycyclic fused aromatic hydrocarbons are also usually environmentally persistent.

1.3.2.3 Biodegradability and ionic liquids: the design of biodegradable ionic liquids

Initial studies by Scammells and Gathergood in 2002 concentrated on the design of imidazolium ion-based compounds with each of the factors above considered, while also taking into account the use of the compound (*i.e.* restoring factors which rendered the moiety an efficient catalyst/solvent etc.).[92] During their research they found that cations with long linear alkyl chains and amide functionality such as IL **137**, **138** and **139** possessed poor biodegradability (>5% utilising the Sturm test) (Figure 1.7).[92] They also discovered that despite Jastorffs predictive model (See Section 1.3.2.2), $[bmim]^+$ based ionic liquids showed negligible biodegradation, most likely due to the lack of sufficient oxidase enzymes in the test media. However, upon addition of an ester functional group **140** the biodegradation properties were augmented due to enzymatic hydrolysis of the ester, leading to the further breakdown of the molecule by fatty acid β-oxidation, thereby allowing the resulting compound to be utilised for energy and biomass production.[94] The initial evaluation of the ester containing molecules **140** and **141** was carried out utilising the Sturm test with CO_2 production reaching 48% and 59% respectively (Figure 1.7). The 'Closed Bottle Test' was then used to screen a larger library of ester containing ionic liquids for oxygen depletion (with ester alkyl chain lengths ranging from methyl to octyl) (**142-145**). It was observed that the longer ester alkyl chains were slightly more biodegradable than the shorter methyl to butyl chains (Figure 1.7). The susceptibility of the ester containing molecules to biodegradation is attributed to the presence of a wide variety of esterase enzymes in the environment. These enzymes exhibit broad substrate specificity and their persistence in microbial communities allows for the facile breakdown of ester functional groups.[94]

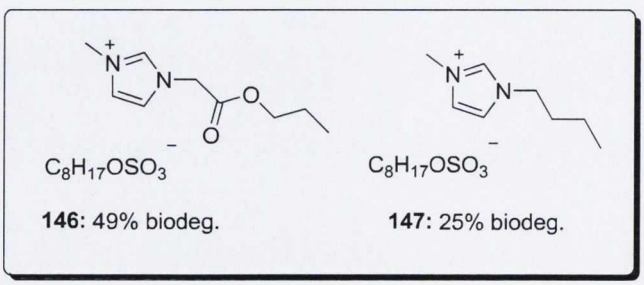


137 R_1 = H, R_2 = Bu: >5% biodeg.
138 R_1 = Me, R_2 = Bu: >5% biodeg.
139 R_1 = Et, R_2 = Et: >5% biodeg.

140 R = Et, X = Br: 48% biodeg.
141 R = Et, X = BF_4: 59% biodeg.
142 R = Me, X = Br: 15% biodeg.
143 R = Bu, X = Br: 20% biodeg.
144 R = Hex, X = Br: 33% biodeg.
145 R = Oct, X = Br: 34% biodeg.

Figure 1.7 Representative examples illustrating the effect of the structure of the cationic component on IL biodegradability.

The effect of the anion on overall biological decomposition was also investigated by Gathergood and Scammels,[95] who determined that the presence of an octylsulfate anion increased the biodegradability of the molecule. For instance, compounds 1-(propoxycarbonyl)methyl-3-methylimidazolium (**146**) and 1-butyl-3-methylimidazolium (**147**) octylsulfates exhibited biodegradation of 49% and 25% respectively in the 'Closed Bottle Test'(Figure 1.8).[95] However, when other anions *e.g.* $[BF_4]^-$,$[PF_6]^-$, $[NTf_2]^-$, $[Br]^-$ were employed it was found that they had a less of an effect on the biodegradation properties although the biodegradability of $[NTf_2]^- > [BF_4]^- > [PF_6]^- > [Br]^- > [Cl]^-$ anions. This increased decomposition of **146** and **147** is due the linear alkyl structure of the octylsulfate anion being readily biodegradable, with enzymatic cleavage of the sulphate ester bond to the inorganic sulphate. This result is unsurprising as linear alkyl sulfates such as SDS are widely known to be readily biodegradable. The results of this study were consistent with those previously reported,[94] in that the imidazolium moiety **146** (incorporating an ester side chain) was considerably more biodegradable than the alkyl substituted analogue **147**.[95]



146: 49% biodeg. **147**: 25% biodeg.

Figure 1.8 Biodegradability of ionic liquids: The influence of the anion.

In 2006, Gathergood *et al.* developed the first readily biodegradable ionic liquids by incorporating both an ester functional group and an octyl sulfate counterion. 1-alkoxycarbony-3-methylimidazolium and 1-alkoxycarbonyl-2,3-dimethyl imidazolium ion-based ionic liquids **148-151** (Figure 1.9) each reached above 60% biodegradability when evaluated in the 'CO_2 Headspace' Test (ISO1493); allowing them to be classified as readily biodegradable. Minor effects were observed with respect to alkyl chain length and the number of methyl groups present.[96]

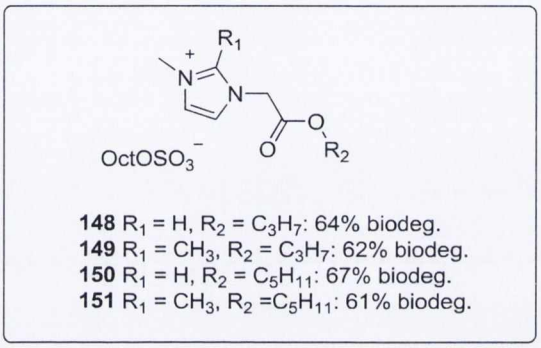
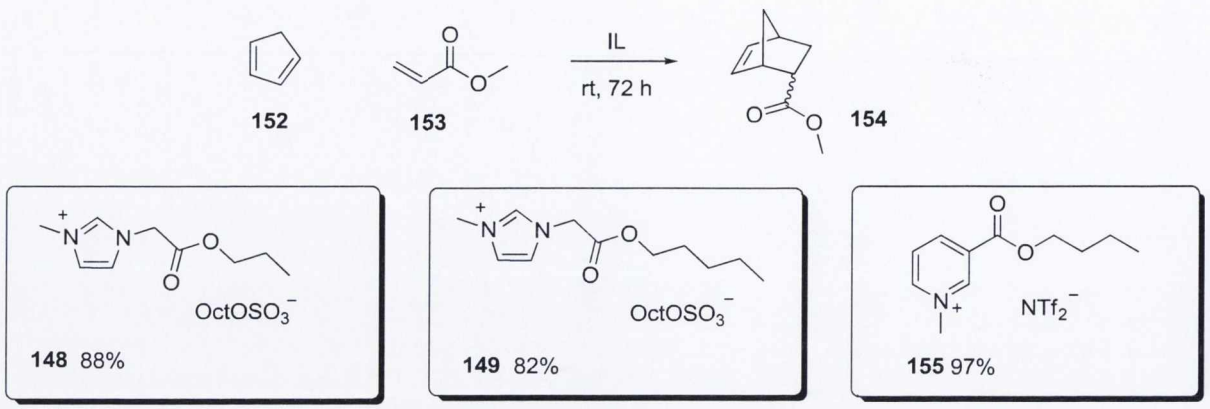


Figure 1.9 The first readily biodegradable imidazolium ion-based ionic liquid compounds.

1.3.2.4 Biodegradable ionic liquids: applications as reaction media

The knowledge gained from these seminal studies has been applied to new ionic liquid reaction media and there are now some examples of the applications of specifically designed "readily biodegradable" ionic liquids as solvents for reactions such as the Diels-Alder reaction and hydrogenation.

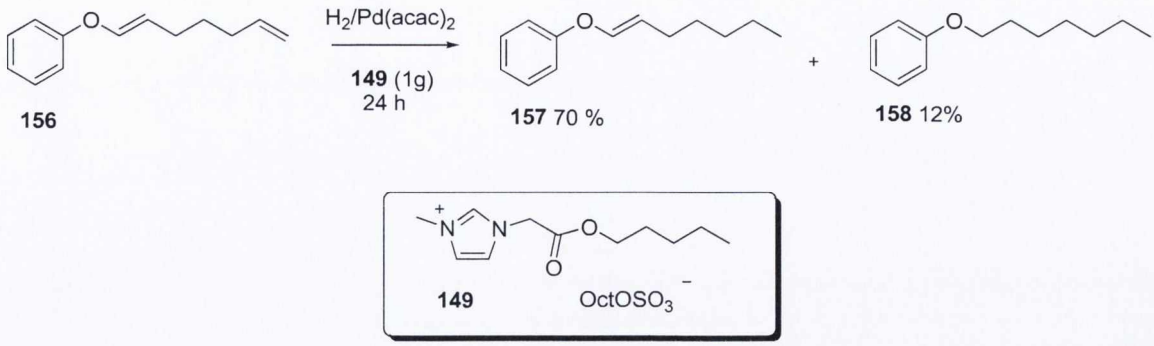
Scammells *et al.* developed ester functionalised imidazolium cationic liquids with octyl sulfate anions **148** and **149** as solvents in the reaction of cyclopentadiene (**152**) and methyl acrylate (**153**) to generate **154**. The reaction, when these biodegradable ionic liquid solvents were employed, exhibited improved *endo* selectivity when compared with conventional organic solvents and water in 72 h with high conversions of 88% and 82% respectively (Scheme 1.29).[97]



Scheme 1.29 Diels-Alder reaction in imidazolium and pyridinium ion-based biodegradable ionic liquid solvents.

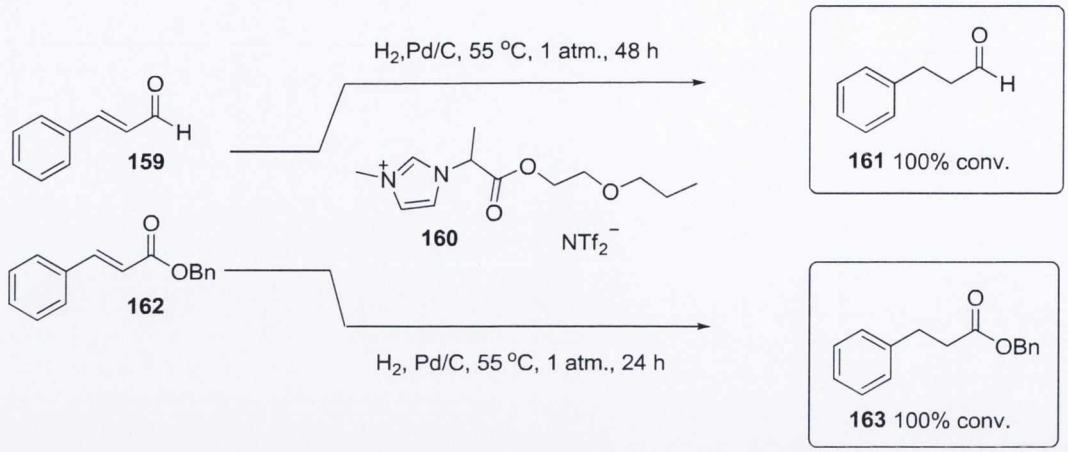
The Diels-Alder reaction was also carried out by the same group using the newly designed pyridinium ion-based ionic liquid **155**, the design of which was based on the seminal results obtained from the study of imidazolium ionic liquids. The presence of the ester functionalised cation rendered the pyridinium ion-based compound readily biodegradable. The activity in the reaction of cyclopentadiene (**152**) and methyl acrylate (**153**) in the pyridinium ion-based solvent **155** resulted in superior conversions to the product **154** of 97% when compared to use of the imidazolium ion-based solvents **148** and **149** (Scheme 1.29).[98]

A second example of a reaction in which these biodegradable ionic liquids are employed is in the hydrogenation of 1-phenoxyoctadiene (**156**) with a high selectivity to the desired 1-phenoxyoct-2-ene (**157**) product (*i.e.* keeping the internal olefin intact). The use of **149** resulted in 85% conversion with 70% isolated yield of **157** and 12% **158**. When [bmim][Br] was utilised a conversion of 85% was obtained with an isolated yield of 57% **157** (Scheme 1.30).[97]



Scheme 1.30 Hydrogenation of 1-phenoxyoctadiene (**156**) in a 3-methyl-1-(pentoxycarbonylmethyl)-imidazolium octyl sulfate (**149**) reaction medium.

In 2009, Morrissey *et al.* carried out the reduction of *trans*-cinnamaldehyde (**159**) to hydrocinnamaldehyde (**161**) using a variety of imidazolium based ionic liquids with highly oxygenated ester side chains including **160**. The conversion in this biodegradable ionic liquid was the same as [bmim][BF_4], [bmim][$OctOSO_3$] and toluene each resulting in 100% conversion. The selectivity of the reduction of **159** generating hydrocinnamaldehyde (**161**) (over cinnamyl alcohol) in **160** was 100% (Scheme 1.31) which was greater than the selectivities in [bmim][BF_4] (87% selectivity), [bmim][$OctOSO_3$] (69% selectivity) and toluene (67% selectivity).[99] The hydrogenation of benzyl cinnamate was also achieved without hydrogenolysis of the benzyl ester. The employment of ionic liquid **160** also enabled the reduction of **162** to take place with 100% conversion and 100% selectivity for **163** (over 3-phenylpropanoic acid), compared to conventional solvents THF, ethyl acetate and also ionic liquid [bmim][$OctOSO_3$] which resulted in 100% reduction of **162** but 0% selectivity for **163** (Scheme 1.31).



Scheme 1.31 Hydrogenation of *trans*-cinnamaldehyde and benzyl cinnamate in biodegradable ionic liquid solvent **160**.

1.3.3 Toxicity and ionic liquids

Toxicity is defined as the degree to which a substance can damage an organism. While the toxic properties of ionic liquids can be an advantage wherein their antimicrobial activity can lead to the development of new antiseptics, disinfectants, antifouling agents and other biocides,[100] for the purpose of ILs as sustainable solvents/catalysts toxicity is of course undesirable. Toxicity and biodegradability are inextricably linked; the toxicity of the molecule will clearly determine if it can be broken down by the micro-organisms and hence biodegrade. Biodegradability is hence a preliminary method to determine the toxicity of a molecule, as if the biodegradability is poor it has a greater potential to bioaccumulate.[90] Therefore, many of the factors which contribute to biodegradability also bestow properties on the compound which will render it of low toxicity.

The presence of long linear alkyl chains were found to be one of the main causes of toxicity in the study of surfactants. Dialkyl dimethyl ammonium salt surfactants which were used as fabric softeners in high volume, such as dihydrogenated tallow dimethyl ammonium salts **164**, were found to be highly toxic and have now been replaced by more biodegradable quaternary ammonium salts containing hydrolysable bonds such as **165**, which has hydrolysable ester side chains which reduce its intrinsic toxicity (Figure 1.10).[93,101,102]

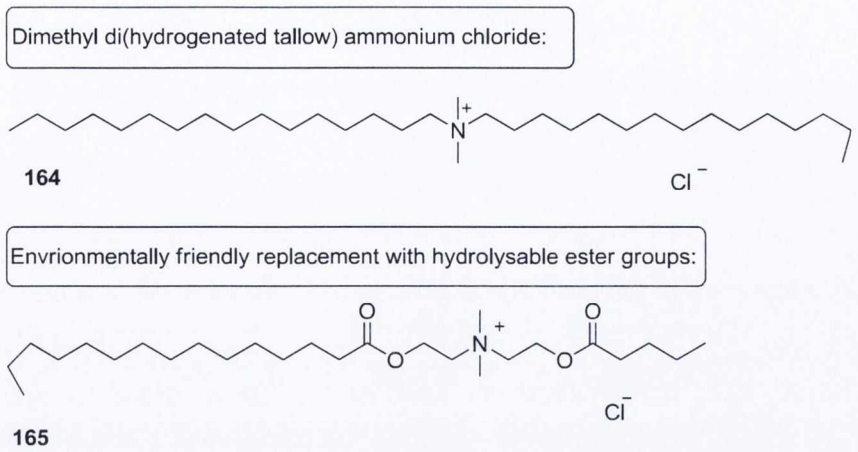
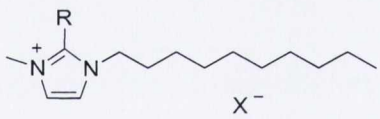


Figure 1.10 Toxic *vs.* non-toxic ammonium chloride salt-based surfactants.

In the theoretical study by Jastorff *et al.* on the structure activity relationship (SAR) of ionic liquids with respect to toxicology and ecotoxicology.[82] It was determined that ionic liquids with long linear alkyl chains would, like surfactants, induce harmful environmental effects. The comparison was drawn with the alkyl chain length in imidazolium ionic liquids such as **166** and the imidazolium plant growth regulator **167**. This highlighted the structural similarities between an ionic liquid and a known environmental toxin (Figure 1.11).



166 R = H, X = Br (ionic liquid moiety)
167 R = CH_3, X = Cl (patented plant growth regulator)

Figure 1.11 Imidazolium ion-based ionic liquids with long alkyl chain lengths.

The toxicity of ionic liquids was then determined in various models involving micro-organisms, aquatic species such as zebrafish (*Danio Rerio*),[103] waterfleas (*Daphnia Magnia*),[104] algae[105] and terrestrial invertebrates such as earthworms.[106] The availability of data on the cytotoxicity of ionic liquids to date is limited, although some ionic liquids have been screened against mammalian cells; including human cells,[107] promyelotic leukaemia rat cell lines (IPC-18) and the rat glioma cell line. In each of these studies it was determined, as expected, that long alkyl chain length (>8 carbons) led to an increase in toxicity.[103-107]

A second contributory factor was found to be the lipophilicity of the molecule. Lipophilicity contributes to the interaction of the ionic liquid with the biological and environmental barriers of micro-organisms, leading to the distribution of the compound in the biological membrane. Lipophilic anions contributed to higher toxicity levels of the ionic liquid while it was again found that shorter alkyl chain lengths led to increased water solubility of the ionic liquid; with longer chains leading to heightened lipophilicity (and therefore greater bioaccumulation). From these studies it was also determined that the toxicity of ionic liquids is generally related to this bioaccumulation, rather than the biological activity of the compound. This is determined from the fact that cationic structures having an augmented contribution to overall toxicity than the anionic component, although as mentioned more lipophilic anions do contribute to an increase in toxicity.

In current studies by Gathergood *et al.*, along with utilising biodegradability to determine toxicity of an ionic the acute toxicity of ionic liquids are also tested against fungal and bacterial cells.[98] The minimum inhibitory concentrations (MICs) are determined by screening the anti-fungal and anti-microbial activity of an ionic liquid. The MIC is defined as the lowest concentration of an anti-microbial/anti-fungal that will inhibit the visible growth of a microorganism after incubation. The growth of the microbes is measured over a period of time in either an agar medium or by a broth dilution method. The inhibition of growth by the test compound is then determined, for yeasts the allowed inhibition is 80% (IC_{80}) and for filamentous fungi it is 50% inhibition (IC_{50}). For bacteria, a 95% inhibition of growth (IC_{95}) must be observed in order for a compound to be considered anti-bacterial. In the case of ionic liquids as catalysts and solvents the results required with respect to these toxicity tests are low or no anti-fungal/anti-bacterial activity in the presence of high concentrations of ionic liquid.

The first study combining both biodegradability and toxicity testing using the above parameters was carried out in 2009 by Morrissey and co-workers.[99] The presence of hydrolysable ester groups such as **171** and **173** (Scheme 1.13) was consistent with previous studies manifesting increased biodegradability by 'CO_2 Headspace' analysis. Additionally, it was discovered with regards to the lowering of toxicity in relation to fungal and bacterial media that the presence of a highly oxygenated ester side chain was influential. MICs of concentrations between 0-20 mg/mL of ionic liquids were obtained against seven strains of bacteria including 4 Gram negative and 3 Gram positive bacteria. The MIC for cationic antiseptic/anti-bacterial agents generally lie in the range of 8 μg/mL to 500 μg/mL, for

instance CPC (cetylpyridinium chloride, **168**)- a known antiseptic used for applications in pesticides and dental hygiene products-containing a pyridinium side chain of 16 carbons in length exhibited MIC values of 8 μg/mL for bacteria including *B. Subtilus* (Figure 1.12). While the imidazolium based ionic liquids **169** and **170** with C-14/C-16 side chains respectively exhibited MIC's of 4μg/mL to 8μg/mL against 10 bacteria and 2 fungi (Figure 1.12).

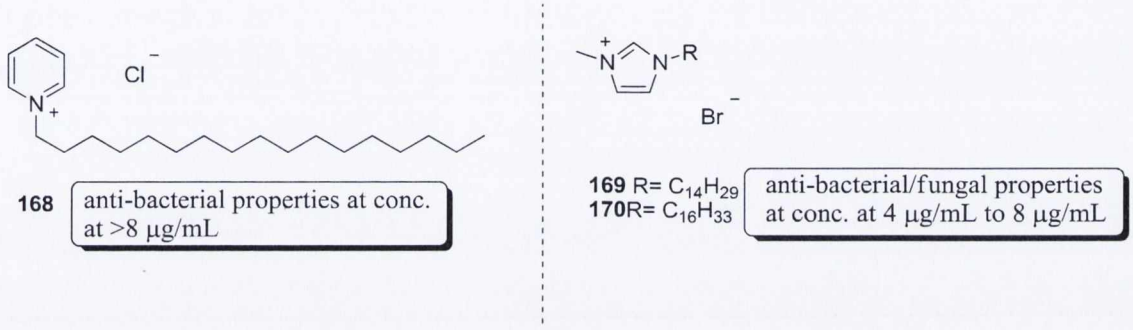


Figure 1.12 Pyridinium and imidazolium ion-based anti-bacterial/anti-fungal ionic liquids

In the study by Morrissey *et al.* it was found that upon addition of etheral side chains linked *via* an ester to the imidazole core such as **171** and **172**, no toxicity was exhibited to the bacterial strains (concentrations of >27 mM to >75 mM) evaluated even with concentrations of ionic liquid above 20mg/mL. The incorporation of an oxygen atom in the amide derived side chain was also found to decrease its toxicity, with **173** exhibiting low toxicity when compared with ionic liquids containing hydrocarbon side chains. However, it is noteworthy that these amide compounds were again found to be less biodegradable; with none reaching above 40% biodegradability within the same time period (Figure 1.13).

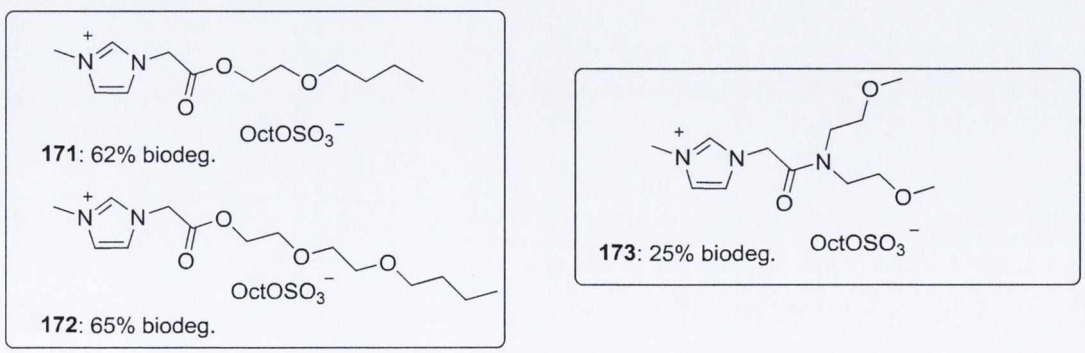
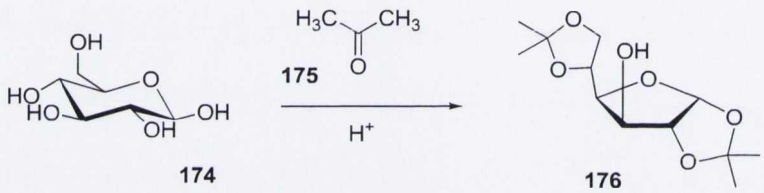


Figure 1.13 Biodegradable and low toxicity imidazolium ion-based ionic liquids

1.4 Protecting group chemistry

Protecting group chemistry is one of the cornerstones of organic synthesis. Fischer first identified the problem of functional group incompatibilities in the synthesis of complex molecules during the development of carbohydrate synthetic methodologies.[108] One of his many enduring contributions to organic synthesis was to render an otherwise reactive functional group temporarily inert by appending a protecting group which could be removed later. He first introduced this through the protection of different carbohydrates including the reaction of sugar **174** with 2,2-dimethoxypropane (**175**) producing the isopropyldiene protected sugar **176** (Scheme 1.32).[109,110]



Scheme 1.32 Early use of protecting group by Emil Fischer in protection of **174** with an isopropylidene group.

Contemporary synthetic plans for complex molecules now involve several strategies, including the synthesis of the separate fragments which make up the complex molecules and linkage of these fragments, while also taking into account stereochemistry, functional group interconversion and protecting groups.[108] A protecting group must meet a number of criteria including, the ability to react selectively in good yield and cede a protected compound that is stable under conditions required during subsequent protection reactions.[111] The precursor to the protecting group should preferably be cheap and readily available. It additionally must have the ability to be selectively removed in good yield with reagents which have no effect on the restored functional group. The newly protected compound should also be free from the generation of new stereogenic centres and must have the ability be easily separated from any side products, which are associated with the formation of the protected compound or cleavage of the protecting group.[111] The method of cleavage of the protecting group should be efficient and have no effect on any other protecting groups present in the molecule, *i.e.* one protecting group may be required to be stable to conditions that cleave another and *vice versa*. It should also be stable enough to survive any reaction conditions induced after protection including

chromatography. Finally, additional functionality introduced through the installation of the protecting group, should be at a minimum in order to avoid further sites of reaction.[108,111]

Few, if any, protecting groups meet all of these requirements and for elaborate substrates *e.g.* in natural product synthesis, a number of complimentary protecting groups are required. For these reasons, there is continued and widespread development of satisfactory protective groups, along with more effective and efficient methods for their formation and cleavage.

1.4.1 Acid catalysed protection/deprotection

The functional groups which, most commonly, require protection include hydroxyl groups, ketones and aldehydes, amines, carboxylic acids and alkynes. While protecting groups can be formed/cleaved in a number of ways such as hydrogenolysis, acidic catalysis, basic catalysis, enzyme catalysis and photocleavage, a review of these methods is beyond this thesis, where the focus shall be on acidic catalysis in protecting group (PG) chemistry.

The cleavage/formation of protecting groups by acid mediated hydrolysis/protection is one of the most established methods in PG chemistry and one of the mainstays of the subject. One of the main classes of acid-labile protecting groups are moieties that form stable cations upon cleavage.[111] An example of these protecting groups include *t*-butyl ether (**177**) and *t*-butyloxycarbonyl (BOC) (**178**), utilised in the protection of alcohols, amines, thiols and carboxylic acids. The cleavage of this PG results in the generation of a *t*-butyl cation. Benzyl cations are generated when benzyl PG's, used for the protection of hydroxyl, thiol, ester and amino groups, are cleaved.[112] The introduction of additional substituents to these PG's will either increase or reduce the stability of the cation with respect to the acid lability, allowing the chemist to design a suitably reactive PG for their synthesis. An example of this stability can be observed when you compare the more acid labile adamantyoxycarbonyl (Adoc) (**179**) to BOC (**178**), while *p*-methoxybenzyloxycarbonyl (MOZ) (**180**) is more labile than benzyloxycarbonyl (Cbz) (**181**) (Figure 1.14).[108,112]

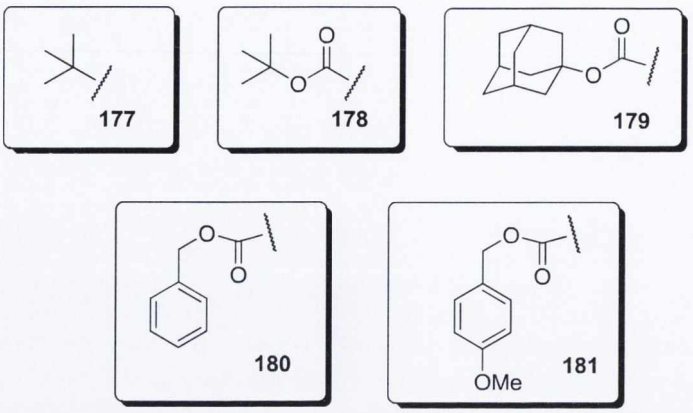


Figure 1.14 Acid labile protecting groups which generate stabilised cations upon cleavage.

Silyl ethers (**182-186**, Figure 1.15), used in the protection of alcohols, are removed under mildly acidic conditions in the presence of fluoride ions, the presence of which generally has little or no effect on other protecting groups, making these protecting groups one of the essential cornerstones of PG chemistry. The stability of these groups towards acids and bases is governed by the variation of substituents with greater steric demand leading to greater stability.[108,112]

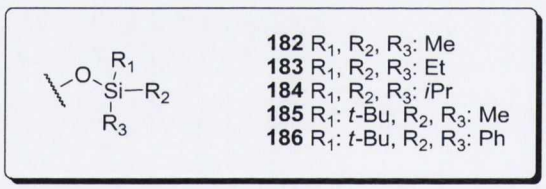


Figure 1.15 Silyl ether protecting group examples.

Acetals are formed and cleaved by acid catalysed hydrolysis or transacetalisation and are used in the protection of carbonyls and alcohols. The protection of carbonyl groups *via* this method will be discussed in more detail in Section 1.5.2. The protection of alcohols is often achieved using acetals such as tetrahydropyranal (THP) (**187**), methoxymethyl (MOM) (**188**), methoxyethoxymethyl (MEM) (**189**), or benzyloxymethyl (BOM) (**190**) (Figure 1.16).[108,111,112] These protecting groups are commonly used due to their susceptibility to cleavage through mild acid catalysed-hydrolysis.

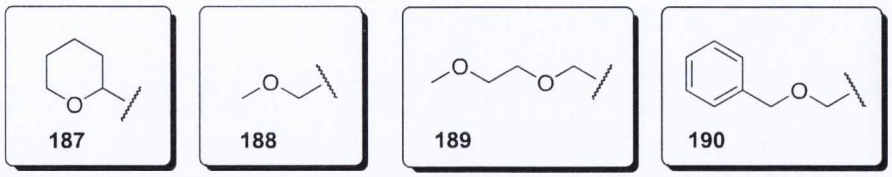


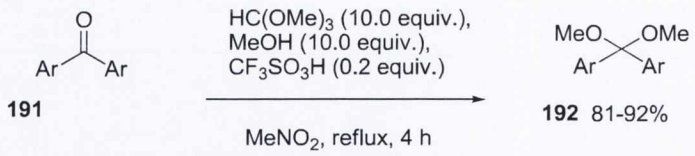
Figure 1.16 Acetal alcohol protecting groups which are susceptible to mild acid hydrolysis.

1.4.2 Acetals: protection of carbonyl groups

A major problem in protective group chemistry involves the shielding of highly electrophilic carbonyl groups from nucleophilic attack until such a time as its electrophilic properties are required. This problem is heightened when the carbonyl group is a component of the final target compound, making it necessary to protect this very reactive functional group until the end of the synthetic route when it can be liberated. The protection of aldehydes and ketones is carried out mainly by acyclic and cyclic acetals or thioacetals. Acetals are employed as they are stable to aqueous and non-aqueous bases, nucleophilic reagents (including organometallic reagents) and hydride reduction.[111]

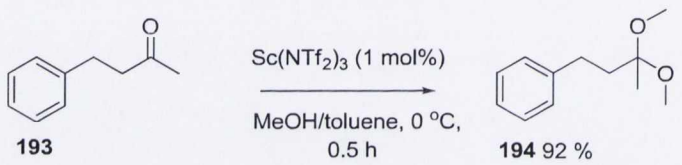
Dimethyl acetals are one of the most commonly used and simplest forms of acetal protecting groups. Their formation usually involves the reaction of either an aldehyde or ketone with methanol in the presence of an acid (either a Brønsted acid or Lewis acid). The generation of water during the reaction is a problem as it will facilitate a shift in the equilibrium of the reaction towards the carbonyl compound, therefore the reduction of the water content in the reaction medium is paramount. This can take place by physical means (such as distillation, using a Dean Stark apparatus) or by addition of molecular sieves or drying agent such as sodium sulfate however, the method most applied in current syntheses involves the presence of a water scavenger such as trimethylorthoformate or triethylorthoformate.[108]

The types of acids used in dimethyl acetal protection reactions include Brønsted acidic compounds such *p*-TSA,[113] HCl,[114] PPTS[115] or trifluoromethansulfonic acid.[116] An example of the use of the latter acid can be observed in the work carried out by Rice *et al.* who used this strong Brønsted acid (BA) in the presence of trimethylorthoformate, methanol and nitromethane to ketalise sterically hindered diaryl ketones **191** to dimethyl ketals **192** with nitro, halo and methoxy functionality in high yields (Scheme 1.33).[116]



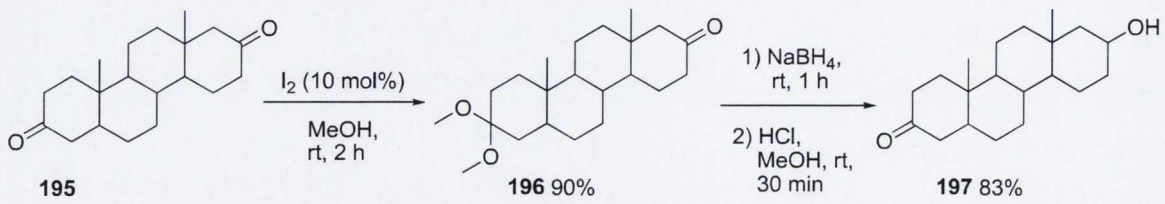
Scheme 1.33 Dimethyl ketalisation of diaryl ketones using catalytic trimethanesulfonic acid.

While Brønsted acidic catalysis is the most widely used method for the formation of acetals, some Lewis acidic methods exist, including the use of $LiBF_4$[117] and scandium triflimide ($Sc(NTf_2)_3$) catalysts. The use of $Sc(NTf_2)_3$ was found to be superior to the highly Brønsted acidic *p*-TSA in the ketalisation of the ketone 4-phenyl-2-butanone (**193**) with methanol in the presence of trimeythylorthoformate: catalysis using $Sc(NTf_2)_3$ yielding 92% of **194** while the use of *p*-TSA produced only 23% of **194** under the same conditions (Scheme 1.34).[118]



Scheme 1.34 Lewis acid-catalysed ketalisation of 4-phenyl-2-butanone.

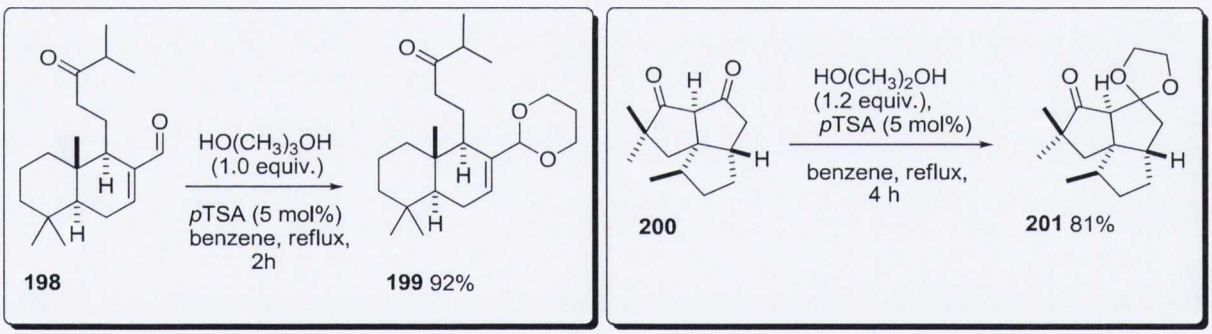
More recent developments of more selective acetal/ketal catalysts have included the use of iodine, which has been found to give varying degrees of selectivity with respect to the blocking of a particular carbonyl in the presence of another, using catalytic amounts of iodine and methanol. For example, the selective protection of **195** forming the mono-ketal **196**. The utilisation of iodine as the catalyst then allowed for the selective reduction of the other free carbonyl group of **196** in the presence of $NaBH_4$, followed by the deprotection of the ketal in the presence of an acid generating **197** (Scheme 1.35).[119]



Scheme 1.35 Selective iodine-catalysed mono-ketalisation of the diketone **195**.

Cyclic *O,O*-acetals are a more stable form of carbonyl protection than acyclic acetals, their stability rendering them less susceptible to acid hydrolysis.[111] Examples of these acetals include 1,3-dioxolanes and 1,3-dioxanes, the former in particular are probably one of the most prominent carbonyl protection groups. The formation of these acetals is generally undertaken using the strong acid catalysts associated with acyclic acetal formation such as *p*-TSA (probably the most commonly employed reagent),[120,121,122] PPTS[123,124] and HCl[125] along with sulfonic acid exchange resins (Amberlyst, Dowex)[126] in the presence of ethylene glycol (1,3-dioxolane) or 1,3-propanediol (1,3-dioxane).

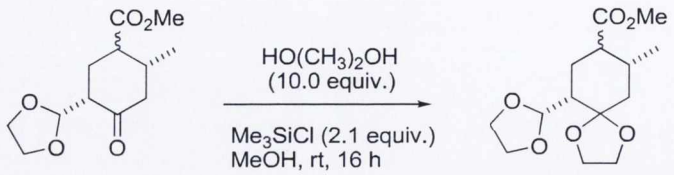
In molecules incorporating both aldehyde and ketone functional groups, acetal formation generally occurs faster than ketal formation; as observed in the protection of **198** generating **199** catalysed by *p*TSA (Scheme 1.36).[127] The ketalisation of the less hindered ketone will also generally take place faster than the ketalisation of a hindered ketone: for example the diketone **200** underwent regioselective/chemoselective mono-ketalisation in the presence of 1,3-propanediol and *p*TSA (Scheme 1.36).[128]



Scheme 1.36 The steric selectivity of acetal/ketal formation processes: representative examples.

Besides the utilisation of conventional acids as described above, novel reagents have also been employed. As previously mentioned, the generation of water is a problem in acetal formation. Chan *et al.* introduced a solution to this by catalysing the acetalisation of aldehydes and ketalisation of ketones using 1 equivalent of the reagent chlorotrimethylsilane. The reaction is catalysed through the generation of HCl *in situ* while generated water is removed from the reaction as hexamethyldisiloxane (TMS_2O).[129] An example of the utilisation of this catalyst can be observed in the total synthesis of chlorothricolide by Schmidt

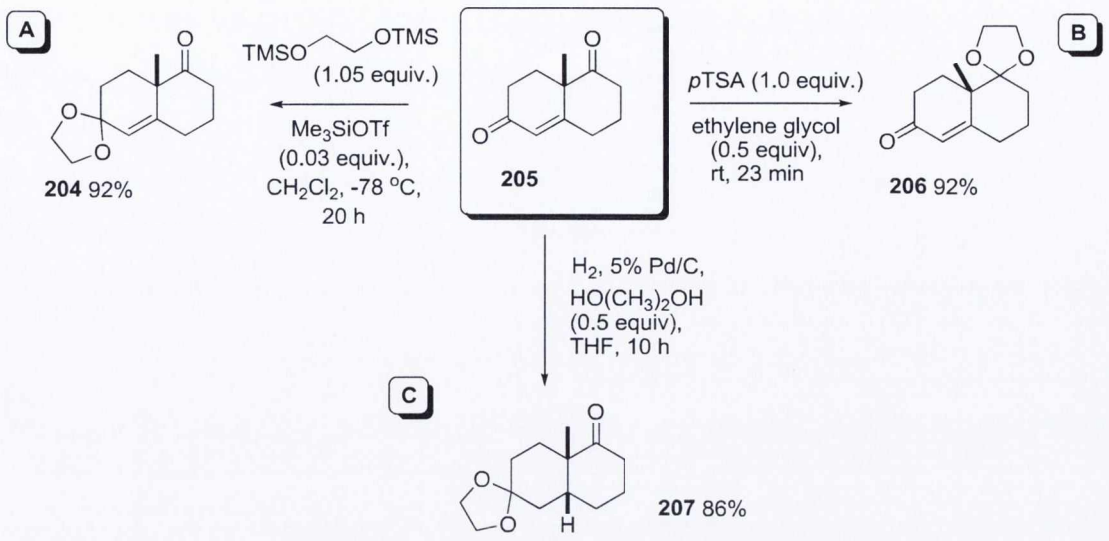
et al., where chlorotrimethylsilane catalysed the protection of the cyclic ketone **202** with ethylene glycol leading to the generation **203** in good yield, a key step in the synthesis of the 'top' half of the target molecule (Scheme 1.37).[130]



202 **203** 85%

Scheme 1.37 Ketalisation of **202** in the presence of ethylene glycol and chlorotrimethylsilane: a key step in the total synthesis of chlorothricolide

The Wieland-Miescher ketone (**205**)[131] is a widely used and versatile synthon employed in the total synthesis of a variety of natural products, including terpinoids and steroids.[132] The ketal protection of this diketone is an important transformation in many of these natural product syntheses.[133,134] Due to a difficulty associated with the migration of the alkene under ketalisation conditions, a number of specialised methods for the ketalisation of **205** have been developed. The olefin location, which is determined by the acidity of the reaction medium, must be controlled; as catalysts of high acidity will generally lead to the migration of the alkene double bond, while mildly acidic conditions generally do not cause double bond migration.[111] The methods to counteract this phenomenon include the reactions in Scheme 1.38 (*vide infra*). One method for the protection of **205** involves the use of TMSOTf in conjunction with the bistrimethylsilyl derivative of 1,2-ethanediol in pyridine, this results in the formation of **204** without double bond migration and selective ketalisation of the less hindered ketone (A, Scheme 1.38).[135] A second example (B, Scheme 1.38) details a method in which a stoichiometric amount of *p*TSA is used in ethylene glycol as the reaction solvent. This produces the ketal **206** at the more hindered position in a 92% yield.[136] The use of Pd/C in the hydrogenation of the diketone in the presence of diol was also found to give the acetal protected compound **207** with reduction of the olefin in excellent yields (C, Scheme 1.38).[137]



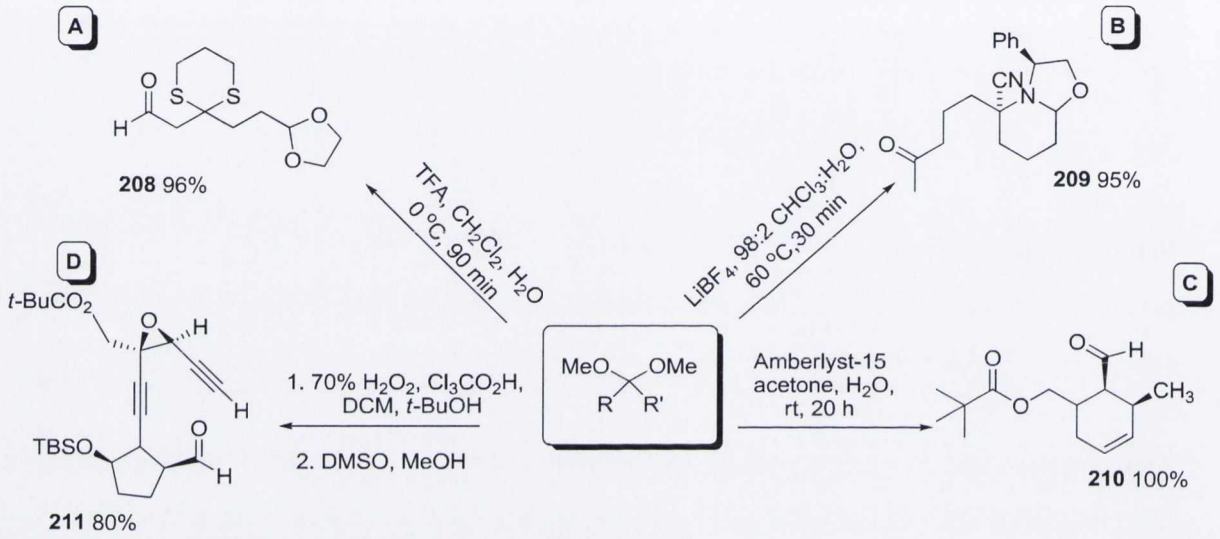
Scheme 1.38 Methods for the ketal protection of Wieland-Miescher ketone (**205**).

1.4.3 Hydrolysis: acyclic and cyclic acetals

Acid catalysed cleavage of *O,O*-acetals occurs when the equilibrium of the reaction is reversed, towards the formation of the parent aldehyde/ketone, due to the presence of excess water, this is usually catalysed by an acidic compound. The most commonly used method involves the Brønsted acidic catalysed hydrolysis of acetals. However, the use of Lewis acids, metal based compounds and various other methods have also been employed.

The hydrolysis of acyclic dimethyl acetals can be carried out using the conventional BAs used in acetal formation such as *p*-TSA,[138] acetic acid[139] and H_2SO_4.[140] An example of the use of a Brønsted acid can be observed in the employment of CF_3COOH (A, Scheme 1.39) which catalysed the cleavage of the dimethyl acetal in the presence of the more stable cyclic *O,O*-acetal and a 1,3-dithiane moiety generating **208** in 96% yield.[141] The utilisation of Lewis acids such as $LiBF_4$ was found to allow for the cleavage of the dimethyl ketal to its parent ketone in the presence of an acid sensitive group such as the oxazolidine in compound **209** (B, Scheme 1.39).[142] The use of the sulfonic acid resin Amberlyst-15 is another method through which the cleavage of acetals/ketals can occur (*e.g.* **210**), the employment of this acidic resin allows for the easy separation of catalysts and product (C, Scheme 1.39).[143] The use of hydrogen peroxide in the presence of trichloroacetic acid has been described as a method to hydrolyse dimethyl acetals in the presence of acid sensitive groups, including epoxides. An example of

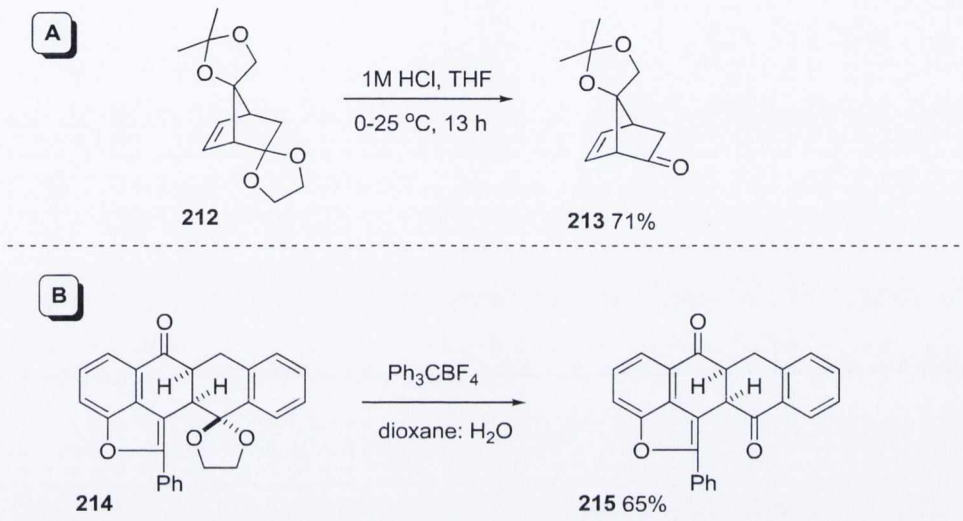
the use of these conditions can be seen below (D, Scheme 1.39) in which the deprotection of the acetal takes place generating aldehyde **211** in 80% yield with no epoxide ring opening and retention of the β-siloxy group.[144] Metal catalysis can also be employed to cleave these acetals with methods developed using $ZnCl_2$[145] and $FeCl_3$[146] amongst others. There are various other reagents utilised in both complex molecule protection and also with more simple systems.[108,111]



Scheme 1.39 Representative example of reagents for the deprotection of acyclic dimethyl acetals/ketals.

The hydrolysis of cyclic *O,O*-acetals as can be deduced from the examples outlined above is more demanding due to the augmented stability of the cyclic protecting group. Brønsted acids such as PPTS,[147] *p*-TSA,[148] AcOH[149] and HCl[150] can be used to cleave the acetal functionality, however either higher temperatures, higher catalyst loadings or longer reaction times are generally required. The employment of HCl is prevalent in the hydrolysis these cyclic moieites, an example of which can be observed in the total synthesis of (±)12-hydroxyprostaglandin $F_{2\alpha}$ by Greico *et al.* A key step in this synthesis involves the cleavage of a 5-membered cyclic *O,O*-acetal in the presence of another **212**, this results in the regeneration of the ketone with retention of the acetonide functionality **213** (A, Scheme 1.40).[151] Lewis acidic reagents such as $LiBF_4$[152] and Ph_3CBF_4[153] are also employed. Barton *et al.* highlighted the utility of trityl fluoroborate as a useful reagent for the deprotection of 1,3-dioxolanes. The deprotection of the acetal in the tetracycline structure **214** was carried out

employing this reagent, giving 65% of **215**, this yield was much higher than conventional acids previously used such as HCl, which generated <10% **215** (B, Scheme 1.40).[153] Other methods include the use of metal containing catalysts such as $PdCl_2(CH_3CN)_2$,[154] $CuSO_4.SiO_2$[155] and $FeCl_3.6H_2O$.[156] The cleavage of 1,3-dioxanes are generally carried out employing the same reagents as 1,3-dioxolanes.



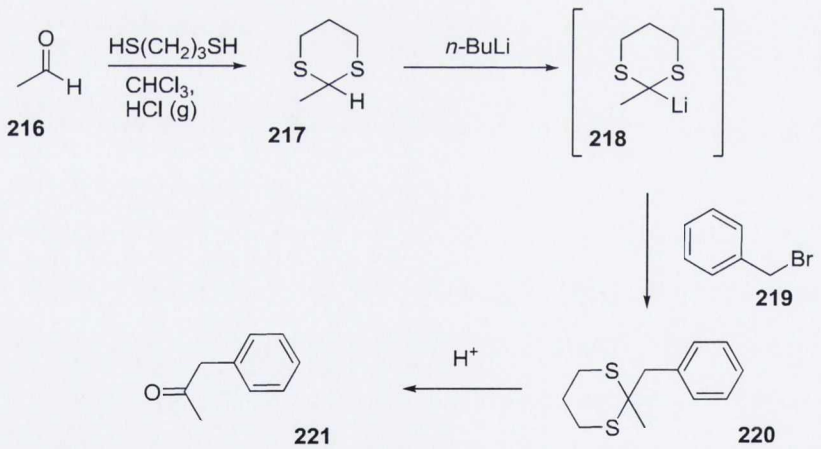
Scheme 1.40 Representative examples of reagents employed to cleave 1,3-dioxanes/dioxolanes.

1.4.4 Conclusions: acetal protection/deprotection

The discussion above has highlighted some of the vast array of reagents used and methods through which acyclic and cyclic *O,O*-acetals can be both formed and cleaved. The number of examples mentioned above trivial however, when compared to the breadth of reagents available. This variety of reagents ranges from conventional Brønsted acids to metal catalysts, however it should also be highlighted that the majority of catalysts used are either corrosive, toxic, expensive or all of the above. These properties contribute to negative connotations with respect to handling, safety, expense and environmental impact, therefore there is a considerable scope for the development of new safer reagents to carry out these invaluable protection reactions.

1.5. Dithianes/Dithiolanes

The popularity of the dithiane group in protecting group chemistry is largely due to its ability to be deprotonated by *n*-BuLi to form an anion that reacts with a wide variety of reagents to form a C-C bond. This *umpolung* effect means dithianes are useful in a range of chemical transformations. This idea was first introduced by Seebach and Corey in 1965,[157,158,159] the formation of a dithiane from an aldehyde or ketone resulted in a reversal of polarity of the carbonyl (an a^1-reagent, Seebach's nomenclature)[160] generating a masked nucleophilic acylating agent (a d^1-reagent, Seebach's nomenclature).[160] The protection of the carbonyl moiety is carried out under acidic conditions *e.g.* the protection of ethanal (**216**) with 1,3-propanedithiol in the presence of HCl as a catalyst generating dithiane **217**. The reaction of this dithiane with *n*-BuLi results in the generation of a 2-lithio-1,3-dithiane **218**, which then reacts as a nucleophile in the nucleophilic displacement of alkyl halides or other carbonyl compounds. An example of this can be seen in the reaction of **218** and benzyl bromide (**219**) generating a new C-C bond to the dithiane protected compound **220**. This can then be hydrolysed in the presence of an acidic reagent yielding the ketone product **221** (Scheme 1.41).[159,161]

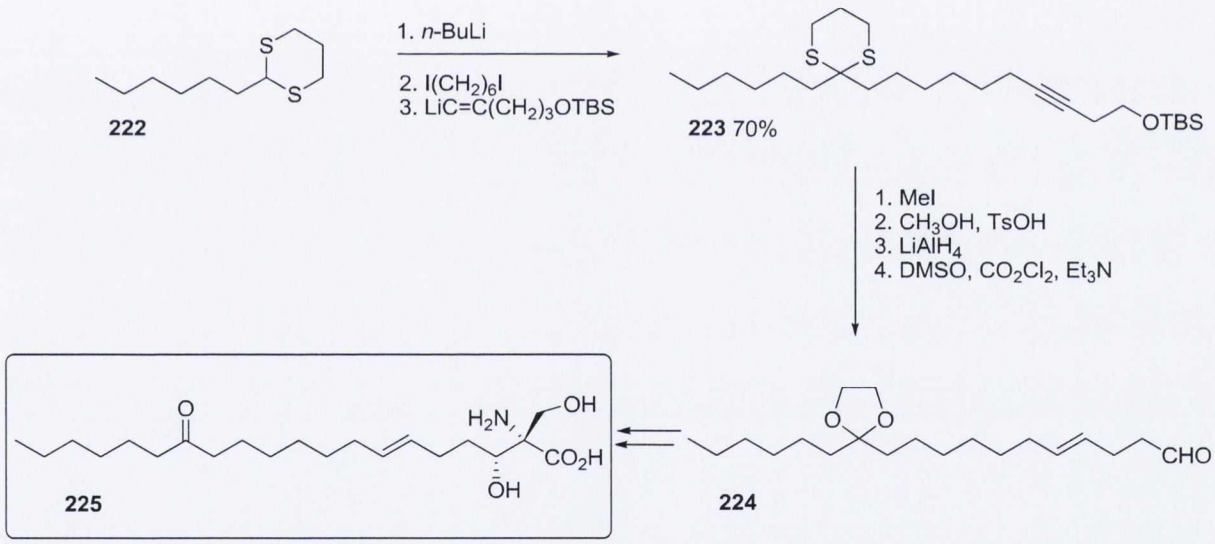


Scheme 1.41 Generation of a new C-C bond using dithiane chemistry.

The 2-lithio-1,3-dithiane species are quite stable when compared to other intermediates containing cations other than lithium for example Mg^+, K^+ or Na^+. This stability is due to the effect of the sulfur atoms on adjacent carbanions by electron back donation into vacant sulfur *d*-orbitals.[160] These 2-lithio-1,3-dithianes are of great synthetic significance as they react with

multiple electrophiles resulting in carbon-carbon bond formation, while the scope of these reactions is too broad to be fully discussed in this thesis[162] some examples are outlined below.

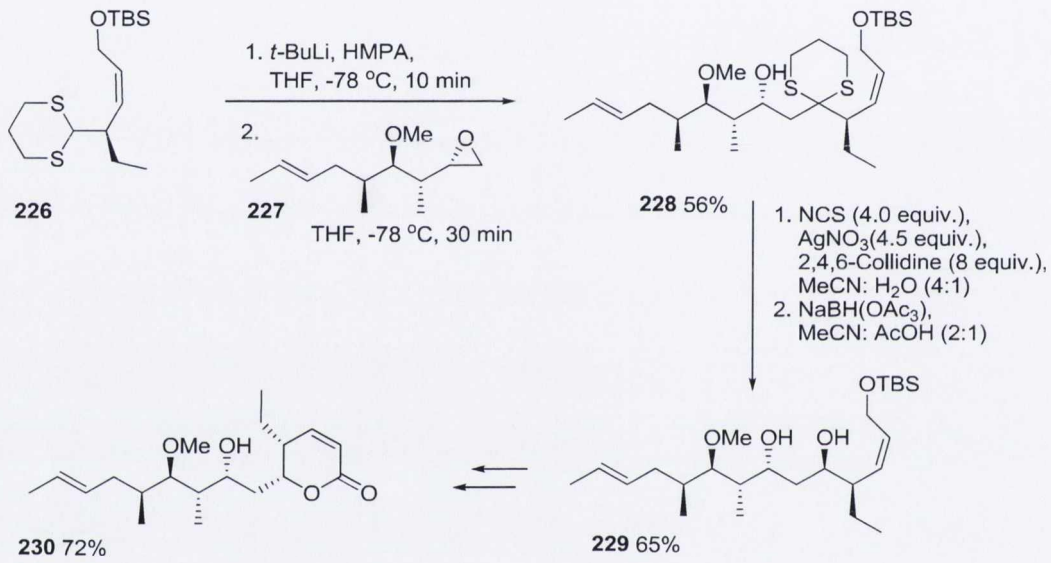
Alkylation reactions of 1,3-dithianes have been used in the total synthesis of a wide range of natural products. Alkyl halides, sulfonates and triflates are common electrophiles employed in dithiane chemistry. Hatakeyama *et al.* carried out the first enantioselective synthesis of (-)-mycestericin E (**225**);[163] a potent immunosuppressant obtained from the fungus *Mycelia Sterilia*. This long chained compound was prepared by the initial reaction of dithiane **222** (after lithiation), with diiodohexane and then a second alkyl iodide resulting in the formation of **223** (70% yield). The dithiane was then exchanged for a dioxolane, using methyl iodide followed by ketalisation (catalysed by *p*-TSA). The subsequent reduction of the triple bond and a Swern oxidation produced the precursor **224** eventually affording **225** in 78% overall yield (Scheme 1.42).[163]



Scheme 1.42 Utilisation of a 2-lithio-1,3-dithiane intermediate for C-C bond formation in the total synthesis of (-)-mycetericin E.

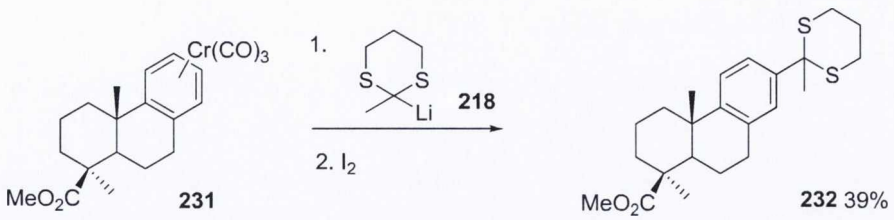
Epoxides are another commonly used electrophile due to their availability in enantiomerically pure form (allowing for the production of chiral alcohols through the reaction of the epoxide with the generated nucleophile). The most common employment of this method in natural product synthesis, is the reaction of the epoxides with 2-lithio-1,3-dithianes; generating enantiomerically pure *β*-hydroxycarbonyl compounds in a single step.[161] An example of this is

a key step in the synthesis of pironetin, a natural product which exhibits plant growth regulatory activities and is isolated from *Streptomyces*. Chida *et al.* carried out the alkylation of the conjugate base of **226** with the enantiomerically pure epoxide **227**, generating compound **228** in 56% yield. The cleavage of the dithiane was carried out using *N*-chlorosuccinimide and silver nitrate followed by reduction of the resulting ketone leading to the formation of **229**. This was followed by the removal of the *O*-silyl group and oxidation with manganese dioxide to afford the final product pironetin (**230**) with an overall yield of 72% (Scheme 1.43).[164]



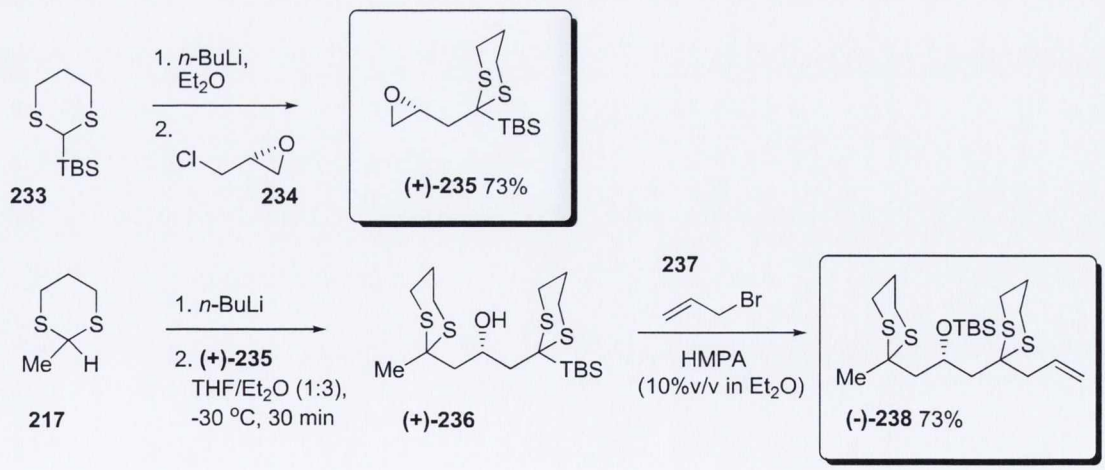
Scheme 1.43 The reaction of chiral epoxide **227** and the 2-lithio-1,3-dithiane derived from **226** as a key C-C bond forming reaction in the total synthesis of pironetin.

Metal-arene complexes such as chromium containing arene derivatives can be manipulated into useful organic compounds. For example, Woodgate *et al.* observed the regioselective attack on the chromium complex **231** with 2-lithio-2-methyl-1,3-dithiane (**218**) to generate **232** after treatment with iodine in 39% yield (Scheme 1.44).[165]



Scheme 1.44 Generation of new C-C bond using a metal-arene complex and a 2-lithio-1,3-dithiane compound

This dithiane chemistry was also exploited by Smith *et al.* in 2006, who carried out anion-relay chemistry (ARC) in which an anionic functional group, resulting from an initial organic reaction is transferred to a different location within the same carbon framework and becomes available for a secondary reaction.[166] A one-pot, three component reaction was undertaken involving the initial preparation of the linchpin molecule (+)-**235** out on a multigram scale by the treatment of the lithium anion of dithiane **233** in ether with the epoxide (-)-epichlorohydrin (**234**) with a 71% yield. This was then reacted with a second lithium anion of a different dithiane for example **217** in the presence of a THF/Et_2O mixture yielding **236**. This was then reacted, in one pot, with an alkyl halide such as allyl bromide (**237**) with HMPA in ether to obtain (-)-**238** in 73% yield (Scheme 1.45).[166] This is an example of the utilisation of various electrophiles to generate new C-C bonds in one-pot.

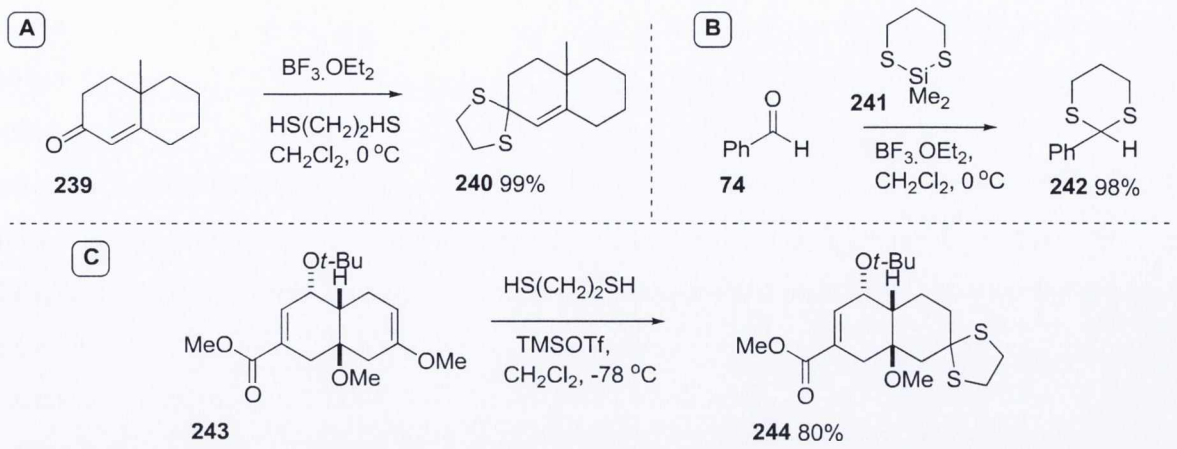


Scheme 1.45 Employment of 2-lithio-1,3-dithiane chemistry in anion relay chemistry.

1.5.1 Dithiane formation

The dithiane group is also exceedingly acid stable when compared to the 1,3-dioxolane and 1,3-dioxane PG and it is therefore not only employed to generate lithio-dithianes, it is also utilised as an extremely stable protecting group. This is due to the acid stability making dithianes harder to cleave, generally requiring harsh conditions and the use Lewis acidic metal complexes or oxidation to remove them. The formation of dithianes are generally catalysed by Lewis acids, solid-supported reagents or the formation of an acid *in situ*.

The use of Lewis acids such as $BF_3{\cdot}OEt_2$,[167,168,169] $SnCl_2$,[170] $Zn(OTf)_2$[171] and $LiBF_4$[172] are regularly employed as catalysts for dithiane protection. Variations on the conditions for utilisation of $BF_3{\cdot}OEt_2$, which is probably the most commonly employed Lewis acidic reagent, have generated a few methods for dithiane formation including early work by Sondheimer and Rosenthal in 1958. During the synthesis of intermediates for the total synthesis of pentacyclic triterpenes, they catalysed the dithiane protection of α,β-unsaturated ketones without migration of the double bond to the β,γ-position, generating **240** from **239** in 99% yield (A, Scheme 1.46).[167] The use of this reagent in conjunction with ethanedithiol and propanedithiol is widespread, while Soderquist and co-workers employed $BF_3{\cdot}OEt_2$ in the presence of the silica containing thiol 2,2-dimethyl-2-sila-1,3-dithiane **241** used, for example, in the generation of the dithiane **242** from benzaldehyde (**74**) in 98% yield (B, Scheme 1.46). This utilisation of this thiol generally led to cleaner products and high yields, when compared to the conventional methods developed.[168] More recently developed Lewis acidic reagents include TMSOTf, which is used to protect the ketone enol ester based compound **243** in the presence of a *t*-butoxy group. This group is labile under acidic conditions which results in the generation of degradation products when protected with more conventional acids, such as $BF_3{\cdot}OEt_2$, $TiCl_4$ and $ZnOTf_2$. The protection of **243** with ethanedithiol generating **244** occurred employing TMSOTf in CH_2Cl_2 with 1,2-ethanedithiol in 94% yield, where protection of the enol ester group occurred (C, Scheme 1.46).[173]



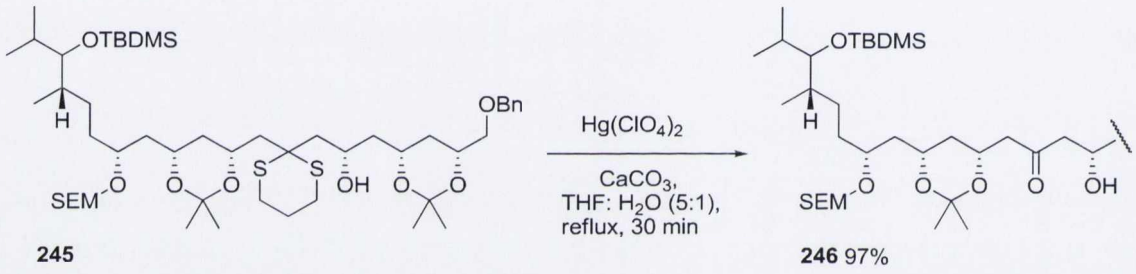
Scheme 1.46 Representative examples of Lewis acid catalysed dithiane formation

Solid supported reagents can also be used, these include montmorillonite KSF clay which allows for the solvent free protection of aldehydes and ketones with yields ranging from 85%-90%.[174] Silica supported reagents have also been employed including $SOCl_2$-SiO_2[175] and $AlCl_3$-SiO_2.[176] Other reagents include acid supported resins such as Dowex[177] and Amberlyst-15.[178] A third method for the formation of dithianes involves the generation of the acid *in situ*. These reagents include $Me_2S{\cdot}Br$, through which HBr is generated by oxidation of the dithiol.[179] Similarly I_2 can be utilised to generate HI *in situ* catalysing the protection of carbonyl groups.[180] The use of NBS,[181] $Bi_2(SO_4)_3$[182] and trichloroisocyanuric acid[183] are other methods through which the generation of an *in situ* acid catalyst can form dithianes.

1.5.2 Hydrolysis of dithianes: metal catalysis

It can be observed from both the stability of the dithiane protective group and the earlier examples outlining the use of dithianes in natural product synthesis that the cleavage of the cyclic thioacetal protecting group requires generally harsh conditions. Due to the resistance of these *S,S*-acetals to hard acid/base catalysis, specialised reagents have been developed to hydrolyse these protecting groups. The first method discussed is based on metal derived compounds taking advantage of the soft-soft interactions between sulfur and metals, which involves the coordination of the sulfur atom to the metal component of the catalyst, forming a thiometallic intermediate. This is followed by the addition of H_2O (usually) and the subsequent hydrolysis of the coordinated dithiane. Two equivalents or more of the metal compound are usually required for the efficient hydrolysis of dithianes.[184,185]

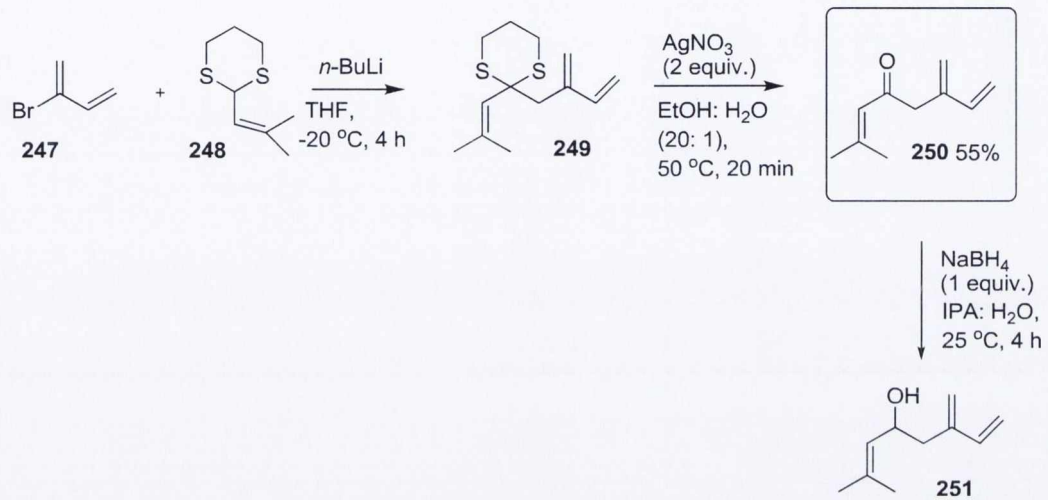
Early hydrolyses of dithianes were carried out using mercury (II) chloride, the first example of which was reported by Fischer in 1894 during his work with glucose.[186] This is still one of the most commonly employed reagents in dithiane deprotection chemistry today due to its low cost and versatility. However its use would be ideally avoided where possible due to its toxicity and environmental precariousness.[183] An example of the use of a mercuric based reagent for the cleavage of the dithiane protecting group can be observed in the synthesis of the 36-membered polyene macrolide, Roflamycoin carried out by Lipschutz *et al.* A key step involved in total synthesis involves the dithiane protection of a ketone in the long chain molecule **210** which is then cleaved using $Hg(ClO_4)_2$ with calcium carbonate in MeCN, generating **211** in 97% yield (Scheme 1.47). The role of calcium carbonate is to neutralise the excess acid generated during the reaction.[187]



Scheme 1.47 Deprotection of dithiane **210** using a mercury-based catalyst in the synthesis of Roflamycoin

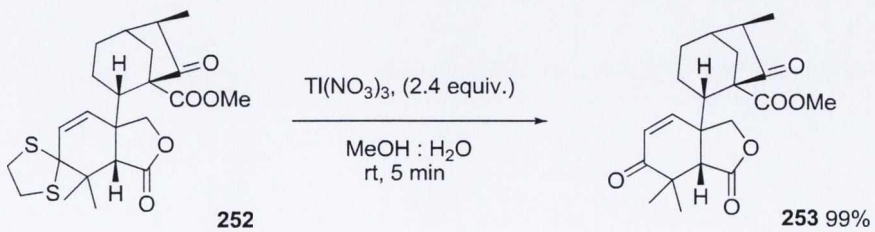
There are a wide variety of metal-based catalysts which have been developed to hydrolyse dithianes to replace the effective yet inherently toxic mercury-based compounds. These catalysts are generally specific to certain reaction conditions and used in stoichiometric amounts. The use of the less toxic yet more expensive, silver based compounds in an alcohol/water solvent system is a second common catalyst for thioacetal cleavage. The use of $AgNO_3$ was introduced by Reece and co-workers in 1968, during the investigation of terpene alcohols, principal components of the sex attractant produced by the bark beetle, *Ips confusus*.[188] One of these alcohols was 2-methyl-6-methylene-2,7-octadien-4-ol (**251**), the synthesis of this compound involved the reaction of **247** and **248** in the presence of *n*-BuLi to generate the protected compound **249**. It was found that the use of mercuric (II) chloride to oxidise the dithiane was unsuccessful resulting in extremely low yield. Silver nitrate was therefore used in its place, converting **249** to **250** with a synthetically acceptable yield of 55%.

This was then reduced using $NaBH_4$ yielding the desired alcohol **251** (Scheme 1.48). Although silver based compounds are less toxic than their mercury-based predecessors the relative expense of utilising these compounds has meant they are not as widely used by synthetic organic chemists, and are generally used only in cases in which, as in this case, mercuric-based compounds are ineffective.[188]



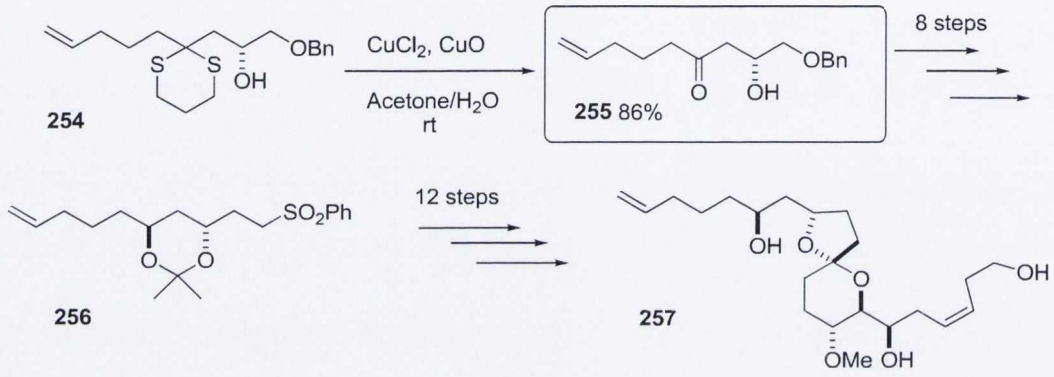
Scheme 1.48 The use of $AgNO_3$ in the hydrolysis of dithiane **249** to ketone **250**.

Other metal based deprotection agents include $Tl(NO_3)$ which was first reported as a dithiane group deprotection reagent by Fujita *et al.* in 1976.[189] This compound allows for the hydrolysis of dithianes in the presence of sensitive moieties such as esters, lactones, or bicyclic moieties which are susceptible to rearrangement (such as **252**), where the dithiane group was cleaved to the ketone, generating **253** in almost quantitative yield (99%) (Scheme 1.49).[190]



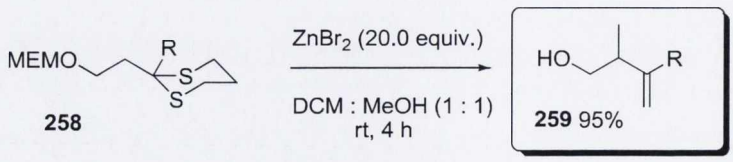
Scheme 1.49 Utilisation of $Tl(NO_3)$ as a metal based cleavage reagent in deprotection of **252** to **253**.

Cerium (IV) ammonium nitrate (CAN)[191] and clay-supported CAN[192] based reagents have also proved effective under certain conditions, whilst the utilisation of copper based compounds is another popular method with the use of $CuCl_2$ prominent.[193,194] Uemura *et al.* carried out the deprotection of dithiane **254** to **255** using $CuCl_2$ and CuO, in the synthesis of the C_{12}-C_{21} segment **256** of Attenol A (**257**): a spiro compound isolated from the shellfish *Pinna attenuata*, which has exhibited cytotoxic properties against P388 cells (Scheme 1.50).[195]



Scheme 1.50 Deprotection of **254** using $CuCl_2$ in the presence of CuO: a key step in the total synthesis of Attenol A (**257**).

Other recent examples of metal-mediated reactions include the use of Fe (III) chloride,[196] Sb (IV) chloride[197] and gallium (III) chloride[198] in the hydrolysis of dithiane protected molecules. While Hoffmann *et al.* have utilised the zinc based catalyst, $Zn(Br_2)$ in the simultaneous deprotection of the dithiane group and MEM group in compound **258** forming **259** in high yield at room temperature in a relatively short reaction time, the requirement of large amounts of the zinc based catalyst was however a significant drawback (Scheme 1.51).[199]

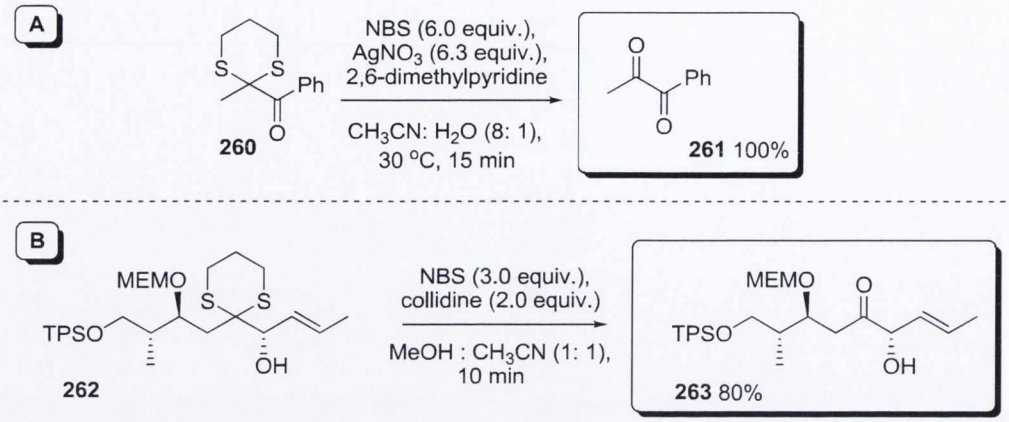


Scheme 1.51 Use of a zinc-based reagent to simultaneously remove dithiane protecting group and MEM alcohol protecting group in compound **258**.

1.5.3 Hydrolysis of dithianes: non-metal based cleavage of dithianes

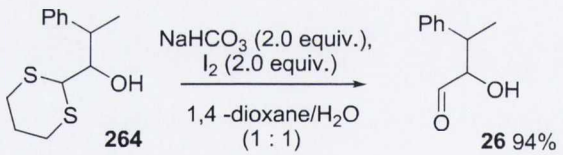
The cleavage of dithiane groups through the oxidation of dithianes to generate sulfoxides, which are significantly better leaving groups than thioacetals, was first developed in the deprotection of steroid-based molecules. These moieties were protected as closed thioacetals but were resistant to existing mercury-mediated hydrolysis methods. Initial oxidation was carried out in the presence of monoperoxyphthalic acid, followed by treatment with sodium ethoxide allowing for the eventual cleavage of the dithiane.[200] Though the number of oxidation methods for dithiane protection are vast, they are generally employed less frequently than metal-based reagents. The most widely used reagents include *N*-halogensuccinimides or hypervalent iodine.

N-bromosuccinimide was the focus of extensive studies by Corey *et al.* in the removal of thioacetals from complex structures (where the use of $HgCl_2$ and HgO were ineffective) in the 1970's.[201] NBS is one of the most widely employed dithiane cleavage agents today due to its reliability, compatibility with sensitive substrates and lower toxicity compared to heavy metal-based adducts. Each of these advantages outweighed the relatively high cost of the implementation of this process, as initial studies required the use of excess $AgNO_3$, in conjunction with high quantities of NBS to scavenge any free bromine released during the reaction. The use of 2-methylpyridine was also required to neutralise the reaction carried out by Corey and co-workers in this investigation during the deprotection of **260** generating the parent ketone **261** in quantitative yield (A, Scheme 1.52).[201] Williams *et al.* carried out the deprotection of a dithiane substrate containing an α-hydroxy-β,γ-unsaturated group **262** with NBS in the presence of 2,3,5-trimethylpyridine (collidine) and in the absence of a $AgNO_3$ scavenger, yielding 80% of the ketone **263** (Reaction B, Scheme 1.52).[202] *N*-chlorosuccinimide was also investigated by Corey *et al.* and found to be more effective than NBS for dithiane deprotection of alkenes[201] and was utilised in the deprotection of Baylis-Hillmann and vinylalumination adducts in which metal based deprotection was not efficient.[203]



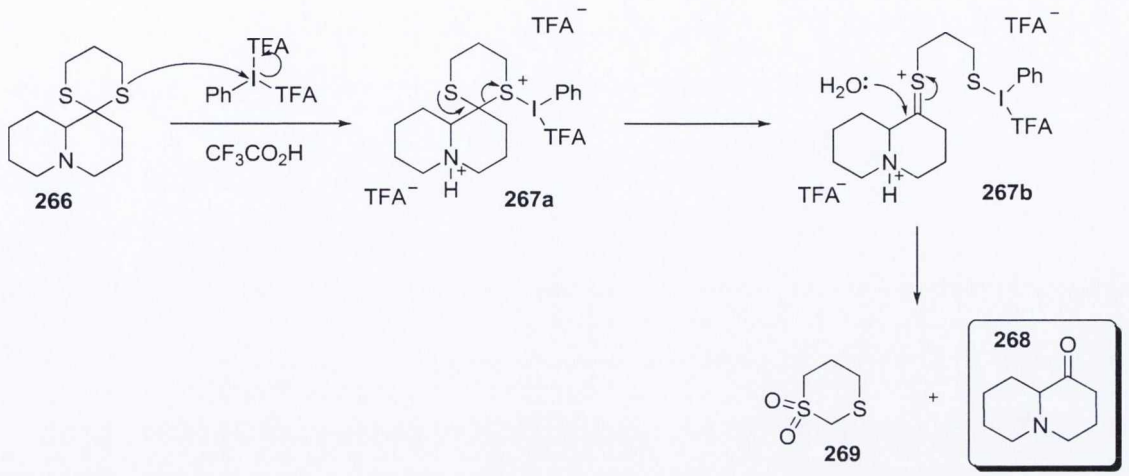
Scheme 1.52 Representative examples of the use of NBS as an oxidising agent in the hydrolysis of dithianes.

Iodine is another compound employed in the oxidation of thioacetals; with I_2 utilised in the study of α-hydroxymercaptals. The deprotection of **264** took place (in the presence of the mild base $NaHCO_3$ to maintain neutral reaction conditions), producing ketone **268** in 85% yield (Scheme 1.53).[204] The employment of iodine proved extremely useful in this case, as the use of mercury based compounds led to long reaction times and difficulty with product separation, while the use of NBS led to the undesirable rearrangement of the product.



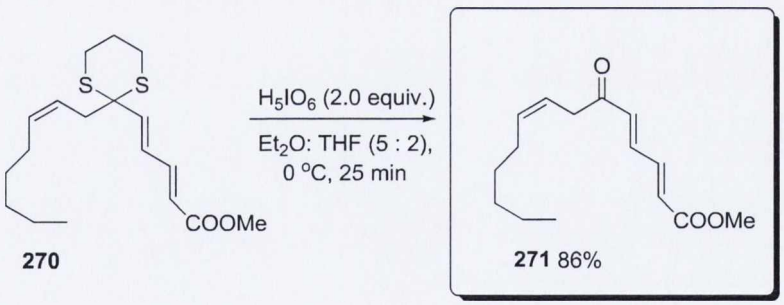
Scheme 1.53 Deprotection of dithiane **265** using iodine.

The most common iodine-based compound is *bis*(trifluoroacetoxy)iodobenzene, which was introduced in 1989 by Stork and co-workers.[205] This has since emerged as one of the most widely used methods for the removal of dithianes, despite its high cost and low atom economy. The mild deprotection technique proceeds *via* the attack of sulfur of the cyclic dithiane, *e.g.* **266**, on the hypervalent iodine, this leads to the breaking of the cyclic dithiane sulfur-carbon bond **267a** generating **267b**, subsequent addition of H_2O leads to the generation of the free carbonyl compound **268** and the sulfur-based side product **269** (Scheme 1.54).[205]



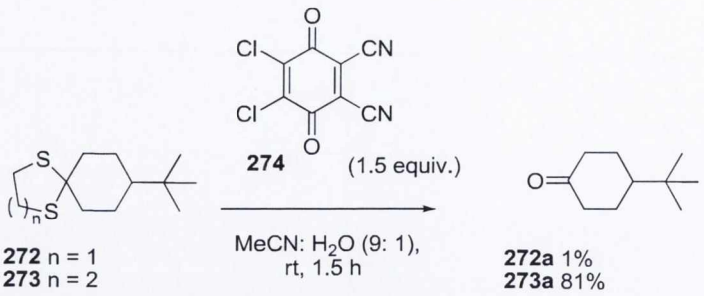
Scheme 1.54 Mechanism for the deprotection of cyclic dithianes in the presence of *bis*(trifluoroacetoxy)iodobenzene.

Periodic acid has been found to be a useful deprotection agent in the presence of acid sensitive moieties[206] such as α,β-unsaturated aldehydes and *O,O*-acetals. Additionally, it was found to efficiently hydrolyse the dithiane in the acid sensitive ester **270** to **271** with a 86% yield and no effect on any other functional groups present was observed (Scheme 1.55).[207] Nicolau and co-workers also developed a procedure using *o*-iodobenzoic acid (IBX) in the solvent-free deprotection of various dithianes.[208]



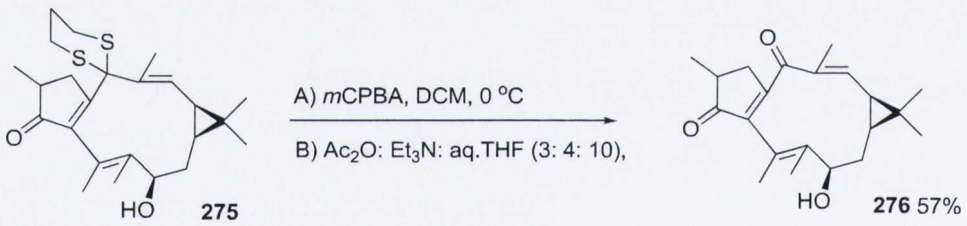
Scheme 1.55 Cleavage of dithiane **270** in the presence of periodic acid.

The selective deprotection of 1,3-dithiane moieties in the presence of 1,3-dithiolane protected carbonyls can be carried out using DDQ (**274**).[209] Tanemura *et al.* carried out the deprotection of **273** to **273a** in 81% yield, while the hydrolysis of the dithiolane **272** proceeded with a minimal yield of 1% **272a** afforded (Scheme 1.56).[210]



Scheme 1.56 Selective deprotection of dithiane **273** over dithiolane **272** using DDQ.

The use of 3-chloroperoxybenzoic acid (*m*CPBA) to deprotect a thioacetal protected ketone was first reported in the total synthesis of bertyadionol (**276**) by Smith and co-workers in 1986.[211] The 1,3-dithiane **275** was oxidised to its monosulfoxide which then decomposed when treated with acetic anhydride giving the desired product **276** in 57% yield (Scheme 1.57).[211] The use of this reagent was discovered after multiple other protocols had been attempted and had failed. *m*CPBA continues to be one of the most commonly employed in modern day reagents in the cleavage of dithianes.



Scheme 1.57 *m*CPBA as an oxidising agent in the cleavage of 1,3-dithiane protected carbonyls.

Various specialised reagents have been developed over time including lithium diisopropylamide,[212] Oxone™ (potassium persulfate on wet silica),[213] Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabucyclo[2.2.2]octane bis(tetrafluoroborate)[214] and Clayfen.[215] Each of which have exhibited efficacy in the hydrolysis of various dithiane and dithiolane protected moieties.

1.5.4 Conclusions: hydrolysis of dithianes

There are a vast array of methods, so vast that the examples outlined above exhibit only a small representative portion of those existing, for the cleavage of dithiane groups to generate their parent carbonyls. The most widely used methods today involve $HgCl_2$ and $Hg(ClO_4)_2$, which are still being used despite their toxicity and environmental concerns. The use of iodomethane and bis(trifluoroacetoxy)iodobenzene are also popular, however these reagents and each of the various alternative methods discussed above require the use of stoichiometric amounts of the deprotecting reagents, harsh reaction conditions or long reaction times to generate the desired aldehyde/ketone derived products, sometimes with low yields and with unwanted side products. The plethora of novel protocols and methods which are constantly being developed, along with the multiple difficulties reported above, highlight the fact that the removal of thioacetal protecting groups is still not a straightforward task. There is considerable scope for the development of new, safer, more efficient methods for the regeneration of carbonyl molecules from their protected dithiane state.

1.6 *N*-Heterocyclic carbenes

It has been highlighted already (utilising dithiane chemistry) how the inversion of stereochemistry in a functional group opens up a wide variety of new synthetic pathways. Carbene nucleophiles are another example of nucleophilic compounds which can facilitate *umpolung* chemistry to enable the chemist to generate new carbon-carbon bonds.[216] The co-enzyme thiamine (Vitamin B1) (**277**) (Figure 1.17) is a naturally occurring thiazolium salt which utilises this *umpolung* concept and catalyses various biochemical processes.[217] An example of a class of thiamine dependent enzyme are the transketolases; which are involved in the phosphogluconate pathway in animals, generating NADPH and pentoses and the Calvin cycle *i.e.* the synthesis of carbohydrates in plants. The enzymes operate through the catalysis of the transfer of a 2 carbon fragment from a phosphate ketose donor to a phosphate aldose acceptor.[217]

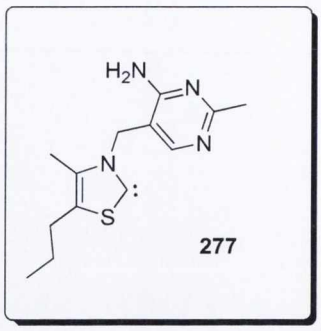
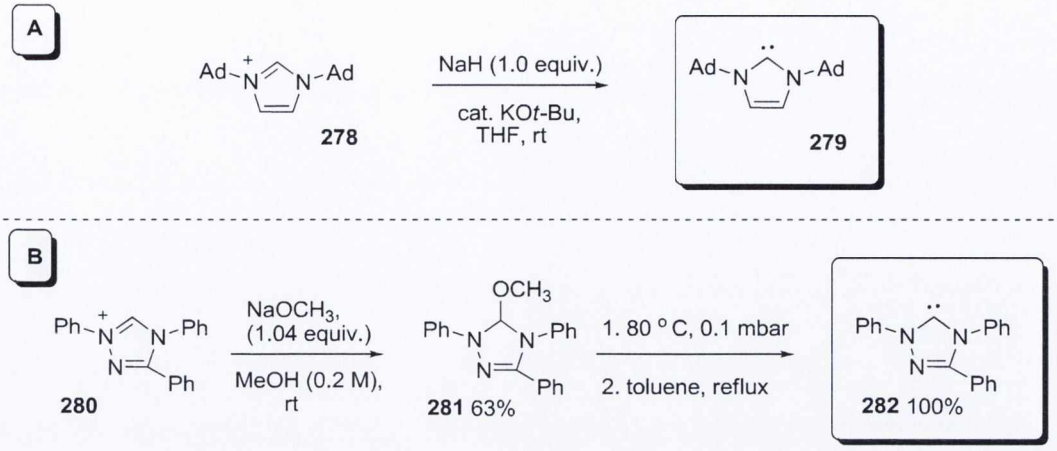


Figure 1.17 Structure of thiamine (Vitamin B_1).

Carbenes are now one of the most investigated reactive species in organic chemistry, they were first discovered in the late 19th century by Staudinger and Kupfer.[218] However, due to their highly reactive nature the isolation of carbenes was difficult. It wasn't until the late 1980's and the independent work of Bertrand[219] *et al.* and Arduengo[220] *et al.* on stable *N*-heterocyclic carbenes (NHCs), that the use of these compounds in organic chemistry was fully understood. Arduengo *et al.* isolated and characterised the first NHC in 1991, based on a heterocyclic imidazolium salt precursor, when they prepared the imidazolin-2-ylidene **279** by deprotonation of the salt **278** (Reaction A, Scheme 1.58).[220] Since, numerous NHC's have been isolated and characterised, including the triazolin-2-ylidene **282**, studied by Enders and Teles.[221] This carbene was obtained by addition of sodium methanolate to the triazolium salt **280** generating the stable moiety **281**, the α-elimination of methanol then took place either at 80 °C under vacuum or by heating **281** in toluene under reflux. This carbene **282** was the first commercially available carbene (Reaction B, Scheme 1.58).[221]

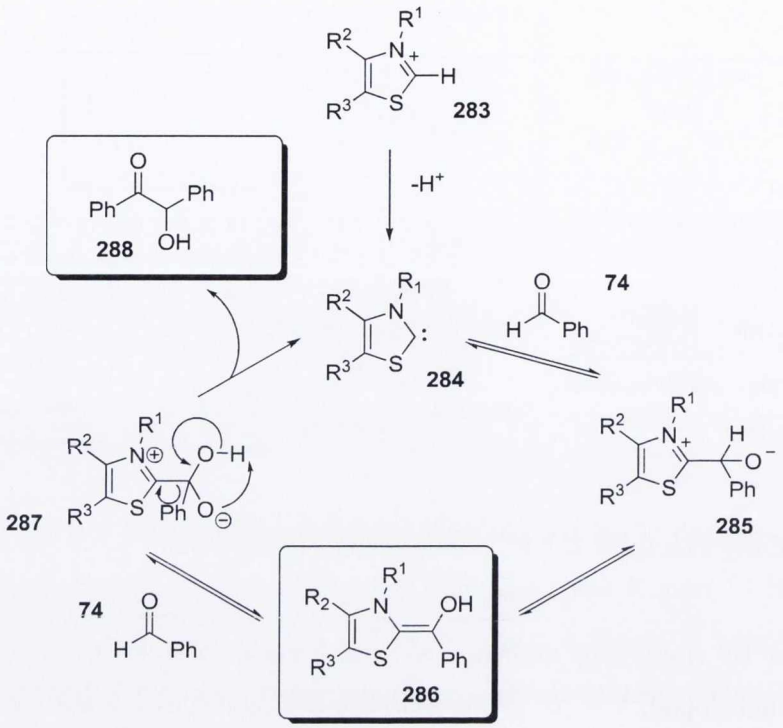


Scheme 1.58 Early examples of NHC compounds **279** and **282**.

Whilst the area of employing carbenes as metal-based ligands in catalytic reactions is extremely well developed,[222,223,224] for the purpose of this discussion the use of these NHC's in organocatalysis will be focused on, in particular their use in the benzoin condensation reaction.

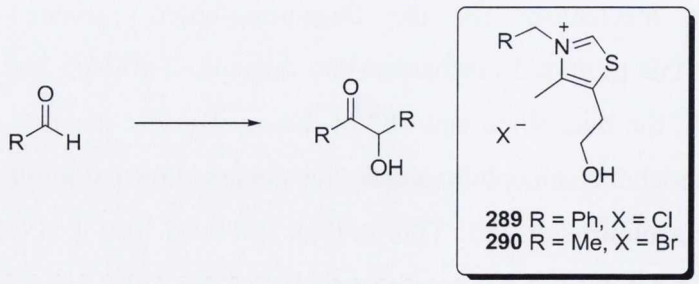
1.6.1 *N*-Heterocyclic carbenes: the benzoin condensation

The mechanism for the reaction in which an intermediate carbanion is formed between hydrogen cyanide and benzaldehyde by deprotonation, hence inverting the formerly electrophilic carbonyl features to nucleophilic reactivity, was first introduced by Lapworth in 1903.[225] This intermediate formed an active aldehyde which embodies the '*umpolung*' concept defined by Seebach and Corey.[158-160] On the basis of Lapworth's work, Breslow in 1958, proposed a mechanism for the thiazolium-based carbene catalysed benzoin condensation.[226] In this proposed mechanism the thiazolin-2-ylidene **284**, formed *in situ* by the deprotonation of the thiazolium salt **283** at the most acidic position, is the catalytically active carbene compound. Nucleophilic attack then occurs at the carbonyl of an aldehyde, *e.g.* **74**, creating the thiazolium salt **285**. This is then followed by the proton transfer process forming the resonance-stabilised Breslow intermediate **286**. This d^1-synthon then reacts again with an electrophilic substrate for example a second aldehyde moiety. The generated intermediate **287** then eliminates the benzoin product **288** regenerating the original carbene **284** (Scheme 1.59).[226]



Scheme 1.59 Breslow's mechanism for the thiazolium-carbene catalysed benzoin condensation reaction.

Stetter *et al.* developed thiazolium salt-based precatalysts for the synthesis of acyloin and benzoin compounds on a large scale and subsequently used the synthetic concept for the preparation of a variety of α-hydroxyketones.[227] Aliphatic aldehydes could be transformed in good yields with catalyst **289** while aromatic aldehydes performed best when **290** was employed (Scheme 1.60).



Scheme 1.60 First generation thiazolium based catalysed developed by Stetter *et al.* for generation of a variety of α-hydroxyketones.[227]

The first chiral, NHC-based catalysts for the asymmetric benzoin condensation were designed by Sheehan and Hunnemann in 1966.[228] This seminal thiazolium salt-based catalyst **291** resulted in low yields (10%) and low enantioselectivities (22% *ee*) when the asymmetric benzoin condensation of benzaldehyde was carried out (Figure 1.18).[228] The same group introduced a second generation catalyst **292** which generated a higher enantioselectivities of 52% but with lower yields (6%).[229] Various groups then set about designing improved thiazolium salt variants based on this seminal work to enhance both the product yield and the catalyst's enantioselective performance. Examples of these catalysts include thiazolium salt **293** and the bisthiazolium salt **294**.[230,231] However, despite improvements in terms of product yield (mainly due to increasing the catalytic loading), none of these catalysts could rival **292** with respect to the promotion of enantioselective reactions (Figure 1.18).

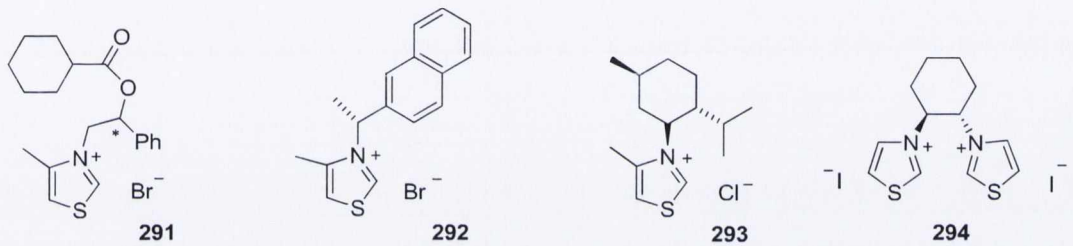
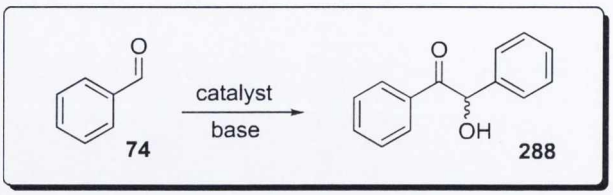


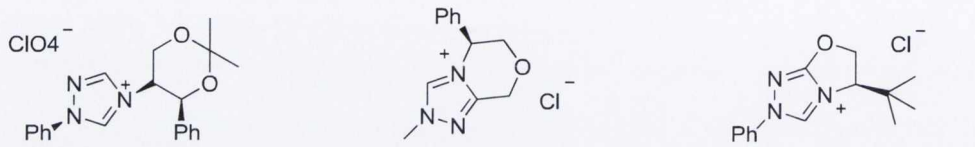
Figure 1.18 Representative examples of early developments in thiazolium based precatalysts for the carbene catalysed benzoin condensation.

1.6.2 *N*-Heterocyclic carbenes: Triazolium salts as NHC precatalysts in benzoin condensation

The first chiral triazolium ion-based NHC precatalyst was developed by Enders and co-workers in 1996.[232] The precatalyst **295** resulted in the selective catalysis of the benzoin condensation of benzaldehyde **74** in the presence of the base K_2CO_3, with the benzoin product **(*R*)-288** generated in 66% yield and 75% *ee* at a low catalyst loading of 1.25 mol% (Scheme 1.61).[232] Leeper *et al.* then developed catalyst **296**, the use of which gave higher product enantiomeric excess, with the generation of the (*S*)-enantiomer in the asymmetric benzoin condensation of benzaldehyde with 45% yield and 80% *ee,* albeit at a much higher loading of 30 mol% (Scheme 1.61).[233] In 2002, Enders *et al.* then developed an improved triazolium ion-based precatalyst **297** based on the work carried out by Leeper, which resulted in a catalyst yielding 83% of **(*S*)-288** in 90% *ee* at a catalyst loading of 10 mol%, an improvement in both

yield and enantioselectivity when compared to both the first generation precatalysts and Leeper's precatalyst (Scheme 1.61).[234]





295 66%, 75% *ee* **(*R*)-288** **296** 45%, 80% ee **(*S*)-288** **297** 83%, 90% ee **(*S*)-28**

Scheme 1.61 Seminal examples of chiral triazolium salt precatalysts for the enantioselective benzoin condensation of aldehydes.

Later Enders *et al.* produced catalyst **298** which gave the benzoin product in 66% yield with a 95% *ee* (Figure 1.19).[235] This was the most efficient precatalyst for the promotion of enantioselective reactions at the time, however as was the case with previous examples, substrates other than benzaldehyde proved to be problematic with respect to enantioselectivity. You and co-workers described the use of precatalyst **299** which catalysed the benzoin condensation of not only benzaldehyde, but also for the first time a variety of other aldehydes, with high yields and enantioselectivities (Figure 1.19).[236]

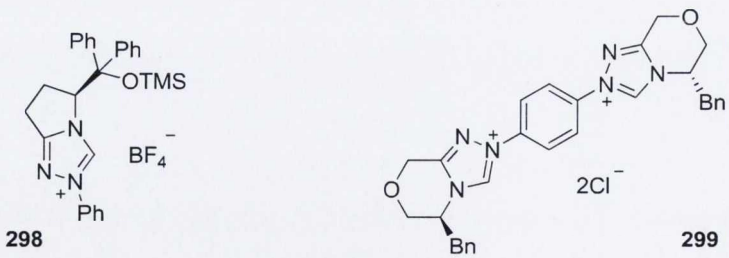
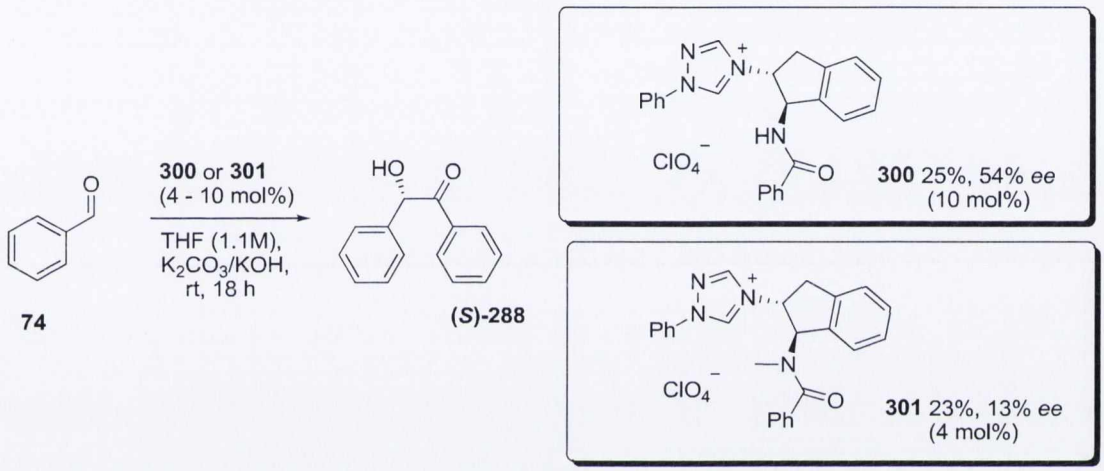


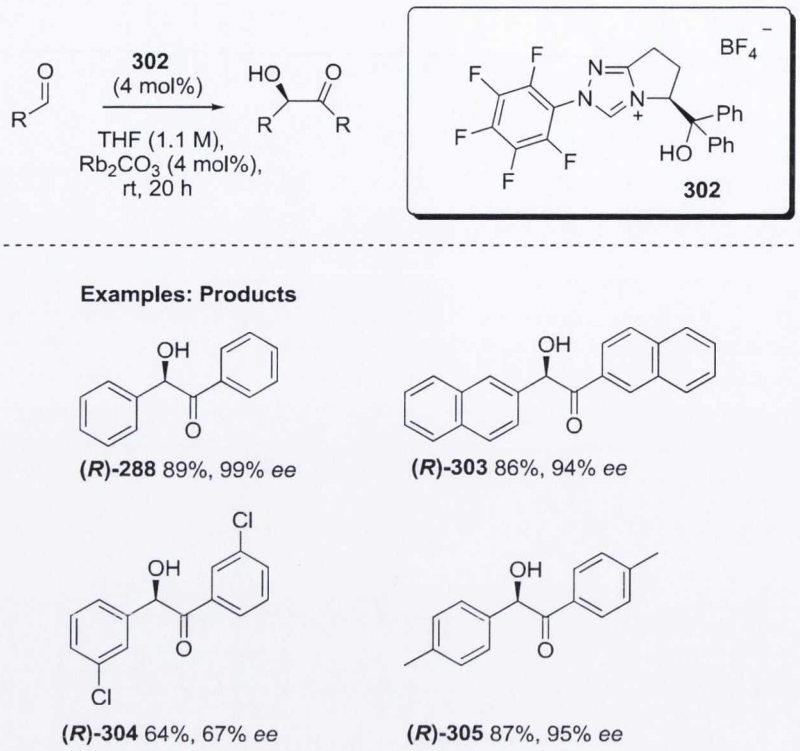
Figure 1.19 Highly enantioselective triazolium ion-based precatalysts developed by Enders **298** and You **299**.

Connon *et al.* in 2009 then introduced the concept of controlling the asymmetric benzoin condensation through hydrogen bond donation.[237] This was observed through the utilisation of the precatalyst **300** containing a secondary amide substituent. This compound allowed for the generation of the benzoin product **(*S*)-288** with 54% *ee* and 25% yield, whilst its *N*-methylated counterpart **301** gave comparatively lower enantioselectivity of 13% and a 23% yield (Scheme 1.62).[237] This initial study was the first example of the concept of enantioselective control by H-bond donation.



Scheme 1.62 Seminal employment of a hydrogen bond donating triazolium ion-based precatalyst to control enantioselectivity in asymmetric benzoin condensation.

This seminal catalyst was then further developed in the same group to improve yields and enantioselectivities to synthetically useful amounts. The introduction of electron withdrawing groups on the triazolium moiety was carried out, as it was speculated that the low yields associated with the catalysts **300** and **301** was perhaps due to the ability of benzoin to reprotonate the carbene.[238] It was noted in the work by Suzuki *et al.* that catalysts incorporating electron-withdrawing substituents were better able to promote the intramolecular benzoin condensation involving traditionally challenging enolisable aldehyde based substrates.[239] These improvements led to the employment of the optimal bicyclic precatalyst **302** containing a chiral protic substituent and a pentafluorophenyl aromatic group.[240] This catalyst was found to promote the reaction with unprecedented enantioselectivities over a range of aldehydes including **(*R*)-288** to **(*R*)-305** (Scheme 1.63).[238]

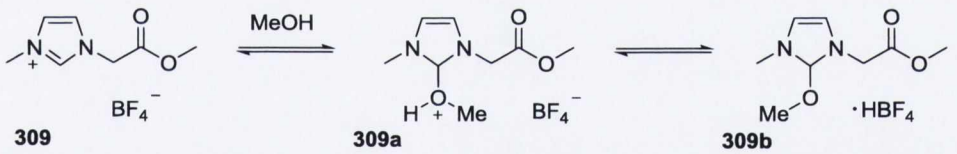


Scheme 1.63 Representative examples of high enantioslectivity of triazolium salt precatalyst **302**- mediated benzoin condensation reactions.

This catalyst represents one of the most efficient, to date, with respect to the promotion of asymmetric benzoin condensation reactions in high enantiomeric excesses and has been further employed in enantioselective crossed-benzoin reactions to great effect.[239,240] Over the last 2 decades there have been great strides made in the development and employment of triazolium ion-based NHC precatalysts in the benzoin condensation. Further investigation of this chemistry is currently of great interest and continues to flourish.

2.1 Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: a new strategy for acid catalysis.

A wide range of developments have been observed, in recent years, in the area of ionic liquid catalysis. These include a number of examples of Brønsted acidic ionic liquids employed as non-volatile acidic materials, in a variety of acid catalysed reactions.[8,41,47,54] Recent studies have also introduced the concept of the design of ionic liquid based compounds (although not, as yet, BAILs), with their biodegradability and toxicity in mind.[92,95,96] Another notable development has been the discovery by our group, that aprotic pyridinium salts can function as Brønsted acidic materials in protic media, allowing for the highly efficient catalysis of the acetalisation of benzaldehyde (see Section 1.2.1).[72] We became intrigued by the possibility of partnering these advances and determining whether aprotic imidazolium ion-derived ionic liquids could be designed to be environmentally benign, while also serving as acid catalysts in protic media. Mirroring the mode of action of pyridinium ion-based salt moieties we proposed that the protic additive, in this case MeOH, could add to the C-2 of the imidazolium ion **309**, generating the acidic species **309a** and **309b** *in situ* (Scheme 2.2). Such a catalyst system would be appealing, as the inherent hazards associated with acid based catalysis, such as corrosion and handling, would be avoided.



Scheme 2.1 Proposed mode of action of a catalytic aprotic imidazolium ions generating a BA species in protic media.

Not only would this be a new departure from conventional methods of acid catalysis, but also from the three existing methods of introducing Brønsted acidic capabilities to an imidazolium ion-based ionic liquid moiety, as discussed in Chapter 1. These include the presence of a covalently bound acidic functionality (*i.e.* **306**, Figure 2.1),[8] a protic imidazolium ion (*i.e.* **307**, Figure 2.1)[47] or an acidic counterion (*i.e.* **308**, Figure 2.1).[41] Furthermore, they would also have the benefit of being the first imidazolium ion-based ionic liquid catalysts designed to work in this way, whilst also being devised to be non-hazardous to the environment.

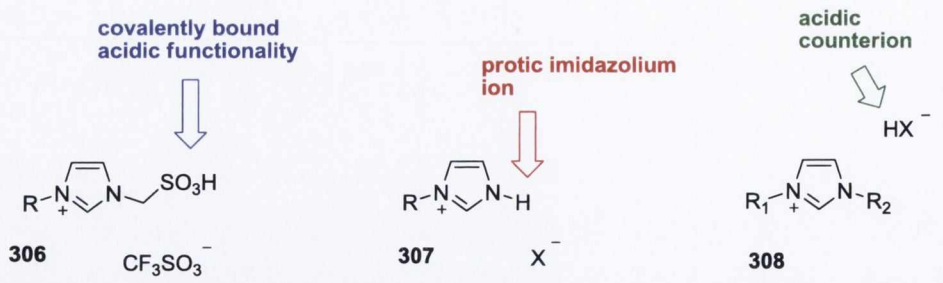


Figure 2.1 Imidazolium ion-based acidic ILs: existing strategies

Additionally, the optimum pyridinium catalyst **121** synthesised by Dr. Barbara Procuranti, in our group, proved to be a highly active catalyst for the acetalisation of benzaldehyde at low loadings (0.1 mol%) However, this material proved to be relatively difficult to synthesise, with the purification of the catalyst proving challenging, while the starting material for the reaction is relatively expensive. The catalyst is also quite unstable; diminishing in activity over time. The high electrophilicity of the compound, whilst giving rise to its excellent activity, also contributes to its hydrolytic instability.

We therefore reasoned that, the general strategy applied for the design of aprotic pyridinium ion- based catalysts could also be applicable to the design of catalysts based on imidazolium ions which, we postulated, should possess potential advantages such as:

a) the imidazolium ion species would, in all likelihood, possess lower resonance stabilisation energy than the corresponding pyridinium ions- thus the addition of protic nucleophiles to the heterocyclic core would be facilitated. This actuality could lead to an increase in catalyst efficacy.

b) the presence of the twin nitrogen heteroatoms would provide considerably enhanced scope (compared to the pyridinium moiety), to fine tune not only the melting point of the material, but also the catalyst's steric and electronic properties, its toxicity and its stability to acid catalysed hydrolysis. The biodegradability characteristics of the moiety could also be adjusted by simply varying the substituents in these positions.

c) since more is known regarding the toxicity and biodegradability of imidazolium ions than is the case for pyridinium ions, the design of environmentally benign catalysts

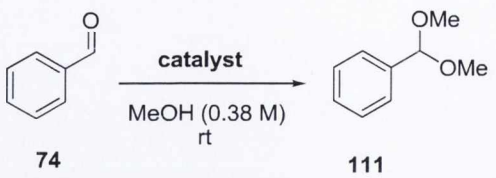
based on the former heterocyclic scaffold would be considerably more facile, through the incorporation of either ester or amide functionality (see also Section 1.3).

2.1.1 Evaluation of imidazolium salts: preliminary screening

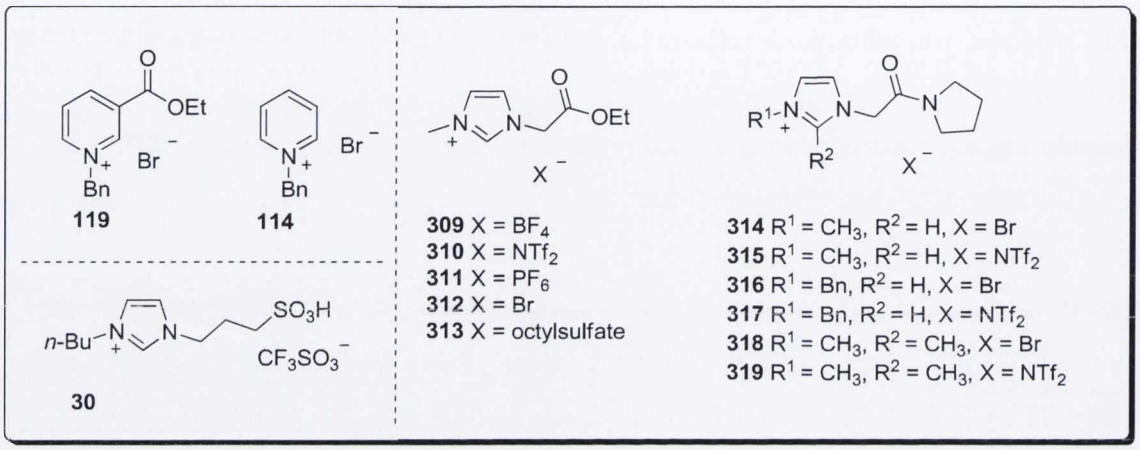
The initial study investigating the catalytic potential of imidazolium ion-based ionic liquids as acidic catalysts was carried out employing salt derivatives, incorporating both ester or amide side chains tethered to one heterocyclic *N*-atom, with methyl or benzyl groups on the other. The side chains, incorporated into our preliminary imidazolium catalyst candidates, were chosen to attempt to confer biodegradability on the salts; a strategy originally pioneered by Gathergood and Scammels.[92] The substitution patterns were selected so that the maximum amount of information regarding the influence of both the catalyst's steric properties and the nature of the substituent on catalyst efficacy, could be gathered from the smallest possible library. The effect of the counterion, if any, was also investigated to determine if there was any relationship between the catalytic activity of the salt and the choice of anion.

Eleven imidazolium ion-derived catalysts (synthesised by Dr. Rohitkumar Gore in DCU) were evaluated as promoters of the acetalisation of benzaldehyde. The evaluation of these compounds as catalysts was carried out at room temperature over 24 hours, under anhydrous conditions, using 5 mol% catalyst loading in methanol (Table 2.1). Anhydrous conditions were necessary, as it was found in previous studies that the presence of either water or moisture (air) were detrimental to the both rate and yield. This was probably due to the oxidation of benzaldehyde to benzoic acid (thereby lowering the final yield of acetal produced) and/or the deactivation of the catalyst *via* hydrolysis/oxidation. Therefore, a strict protocol was developed using distilled methanol, pure aldehyde and carefully purified catalysts under inert conditions. Each of the catalysts also underwent a rigorous drying procedure prior to use.

Table 2.1 First generation imidazolium ions: preliminary catalyst evaluation.



74 **111**



119 **114**

309 X = BF_4
310 X = NTf_2
311 X = PF_6
312 X = Br
313 X = octylsulfate

314 R^1 = CH_3, R^2 = H, X = Br
315 R^1 = CH_3, R^2 = H, X = NTf_2
316 R^1 = Bn, R^2 = H, X = Br
317 R^1 = Bn, R^2 = H, X = NTf_2
318 R^1 = CH_3, R^2 = CH_3, X = Br
319 R^1 = CH_3, R^2 = CH_3, X = NTf_2

30

Entry	Catalyst	Loading	Yield (%)[a]
1	**none**	-	0
2	**114**	5	0
3	**119**	1	96
4	**309**	5	86
5	**310**	5	56
6	**311**	5	36
7	**312**	5	12
8	**313**	5	12
9	**314**	5	14
10	**315**	5	23
11	**316**	5	10
12	**317**	5	35
13	**318**	5	11
14	**319**	5	42
15	**30**	5	83

[a]Average of two experiments, determined by ^{1}H NMR spectroscopy using an internal standard.

It was initially noted that in the absence of catalyst, as expected, no acetal formation was detected after 24 h (entry 1, Table 2.1). Gratifyingly, each of the imidazolium catalysts outperformed its unsubstituted pyridinium ion-based counterpart substantially, with the pyridinium salt **114** completely inactive in the reaction (entry 2). This result underlines, even

in these preliminary studies, the inherent superiority of the imidazolium ion-based salts over pyridinium ions as catalysts in this reaction. None of the moieties investigated however, as expected, exhibited the same activity as the highly electrophilic C-3 substituted pyridnium ion **119** (entry 3).

The initial effect of the counterion was determined through the comparison of the activity of the ester functionalised imidazolium ions **309-313** in the acetalisation of benzaldehyde with methanol. It was observed that the tetrafluoroborate counterion containing catalyst **309** (entry 4) was the most active; promoting the formation of the acetal **111** in 84% yield, while its nearest rival incorporating an NTf_2 anion (*i.e.* 310) catalysed the reaction to afford a 56% yield of the desired dimethyl acetal (entry 5). The PF_6^- containing compound **311** also promoted the generation a moderate yield of **111** (entry 6). Whilst the least effective catalysts incorporated bromide **312** and octylsulfate **313** anions, both promoting the formation of **111** in 12% yield (entries 7 and 8).

It was established that neither the ester nor the pyrrolidinamide substituents, which were designed to facilitate biodegradation, had an influence on catalytic activity to any considerable degree. Furthermore, the effect on catalysis induced by the type of alkyl group incorporated on either of the nitrogen atoms of the imidazolium ring (*i.e.* methyl *vs.* benzyl), though the methyl (**314** and **315**) substituted moieties performed slightly better than the benzyl (**316** and **317**) substituted moieties, was not pronounced (entries 9, 10, 11 and 12). However, it was found that methyl substitution at the C-2 position of the salt reduced the catalytic activity slightly (**318** and **319**, entries 13 and 14). This observation correlates with previous studies carried out by Procuranti *et al.* which found that the introduction of steric bulk at the site which is attacked by the protic additive led to less effective catalysis.[72] It was pleasing to find that the most effective of these newly designed catalysts **309** (entry 4) also proved as active as the sulfonic acid tethered BAIL **30** (entry 15).

The most interesting and significant observation made during these preliminary studies, is the influence of the counterion on catalytic efficacy. As previously noted, the tetrafluoroborate salt **309** (entry 4) and NTf_2 salts **312**, **315**, **317** and **319** (entries 7, 10, 12 and 14) proved to be significantly superior to other salts evaluated.[243] This result illustrated that the strength of the acidic intermediate in this reaction was influenced by the counterion. The highly catalytically active nature of the imidazolium salts incorporating the tetrafluoroborate counterion was

consistent with previous studies on the strengths of acids added to ionic liquids,[244] and investigations into the effect of the counterion on the catalytic activity of protic imidazolium ions.[245]

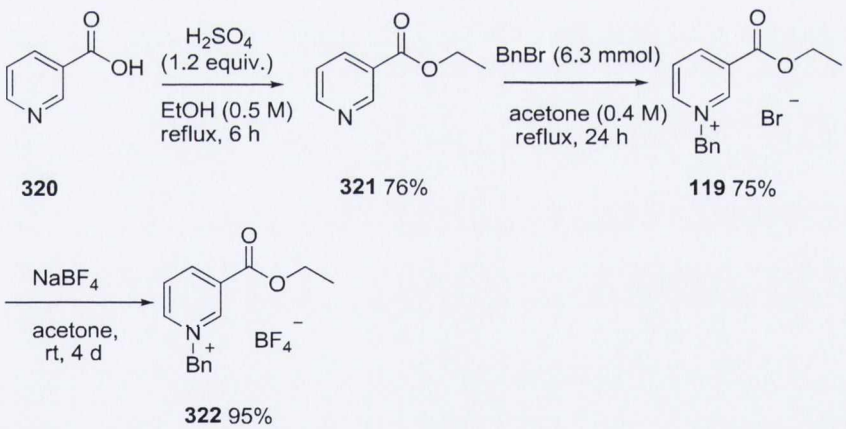
We postulated that the reason for this increase in activity when employing the catalyst containing a tetraflouroborate counterion (*i.e.* **309**) was due to the binding affinity of the counterion with the imidazolium cation. The BF_4^- counterion is loosely bound to the cationic species, which allows for the more facile addition of the methanol nucleophile to the imidazolium moiety generating the active Brønsted acidic species.[51] Whereas other anions, for example halide/octylsulfate counterions, are more tightly bound, hence inhibiting the addition of the alcohol more substantially. This theory is supported by an investigation by Welton *et al.* in 2001, who determined, by both IR and NMR spectroscopic analysis, the ability of various counterions to hydrogen bond with water and in doing so determining the hydrolysis potential of the ionic liquid.[246] Later NMR spectroscopic studies, *via* through space coupling experiments, by Mele and co-workers, further investigated the hydrogen bonding affinity of ionic liquids. They did so by evaluating the interaction of [bmim][BF_4] with water. From these studies, it was determined that anion binding to BF_4 contributes to water coming between the positively and negatively charged ions, hence loosening the binding of the cation and anion.[247] The hydrogen bond distances were later measured with respect to the interaction of a sulfonic acid-based pyridinium ion and various anions, including BF_4^-, $H_2PO_4^-$, HSO_4^- and *p*-TSA^-. It was found when measuring the interaction between a hydrogen atom of the sulfonic acid and either a fluorine in case of BF_4^- or an oxygen atom in the case of the others, that although all strongly interact with the sulfonic acid, the H-bond distances increase in the order BF_4 (H---F = 1.723 Å) > HSO_4 (H---O = 1.714 Å) > *p*TSA (H---O = 1.613 Å) > H_2PO_4 (H---O = 1.564 Å).[248]

It was interesting to note that the tetrafluoroborate ion was more active than the hexafluorophopshate anion, a counterion which had previously been found to induce high catalytic activity in acid-catalysed reactions.[47,51] The generation of HF *in situ* has been suggested as a possible reason for the efficacy of the BF_4 containing compounds. Therefore, we monitored a solution of the catalyst **309** in CD_3OD at room temperature for 24 h by ^{19}F NMR spectroscopy, no degradation of **309** or formation of HF was detected. This spectral evidence was substantiated by the relative inefficiency of the PF_6 containing catalysts in this reaction, which would be more likely to generate HF *via* hydrolysis/methanolysis.

2.1.2 Pyridinium salts: evaluation of counter-ion effect on activity of catalyst

As a consequence of the results obtained above, with respect to the undeniable effect the anion had on catalyst efficacy, it was postulated that the same outcome (*i.e.* an increase in catalytic activity) would be observed in the aforementioned aprotic pyridinium ion-based catalysts. For this reason, a new pyridinium ion-derived catalyst candidate was synthesised containing the BF_4^- counterion.

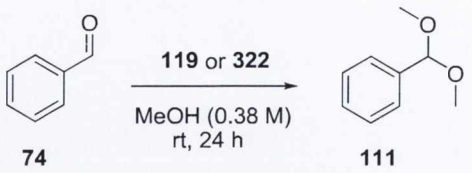
The synthesis of this material involved a simple 3 step procedure, consisting of the esterification of nicotinic acid (**320**) with ethanol; giving rise to the ethyl ester **321**. This was followed by the benzylation of **321** in the presence of benzyl bromide in acetone. These reactions proceeded with yields of 76% and 75% respectively. Following purification of the benzylated compound by recrystallisation, a simple anion exchange protocol was carried out on **119**, using sodium tetrafluoroborate in acetone, generating catalyst **322** in 95% yield (Scheme 2.2).[249]



Scheme 2.2 Synthesis of the pyridinium ion-based catalyst **322**.

With the catalyst **322** in hand, the acetalisation of benzaldehyde in methanol was carried out at room temperature for 24 h. The reaction was studied at both 1 mol% and 0.5 mol% catalyst loadings and the results were compared to those obtained using the bromide ion-based catalyst **119** under identical conditions (Table 2.2).

Table 2.2 Evaluation of counterion effect on pyridinium ion-based catalyst activity.



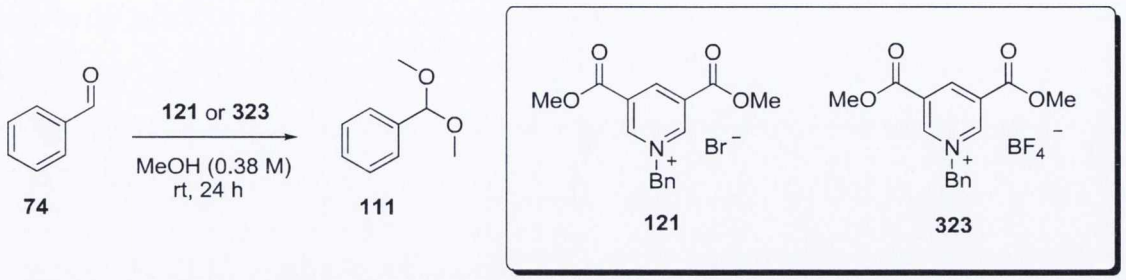
Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**119**	1	95
2	**322**	1	90
3	**119**	0.5	35
4	**322**	0.5	81

[a]Isolated yield after chromatography

It was determined from these results that at 1 mol% loading the activity of **119** and **322** were similar (entry 1 and 2, Table 2.2). However, it is at 0.5 mol% loading that the effect of the counterion can be most clearly witnessed, with the use of the bromide containing moiety **119** yielding a modest 35% of the acetal product, while the tetrafluoroborate salt promotes the synthesis of the dimethyl acetal with a synthetically useful yield of 86% (entry 3 and 4).[249]

The synthesis of the more active *bis*-substituted pyridinium ion-based catalyst **323** was also carried out *via* the same procedure used to prepare **322** (Scheme 2.2). The efficacy of this catalyst was evaluated at 0.1 mol% loading and 0.05 mol% loading in the acetalisation of benzaldehyde. Again it was found that, as expected, the efficacy of the tetrafluoroborate salt **323** was greater than that of the bromide anion containing moiety **121**, though to a lesser degree, than was previously observed in the corresponding experiments involving the mono-substituted analogues **119** and **322** (Table 2.3). This is perhaps due to the catalyst reaching the limit of its efficacy and stability at such low loadings.

Table 2.3 Evaluation of the couterion effect on pyridinium ion-based catalysts **121** and **323**.



Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**121**	0.1	92
2	**323**	0.1	98
3	**121**	0.05	65
4	**323**	0.05	71

[a]Isolated yield after chromatography

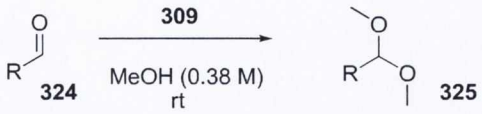
These results are noteworthy, as they further illustrate the importance of the anion in the mode of action of these compounds as Brønsted acidic catalysts. It is also of interest to highlight the fact that compound **322** (derived from the inexpensive starting material nicotinic acid) represents a cheaper alternative (at 0.5 mol% loading) to both **323** and the most efficient catalyst synthesised by Procuranti *et al.* (*i.e.* catalyst **121**, used at 0.1 mol% loading), which are prepared from a much more expensive starting material.

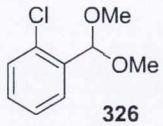
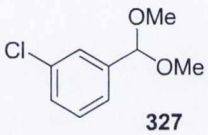
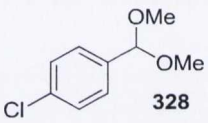
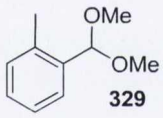
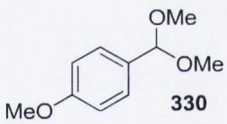
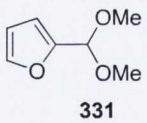
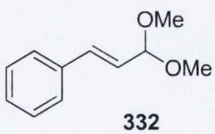
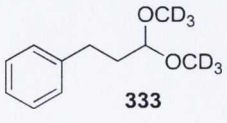
2.1.3 Imidazolium salt-based catalysis: evaluation of substrate scope

As a consequence of the findings of the preliminary studies in relation to the imidazolium ion-based salt catalysts outlined in Section 2.1.1, subsequent evaluation of the substrate scope of the active tetrafluoroborate catalyst **309** in the acetalisation of various aldehydes with methanol was desirable (Table 2.4). It was found that **309** could efficiently promote the protection of aromatic aldehydes, with a range of steric and electronic characteristics, at low catalyst loadings of 5-10 mol% at ambient temperature.

Activated chloro-substituted aldehydes (**326-328**, entries 1-3) could be efficiently transformed into their corresponding acetals irrespective of the substitution pattern, with *ortho*-, *meta*- and *para*- substituted aldehydes producing excellent yields at 5 mol% loading. Both hindered (**329**, entry 4) and electron-rich substrates (**330**, entry 5) proved more challenging, however increasing catalyst loadings to 10 mol%, resulted in high yields of isolated products, without requiring any other modifications to the reaction conditions. The catalyst was also compatible with highly synthetically useful heterocyclic (**331**, entry 6) and α,β-unsaturated (**332**, entry 7) aldehydes. The saturated aldehyde (**333**, entry 8) underwent particularly rapid conversion to its dimethyl acetal; with almost full conversion of the aldehyde to the acetal being achieved at 1 mol% loading, after only 1 minute reaction time.[243]

Table 2.4 The catalytic acetalisation of aldehydes: evaluation of substrate scope.



Entry	Substrate	Loading (mol%)	Time (h)	Yield (%)[a]
1	 **326**	5	24	96
2	 **327**	5	24	93
3	 **328**	5	24	95
4	 **329**	10	24	87
5	 **330**	10	24	87
6	 **331**	10	24	89
7	 **332**	10	24	83
8	 **333**	1	1 min	97[b]

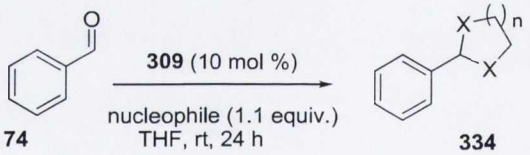
[a]Isolated yield after chromatography. [b]Determined by ^{1}H NMR spectroscopy using an internal standard (*E*-stilbene) due to product decomposition. This reaction was carried out in CD_3OD.

2.1.4 Imidazolium salt catalysis: catalysis of dithiane/cyclic *O,O*-acetal formation

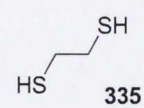
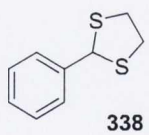
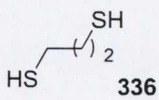
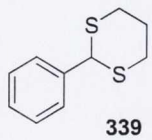
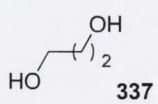
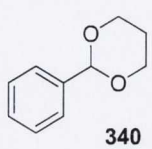
Subsequently, we wanted to demonstrate that the scope of this catalytic strategy was not confined to methanolysis. The protection of benzaldehyde, with only a slight excess of dithiol (1.1 equiv.) and diol nucleophiles **335-337**, was carried out using **309** (10 mol%) at room temperature for 24 h (Table 2.5).

As discussed in the Section 1.5.5, the synthetically useful protection of the aldehyde with dithiol **335** generally requires elevated temperatures using such a mild form of acid catalysis. However, it proceeded in the presence of **309** at room temperature with excellent product yield of 92% (**338**, entry 1). The promotion of the reaction to form the dithiane protected compound **339** (entry 2) also produced a satisfactory yield of 65% (under the same conditions). The efficacy of this aprotic catalyst in these protection reactions at relatively low loadings was particularly gratifying in light of the aforementioned difficulties associated with these reactions using literature methods. While the dioxane protected derivative (**340**, entry 3) was also formed in excellent yield (Table 2.4).[243]

Table 2.5 Catalysis of dithiane, dithiolane and dioxane syntheses by **309**.



74 **334**

Entry	Nucleophile	Product	Yield (%)
1	 **335**	 **338**	92
2	 **336**	 **339**	65
3	 **337**	 **340**	86

[a]Isolated yield after chromatography

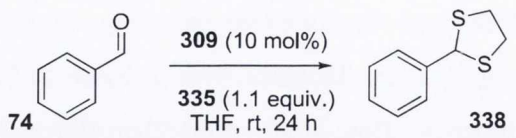
The results of our studies on aprotic imidazolium ions (Tables 2.1, 2.4 and 2.5) strongly indicate that the activity of these materials exhibits the same dependence on steric and electronic characteristics to that previously observed using the analogous pyridinium-based systems.[72] In addition, we observed similar influences in terms of the nature of the anion, and the steric/electronic characteristics of the aldehyde electrophile in acetalisations catalysed by both heterocyclic classes of catalysts. Therefore we would conclude that these materials are likely to operate *via* the same mechanism, namely those shown in Schemes 1.27 and 2.1.

2.1.5 Imidazolium catalysis: recyclability studies

Ionic liquids, as outlined in Section 1, are of interest due to characteristics which render them potentially useful as green solvents. As a result of the studies outlined above, the ability of **309** to accelerate these acid catalysed reactions, more efficiently than either some conventional acidic moieties (e.g. HCl, H_2SO_4 or *p*TSA) or existing acid functionalised BAIL moieties, contributes to the 'green' characteristics of these compounds. However, an added advantage is the recyclability of the ionic liquid moieties. By definition, a catalyst should be unchanged at the end of a reaction and so be capable of being reused indefinitely. Though this should be accurate, in practice the inexhaustible use of the catalyst is generally not possible either due to degradation of the catalyst or depletion of catalyst activity over time. Therefore, one can only hope for a recyclable catalyst that can be reused, with little loss in activity, for a reasonable number of catalytic cycles.

To evaluate the recyclability of **309** the protection of benzaldehyde (**74**) with 1,2-ethanedithiol (**335**) was carried out using 10 mol% catalyst loading, at room temperature for 24 h. Upon completion of the reaction, the catalyst was recovered in excellent yield by precipitation from the reaction medium using hexane, followed by decantation and drying *in vacuo*. The solid salt **309** was dried further under vacuum, to remove any water and reused in 15 subsequent cycles without any loss in activity being observed. The recycling of the catalyst was discontinued at this point because no decrease in activity was detected after 15 cycles and we had to stop the study at some point (Table 2.6). These results are satisfying, as despite the requirement that **309** be used at higher loadings than the pyridinium ion-based catalyst **121**, its robustness and reusability is a marked advantage. It is also noteworthy that, at the time this study was carried out, **309** was the most recyclable BAIL in the literature.

Table 2.6 Catalyst recycling.



Entry	Cycle	Yield (%)[a]
1	1	92
2	2	90
3	3	89
4	4	91
5	5	90
6	6	90
7	7	91
8	8	90
9	9	90
10	10	90
11	11	89
12	12	90
13	13	90
14	14	91
15	15	90

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

2.1.6. Biodegradability testing

To evaluate the biodegradability of the test ionic liquids, the 'CO_2 Headspace' test (ISO 14593)[19] was implemented (by our collaborators Dr.N Gathergood and Dr. R. Gore in DCU). This method allows for the evaluation of the ultimate aerobic biodegradability of an organic compound, in an aqueous medium at a given concentration of microorganisms, by analysis of inorganic carbon. The test ionic liquid, as the sole source of carbon, was added at a concentration of 40 mg L^{-1} to a mineral salt medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air. Biodegradation (mineralisation to carbon dioxide) was determined by measuring the net increase in total organic carbon (TOC) levels over time.

A representative selection of examples of ionic liquids employed as catalysts were screened. Unfortunately, the five imidazolium ion-based compounds (**309**, **310**, **314**, **316** and **318**)

evaluated did not pass the 'CO_2 Headspace' test (>60% required to pass) (Table 2.7). Low to negligible biodegradation was observed, with amide ionic liquids **314**, **316** and **318** resistant to breakdown. The presence of the amide and benzyl group in **316**, did not facilitate any breakdown of the compound under the conditions of the test. This agrees with previous results and studies from other groups, where amides[97] and benzyl[250,251] substituents did not lead to enhanced biodegradation. Reference experiments, performed concurrently with the biodegradation tests, demonstrated that each of the ionic liquids were non-toxic to the inoculums in which they were tested.

Table 2.7 Evaluation of the biodegradability of imidazolium ionic liquid catalysts using the 'CO_2 Headspace' Test.

Entry	Catalyst	*t* (6 d)[a]	*t* (14 d)[a]	*t* (21 d)[a]	*t* (28 d)[a]
1	**309**	12	12	13	14
2	**310**	14	14	11	10
3	**314**	1	3	4	3
4	**316**	0	0	0	0
5	**318**	0	1	0	3

[a]Percentage biodegradation after *t* (time) in days

Imidazolium ion-derived ionic liquids containing a methyl ester (**309** and **310,** entries 1 and 2, Table 2.7) gave low biodegradation, 14% and 10% respectively after 28 days. No significant effect on the biodegradability is observed between the bromide and BF_4 counterion, as both these anions do not contribute to the carbon dioxide evolved on breakdown, therefore the propensity for the cation to biodegrade was determined. Hydrolysis of the methyl ester, and the conversion of a single carbon in **309** and **310** to CO_2 can account for the degree of biodegradation observed. As is apparent due the increased stability of the amide *vs.* methyl ester, ionic liquids **314**, **316** and **318** (entries 3, 4 and 5), are postulated to remain almost completely intact during the biodegradation test. Therefore, all evidence suggests that the imidazolium core is not cleaved during the 'CO_2 Headspace' Test.

2.1.7 Anti-fungal/anti-bacterial testing

The toxicity of 3 selected ionic liquids was determined to establish the influence of the ester side chain, amide side chain and counterion on the anti-fungal and anti-bacterial properties of the catalyst (screening was carried out by Dr. M. Spulak, Charles University, Czech Republic). The selected examples were chosen based on both their structure and catalytic activity: compounds **309**, **310** and **314** (Figure 2.2). They were evaluated against a broad spectrum of organisms which were selected based on their relevance for environmental and medicinal applications.

309 X = BF_4
310 X = Br

314

Figure 2.2 Imidazolium ion-based catalysts evaluated for anti-microbial activity.

Anti-fungal activities were evaluated *in vitro* on a panel of five clinical yeasts (*Candida krusei* ATCC 6258, *Candida tropicalis* 156, *Candida glabrata* 20/1, *Candida lusitaniae* 2446/I, *Trichosporon beigelii* 1188), four ATCC (American Type Culture Collection) strains (*Candida parapsilosis* ATCC 22019, *Candida albicans* ATCC 90028, *Candida krusei* ATCC 6258 and *Candida albicans* ATCC 44859) and three filamentous fungii (*Aspergillus fumigatus* 231, *Asbidia corymbifera* 272 and *Trichophyton mentagrophytes* 445) Gratifyingly, antifungal activity was not observed for any of the compounds screened at the highest concentration (2.0 mM) in 48 h.

In vitro anti-bacterial activity was screened against a panel of 3 ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Kleibsiella pneumoniae* HK1175/08, *Enterococcus* sp. HK 14368/08 and *Klebsiella pneumoniae* ESBL HK14368/08). Again, as with the fungal strains no antimicrobial activity was observed for **309**, **310** or **314** at high concentrations (2.0 mM) over 48 h.

By avoiding the introduction of long lipophilic alkyl chains[82] into the ionic liquid cationic structure and incorporating ester/amide side chains, it has been determined that these ionic liquid catalysts have no antimicrobial activity at high concentrations against a range of fungal and bacterial strains. The counterion has no effect: changing from a Br to a BF_4 anion has no influence on the toxicity of the ionic liquid compound with MIC values >2.0 mM. While more lipophilic NTf_2 derivatives possess slightly increased antimicrobial and antifungal toxicity, the NTf_2 salts **312**, **315**, **317** and **319** are inferior catalysts (Table 2.1). From an analysis of these results, it can be deduced that these compounds should have a higher degree of environmental inertness than their BAIL predecessors due to their low toxicity towards a vast array of fungal and bacterial strains.

2.1.7 Conclusions: first generation imidazolium catalysts

In conclusion, an evaluation was undertaken of the first small library of aprotic imidazolium ion-based ionic liquid catalysts with low antibacterial and antifungal toxicity, specifically designed to be of reduced environmental impact. These catalysts can behave as Brønsted acids in a controlled fashion, without requiring the precautions usually associated with the storage and use of strongly acidic substances. This proved to be a novel concept in the field of Brønsted acidic ionic liquid catalysis; with existing methods relying on the presence of inherently acidic functionalities.

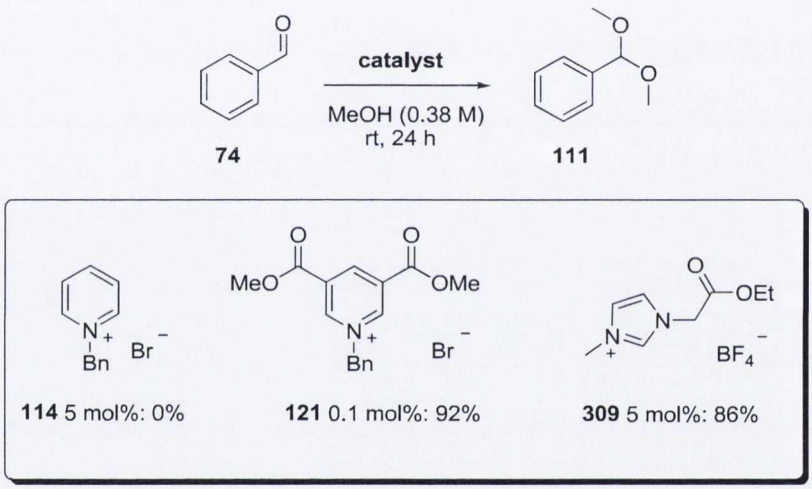
The variation of the catalyst's steric and electronic characteristics, while keeping within the framework of an environmentally benign design, led to the discovery that the counterion makes a key contribution to overall catalyst efficacy. The most active catalyst developed promoted the acetalisation (and thioacetalisation) of a range of aldehydes at low loadings (5 mol% to 10 mol%) and at ambient temperature. Additionally, after the reaction the catalyst can be recovered by simply adding hexane and decanting the product. The recycled catalyst could then be reused in 15 iterative recycles without any discernible loss of catalytic activity.

Although these catalysts had been designed with functionality in mind to render them readily biodegradable, none of the selected imidazolium ion catalysts passed the 'CO_2 Headspace' Test. Gratifyingly, antifungal and antibacterial toxicity studies demonstrated that the three representative ionic liquid candidates (**309**, **310** and **314**) did not inhibit the growth of any

organism screened at concentrations of >2.0 mM. This indicated that, as expected, the inclusion of an ester or amide group, as opposed to an alkyl chain, did not lead to an increase in toxicity. The exchange of the bromide counterion to the tetrafluoroborate anion also did not lead to a significant increase in toxicity. Therefore, although these first generation catalysts are not readily biodegradable, they have proven to be non-toxic over a wide range of bacteria and fungi.

3.1 A second generation of aprotic yet Brønsted acidic imidazolium based ionic liquids: low toxicity, high recyclability and greatly improved activity

Due to the superiority of these first generation imidazolium ion catalysts (*e.g.* **309**, Scheme 3.1), when compared to the unsubstituted pyridinium ion-based compound **114**, we postulated that, as was the case with the pyridinium ion-derived catalysts employed by Procuranti *et al.*,[72] the introduction of additional electron withdrawing groups (*e.g.* **121**) would render these imidazolium salts more active.



Scheme 3.1 Relative activity of the unsubstituted pyridinium ion **114**, the imidazolium ionic liquid catalyst **309** and the substituted pyridinium ion-based catalyst **121**.

As mentioned previously, one of the advantages these imidazolium ion-based moieties have over pyridinium ion-based catalysts is the possession of the former of lower resonance stabilisation energy. The installation of electron withdrawing groups on the imidazolium cation would therefore further reduce delocalisation and activate the ring towards nucleophilic attack by the protic additive on the heterocycle.

Accordingly, we embarked upon the design of new, more efficient, second generation imidazolium salts. In undertaking this design process a number of factors had to be taken into account (in addition to the highly influential impact of the introduction of electron withdrawing groups) with regards the mode of action of the catalyst. These include the

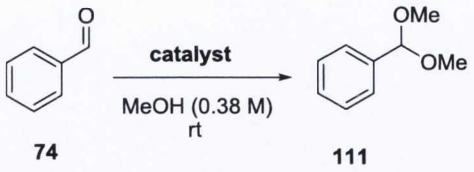
tunability of the imidazolium ion-based based compounds, an added advantage over the pyridinium ion-based moleucles, with an ability to introduce groups to the 2 nitrogen atoms in addition to the 3 carbon atoms of the 5-membered heterocyclic ring. In our preliminary studies, the modification of the counterion was also found to confer a higher degree of catalytic activity to the molecule, as such choice of counterion was deemed important. Furthermore, we also had to take into account the retention of the properties which render the molecule biodegradable and of low toxicity *i.e.* through functionalisation with either an ester or amide side chains and the presence of correct (preferably hydrophilic) counterion.

With each of these factors in mind, the design, synthesis and evaluation of new imidazolium catalysts was undertaken. Our collaborator, Dr. Rohitkumar Gore in DCU carried out the synthesis of C-2 substituted compounds, whilst our work in TCD focused on the synthesis of C-4 and C-5 substituted imidazolium ions. The evaluation of each of these newly designed catalysts (*i.e.* C-2, C-4 and C-4/C- substituted analogues) was then carried out in TCD.

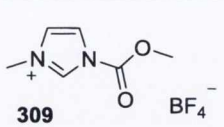
3.1.1 Preliminary screening of C-2 substituted imidazolium ion-based catalyst candidates

Our study began with the evaluation of catalysts incorporating electron withdrawing groups at the C-2 position (synthesised by Dr. Rohitkumar Gore, DCU) These were investigated as promoters of the acetalisation of benzaldehyde (**74**) in methanol (Table 3.1). The data associated with the first generation catalyst **309** is included for comparison (entry 1). It was determined that by employing the C-2 amide-substituted imidazolium ion **341** (at 1 mol% loading, entry 2), the formation of **111** from **74** occurred with a similar yield to that obtained using **309** at 5 mol% levels.[243] Exchange of the counterion from octylsulfate to bromide and tetrafluoroborate (*i.e.* catalysts **342** and **343**), led to a marginal improvement in catalytic activity (entries 3 and 4).

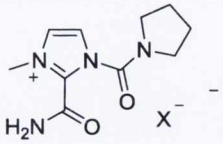
Table 3.1 Aprotic C-2 substituted imidazolium ions: catalyst evaluation.



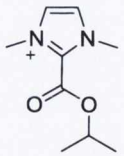
74 **111**



309



341 X = octylsulfate
342 X = Br
343 X = BF_4



344 X = I
345 X = NTf_2
346 X = BF_4

Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**309**	5	85
2	**341**	1	80
3	**342**	1	83
4	**343**	1	86
5	**344**	1	86
6	**345**	1	85
7	**346**	1	91
8	**346**	0.1	72

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

Additionally, the C-2 substituted esters **344-346** also proved capable of promoting the reaction with considerably improved efficacy relative to **309** (entries 5-7). It appears that hydrogen-bonding to the C-2 substituent does not play a significant role in catalysis- as can be deduced from the similar performance of amides **341** and **342** to that of esters **344-345** (entries 2-3 and 5-7). It is also noteworthy that the influence of the anion on catalyst performance (in this library) is considerably less significant than was the case in catalysts devoid of ring substitution, such as catalyst **309**. This we would suggest is a strong indicator that the much more electrophilic imidazolium ion units were making a greater contribution to catalysis in this library, thereby diminishing the importance of the previously discovered anion effect. However, as before, we did observe more efficient catalysis using an imidazolium ion incorporating a tetraflouroborate ion **346**, which allowed for the synthesis of

acetal **111** in 91% yield at 1 mol% catalyst loading (entry 7). It was found that at loadings lower than 1 mol% product yields diminished considerably (0.1 mol%, 72% **111**) (entry 8).

While it was clear that catalysts **341-346** represent a considerable step forward in terms of catalytic activity, when compared to the unsubstituted first generation catalysts, we were aware that the design of these catalysts was not optimal. The cause for concern was particularly based on the location of the electron withdrawing group at the C-2 position. Whilst installation of the electron withdrawing group at this position allows for the maximum amount of both inductive and mesomeric forms of electron withdrawal to be exerted by the amide/ester moiety at the proposed site of nucleophilic attack by methanol; a drawback related to this modification is that it introduces a degree of counterproductive steric crowding (**346a**, Figure 3.1) which could limit catalyst performance.

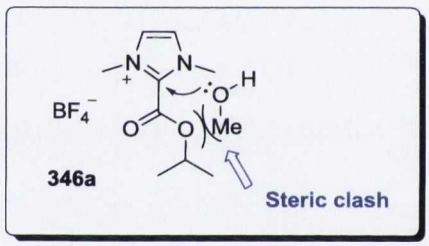


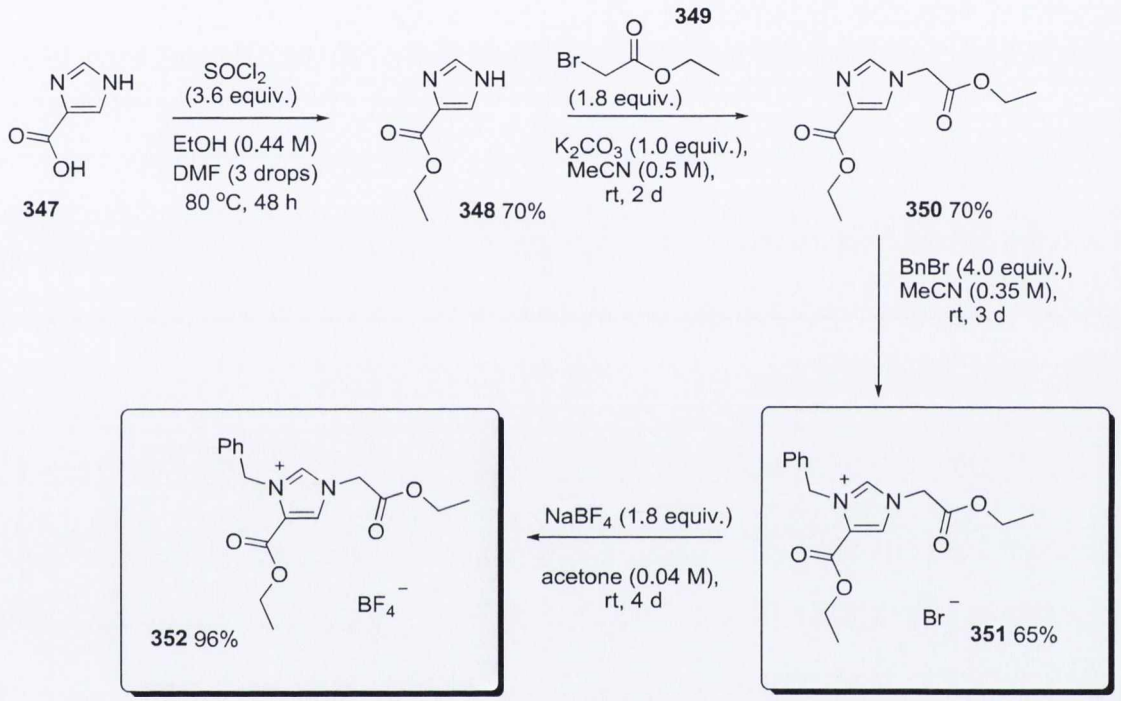
Figure 3.1 Postulated steric clash during alcohol addition to C-2 substituted imidazolium ion.

It therefore seemed prudent to design a library of catalysts characterised by the location of the electron withdrawing group at the C-4 position. The preparation and evaluation of C-4 substituted analogues (under identical conditions to C-2 position imidazolium ions) is discussed below.

3.1.2 Synthesis of C-4 ester substituted imidazolium ion-based catalyst candidates

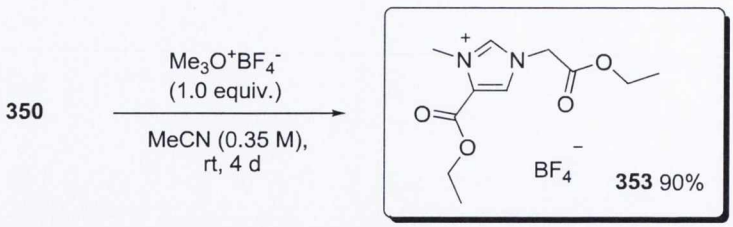
The synthesis of the C-4 ester substituted imidazolium ion **348** was carried out through the initial esterification of the commercially available 4-imidazolecarboxylic acid (**347**) with ethanol in the presence thionyl chloride and DMF to produce **348** in 70% yield (the ethyl ester was synthesised as the methyl ester proved susceptible to hydrolysis upon aqueous workup,

resulting in low yields). This was followed by the alkylation of the heterocyclic ring by deprotonation of the NH group using K_2CO_3, followed by alkylation with ethylbromoacetate (**349**, it is noteworthy that this introduces further ester functionality to the ring system), producing **350** in 70% yield. The quaternisation of **350** using benzyl bromide (4 equiv.) resulted in the generation of the pure catalyst **351** in good yield. A counterion metathesis was then implemented using $NaBF_4$ in acetone affording catalyst **352** in excellent yield (Scheme 3.2).



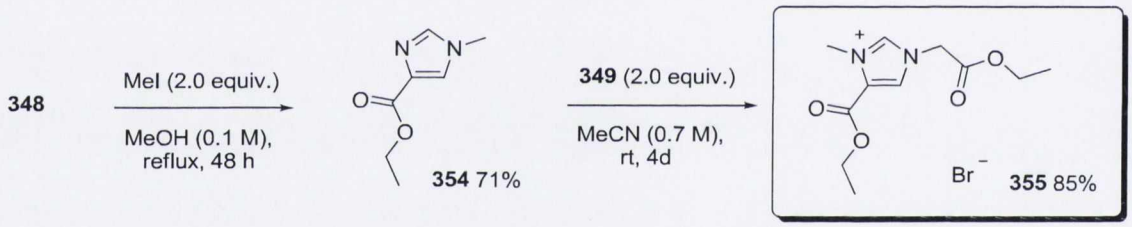
Scheme 3.2 Synthesis of C-4 ester substituted imidazolium ion-based catalyst candidates **351** and **352**.

The synthesis of the *N*-methyl substituted catalyst **353** was undertaken following a similar route to that outlined, the methylation of **350** was achieved, employing the non-volatile methylating agent trimethyloxonium tetrafluoroborate (Meerwein's salt), affording the desired product in high yield (Scheme 3.3).



Scheme 3.3 The methylation of **350** with Meerwein's salt, affording catalyst candidate **353**.

Meanwhile, the *N*-methyl substituted catalyst **355** was synthesised by the methylation of ester **348**, in the presence of methyl iodide and MeOH, affording **354** in 71% yield. This was followed by the quaternisation of the compound using **349** to give catalyst **355** (Scheme 3.4). The alkylation was performed in this way to afford the bromide containing catalyst, as to methylate imidazole **350** to afford **355** would require the use of the environmentally malignant, ozone depleting gas MeBr.[252]

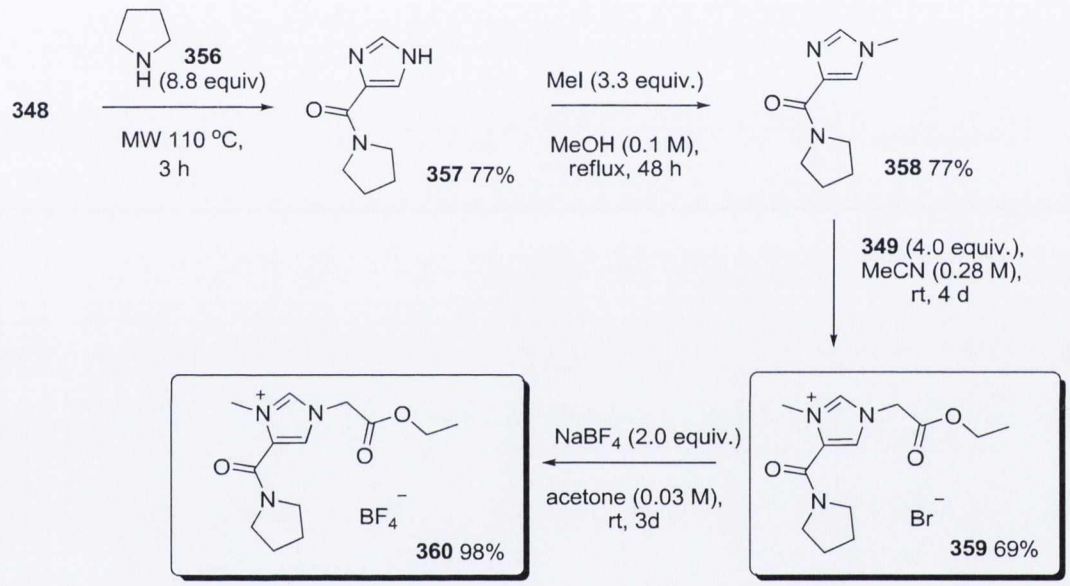


Scheme 3.4 Synthesis of 1-(2-ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1*H*-imidazol-3-ium bromide (**355**) from ester **348**.

3.1.3 Synthesis of C-4 amide substituted imidazolium ion-based catalyst candidates

The introduction of amide functionality was also implemented to compare both the environmental and catalytic activity of these compounds with their ester derived counterparts. The coupling of the carboxylic acid **347** with pyrrolidine (**356**) was initially attempted through DCC coupling, EDC coupling and the employment of a mixed anhydride. However, each of these methods proved unsuccessful due to solubility issues with the starting materials in various solvent systems.

The failure of these methods, after considerable experimentation, led to the development of solvent-free conditions with microwave irradiation for the coupling of **348** with the ester **356**. This reaction took place in 3 h at 110 °C, generating the desired product **357** in satisfactory yield (Scheme 3.5). The mono-substituted amide compound was then methylated following a similar procedure to that used to prepare ester **354** (*i.e.* alkylation using methyl iodide in methanol) to yield **358**. This was followed by the generation of the final bromide counterion containing catalyst **359**, using ethyl bromoacetate in acetonitrile. Again this underwent anion metathesis, using $NaBF_4$ in acetone, to afford **366** in excellent yield (Scheme 3.5).

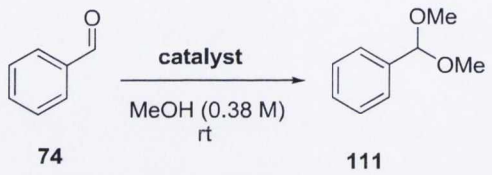


Scheme 3.5 Synthesis of imidazolium ion-derived amide substituted catalysts **359** and **360**.

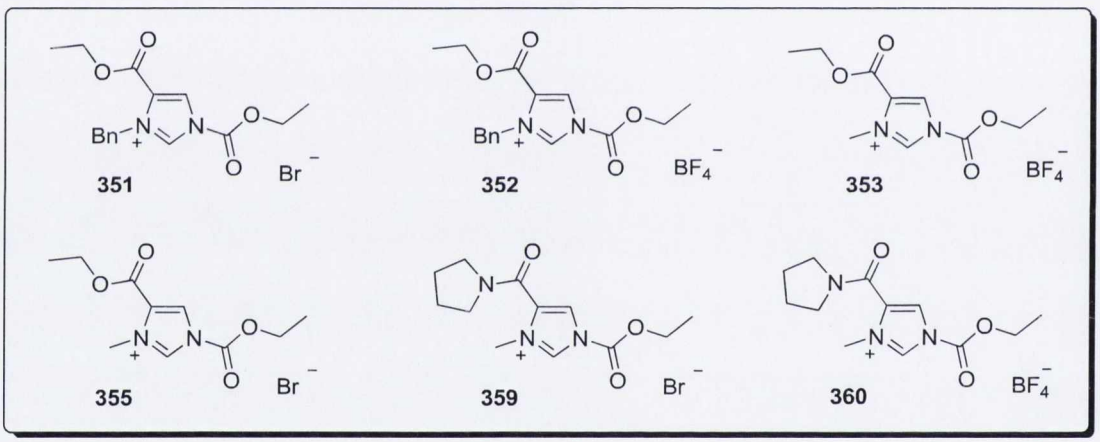
3.1.4 Preliminary screening C-4 substituted imidazolium ion-based catalyst candidates

The C-4 substituted catalysts were evaluated in the same reaction as that used to investigate the activity of the C-2 substituted catalysts (*i.e.* the acetalisation of benzaldehyde with methanol).[243]

Table 3.2 Aprotic C-4 substituted imidazolium ions: catalyst evaluation.



74 **111**



351 **352** **353** **355** **359** **360**

Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**351**	1	>98
2	**352**	1	>98
3	**353**	1	>98
4	**355**	1	>98
5	**360**	1	>98
6	**359**	1	95
7	**351**	0.1	81
8	**352**	0.1	88
9	**353**	0.1	86
10	**355**	0.1	78
11	**360**	0.1	85

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

This strategy was successful – when utilised at 1 mol% loading, catalysts **351, 352, 353, 355** and **360** promoted the reaction in essentially quantitative yield (entries 1-5). Imidazolium ion **359** is also an excellent catalyst (the product is formed in 95% yield), yet is perceptibly less active than the other members of the library (entry 6). Since the ranking of **351-353**, **355** and **360** on the basis of activity could not be determined at 1 mol% loading, these materials were then re-evaluated at 0.1 mol% levels, under otherwise identical conditions. Product yields remained high (entries 7-11), however none of the catalysts were capable of promoting the reaction to >90% yield inside 24 h. The nature of the anion, activating substituent (*i.e.* ester *vs.* amide) and *N*-alkyl moiety appeared to have little impact on catalytic efficacy in these systems. This result correlates well with the results of previous studies with respect to the pyridinium ions[72] (see Section 1.2.1) and the first generation imidazolium ions (see Table 2.1).[243]

The increase in activity at 0.1 mol% loading (when compared to the C-2 substituted compounds, see Table 3.1, entry 8) associated with the catalysts incorporating an electron withdrawing group to enhance the electrophilicity of the ring, yet are relatively unhindered at C-2 provide further evidence supporting our catalysts proposed mode of action (Scheme 2.1). Given the dramatic effect of the introduction of one electron withdrawing group (especially when not located at C-2) on catalyst activity, the final step in our optimisation study involved the design of catalysts characterised by the presence of two such groups at C-4 and C-5.

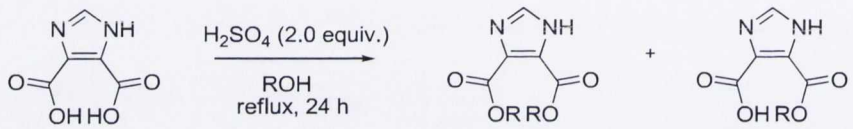
3.1.5 Synthesis of C-4/C-5 ester disubstituted imidazolium ion-based catalyst candidates

The increased activity of the C-4 substituted moieties, when compared to the C-2 substituted candidates, along with the substantial increase in activity in pyridinium ions when electron withdrawing groups were introduced at two positions (C-3 and C-5) on the pyridinium ring,[72] led to the design of imidazolium ions with ester groups tethered to both the C-4 and C-5 positions.

The esterification of the commercially available 4,5-imidazoledicarboxylic acid (**361**) proved to be more challenging than that of the mono-substituted compound. The inherent problems, which were exposed during the esterification of the C-4 substituted acid, were again encountered here with respect to the hydrolysis of the methyl ester during aqueous work up,

resulting in negligible yield of the desired ester product. The introduction of a more hindered alcohol was, in this case, ultimately unsuccessful. However, when compared to MeOH (entry 1, Table 3.3), the employment of ethanol (entry 2) and isopropanol (entry 3) to esterify the *bis*-acid, led to an increase in the production of mono- ester substituted product, hence affording low yields of the desired products even after 24 h (Table 3.3). This problem was probably contributed to by steric limitations, reducing the amount of the desired 4,5-imidazole dicarboxylate formed.

Table 3.3 Percentage of mono- and *bis*-ester product generated employing various alcohols in the esterification of **361**.



361

362 R = Me
363 R = Et
364 R = *i*Pr

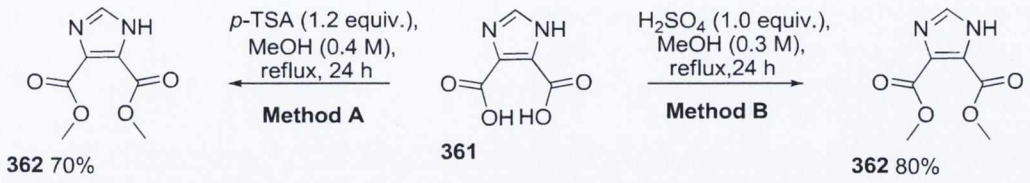
365 R = Me
366 R = Et
367 R = *i*Pr

Entry	Alcohol	Di-ester Yield %[a]	Mono-ester Yield %[a]
1	MeOH	82	5
2	EtOH	48	48
3	*i*PrOH	18	74

[a]Determined by ^{1}H NMR spectroscopy using an internal standard.

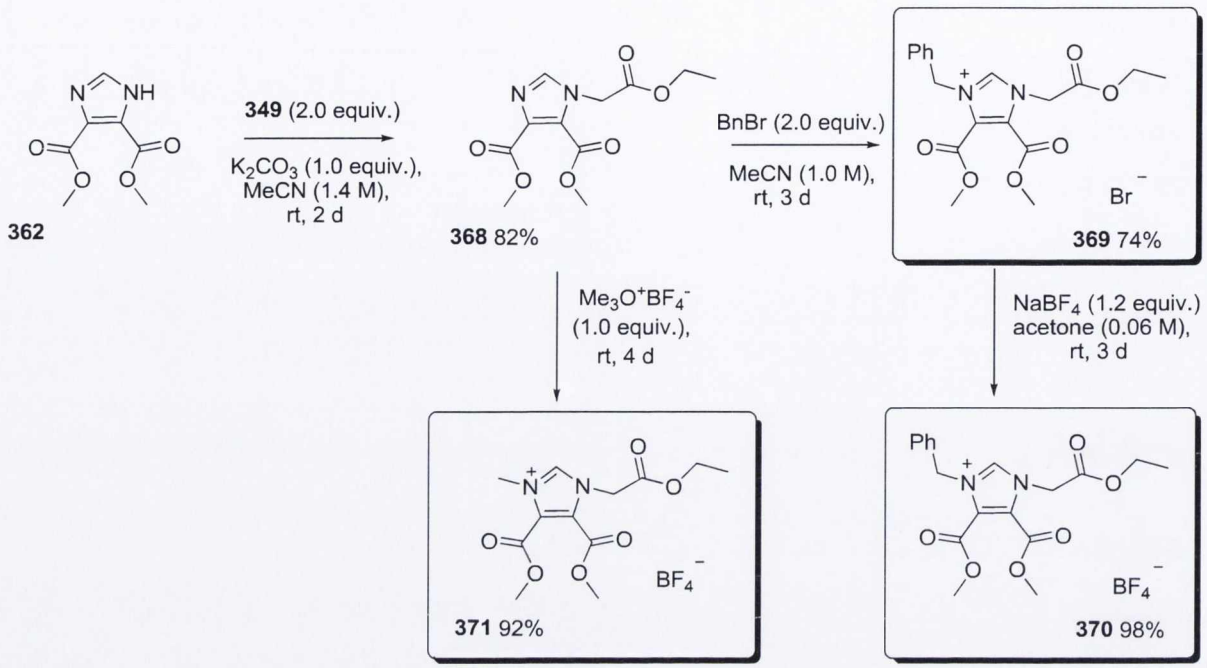
Consequently, the optimisation of the esterification of 4,5-imidazoledicarboxylic acid with methanol was concentrated on. After considerable experimentation undertaken to determine the optimum anhydrous reaction conditions, two methods were developed capable of giving synthetically useful yields of the methyl ester **362**. The first of these involved the use of the solid acid catalyst *p*TSA; it was found that, in the presence of this acid, the esterification of **361** could be carried out under reflux in methanol for 24 h, after which time the ester **362** was successfully synthesised with a small amount of residual acid present. The acid impurity was then removed by recrystallisation (avoiding the requirement of an aqueous work-up), producing the ester **362** in 70% yield (A, Scheme 3.6). The second procedure involved the use of H_2SO_4 in methanol (despite the removal of the large amount of residual acid remaining after the reaction being initially detrimental due to the aforementioned hydrolysis problems).

After multiple experiments using various concentrations of H_2SO_4, the optimum procedure employing just 1 equivalent of sulfuric acid under reflux in MeOH for 24 h led to the generation of **362** in 80% yield, with little comparable hydrolysis of the ester during a basic work-up (B, Scheme 3.6).



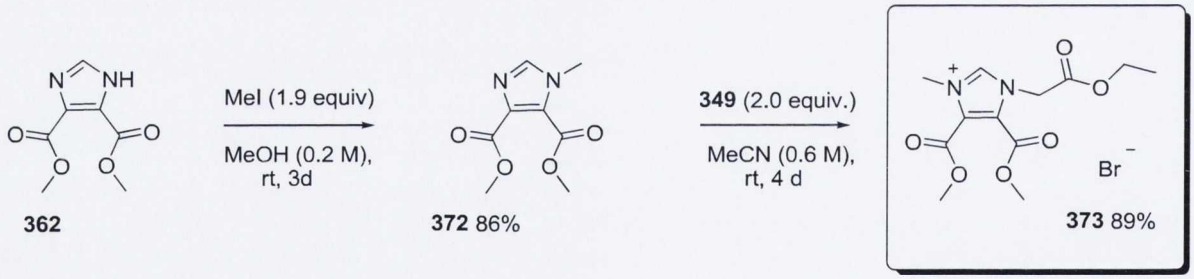
Scheme 3.6 Optimised conditions for the esterification of **361**.

With dimethyl 1*H*-imidazole-4,5-dicarboxylate (**362**) in hand, the alkylation of the ester was undertaken following a similar procedure to that used to prepare the C-4 substituted compounds. To create the *N*-benzyl substituted catalysts the initial alkylation of **362** was accomplished using **349** affording **368** in good yield. This was followed by quaternisation with benzyl bromide to afford **369**, which underwent anion metathesis to produce **370** in excellent yield. The *N*-methyl substituted catalyst **371** was also obtained through the methylation of **368** with Meerwein's salt in 92% yield (Scheme 3.7).



Scheme 3.7 Synthesis of catalysts **369**, **370** and **371**.

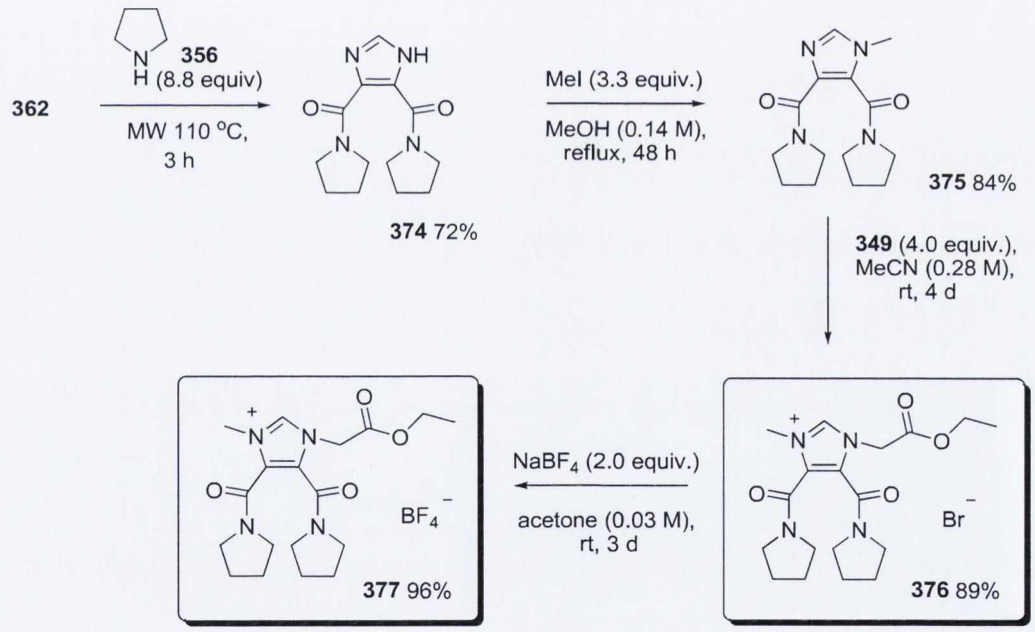
As with the C-4 substituted analogues, the synthesis of the methylated catalyst **373** was achieved through the initial methylation of **362** to **372** with MeI in MeOH followed by alkylation with ethybromoacetate (**349**) to afford the bromide anion containing catalyst **373** (Scheme 3.8).



Scheme 3.8 Synthesis of *N*-methyl substituted bromide counterion containing catalyst candidate **373**.

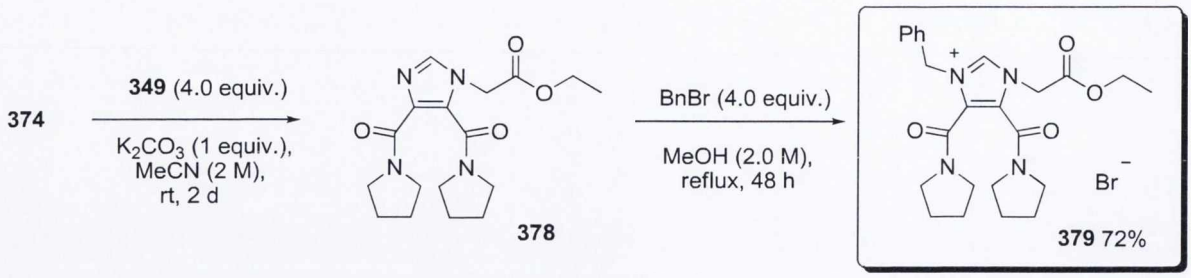
3.1.6 Synthesis of C-4/C-5 amide disubstituted imidazolium ion-based catalyst candidates

The conventional coupling methods (*i.e.* DCC coupling, EDC coupling and the generation of a mixed anhydride) for the synthesis of the amide based C-4/C-4 catalysts, as encountered with the mono-substituted compounds, was complicated by the lack of solubility of the starting material. However, **374** could be produced, under the same conditions employed in the synthesis of the mono- amide **325,** under solvent-free conditions with microwave irradiation the coupling of **362** with **324** occurred in 3 h at 110 °C, affording **374** in good yield (Scheme 3.9). The alkylation of this amide substituted imidazole was then carried out as before, with MeI in MeOH, affording **375** in satisfactory yield**.** This was then quaternised by alkylation using **349** to produce catalyst **376**, while **377** was produced through an anion exchange with $NaBF_4$ in acetone (Scheme 3.9).



Scheme 3.9 Synthesis of 4,5-imidazole substituted catalysts **376** and **377**.

The synthesis of the *N*-benzyl substituted catalyst **379** was also undertaken, to allow for a comparison of the catalytic activity of this material with its *N*-methyl substituted equivalent **376** to be made. The amide **374** underwent alkylation with **349** to afford **378**, which was subsequently alkylated in the presence of benzyl bromide to give catalyst **379** in 72% yield (Scheme 3.10).



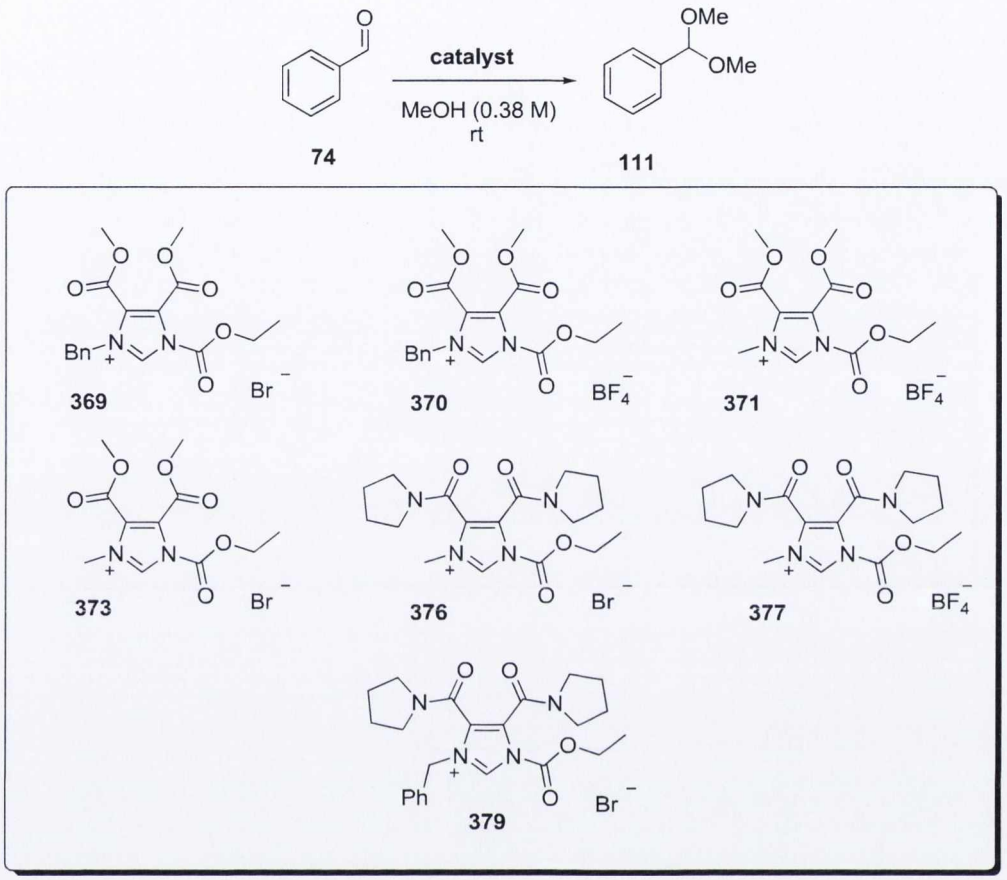
Scheme 3.10 Synthesis of catalyst **379**.

3.1.7 Preliminary screening of C-4/C-5 substituted imidazolium ion-based catalyst candidates

As expected, all catalysts proved highly active at 1 mol% levels (entries 1-8), with each catalyst promoting the reaction to completion. At 0.1 mol% loading, product yields were attenuated, however using catalysts incorporating the tetrafluoroborate counteranion (*i.e.* entries 9-11) yields remained over 90%, while the amide derived catalysts afforded synthetically useful yields of over 80% (entries 12-14, Table 3.4).

Again, the nature of the alkyl substituent (*i.e.* methyl or benzyl) had negligible effect on catalysts efficacy (*e.g.* **370** and **371**, entries 9 and 10). Although the difference was not extremely pronounced, the ester based compounds were slightly more active than their amide counterparts (*e.g.* **370** and **377**, entries 9 and 11, Table 3.4). Gratifyingly, the catalyst activity exhibited by the optimum structure identified by this study (*i.e.* **370**) outperformed all of the C-4 substituted catalysts, none of which were capable of promoting the reaction to above 90% yield at 0.1 mol% loading (*e.g.* optimum C-4 catalyst **352** gave 88% of **111** at 0.1 mol% loading), whilst use of the best C-2 substituted compound gave just 72% yield at the same loading.

Table 3.4 Aprotic 4,5-disubstituted imidazolium ions: catalyst evaluation.



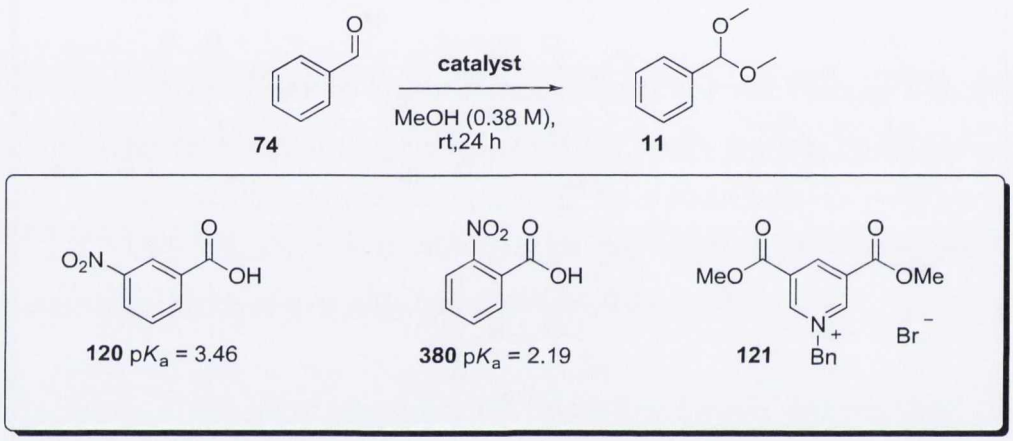
Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**369**	1	>98
2	**370**	1	>98
3	**371**	1	>98
4	**373**	1	>98
5	**376**	1	>98
6	**377**	1	>98
7	**379**	1	>98
8	**369**	0.1	89
9	**370**	0.1	94
10	**371**	0.1	92
11	**377**	0.1	91
12	**373**	0.1	86
13	**376**	0.1	82
14	**379**	0.1	80

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

All catalysts, pleasingly, outperformed 3-nitrobenzoic acid (**120**, pK_a H_2O, 25 °C = 3.46,[253] entry 1, Table 3.5) as a promoter of the acetalisation of benzaldehyde with methanol. It was

particularly satisfactory that (with the exception of **379** which exhibited similar activity) outperformed the 2-nitro analogue (**380**, pK_a H_2O, 25 °C = 2.19,[253] entry 2) which at 0.1 mol% loadings, promoted the formation of **111** in 80% yield. The imidazolium ion-derived catalyst **370** (entry 3) also outperformed the optimum pyridinium catalyst **121** (entry 4, Table 3.5): although the difference in activity was modest, the ease of synthesis and purification of **370** compared to **121**, along with its increased stability, is a major advantage.

Table 3.5 Comparison of the activity of **370** with nitrobenzoic acids **120**, **380** and the pyridinium catalyst **121**.



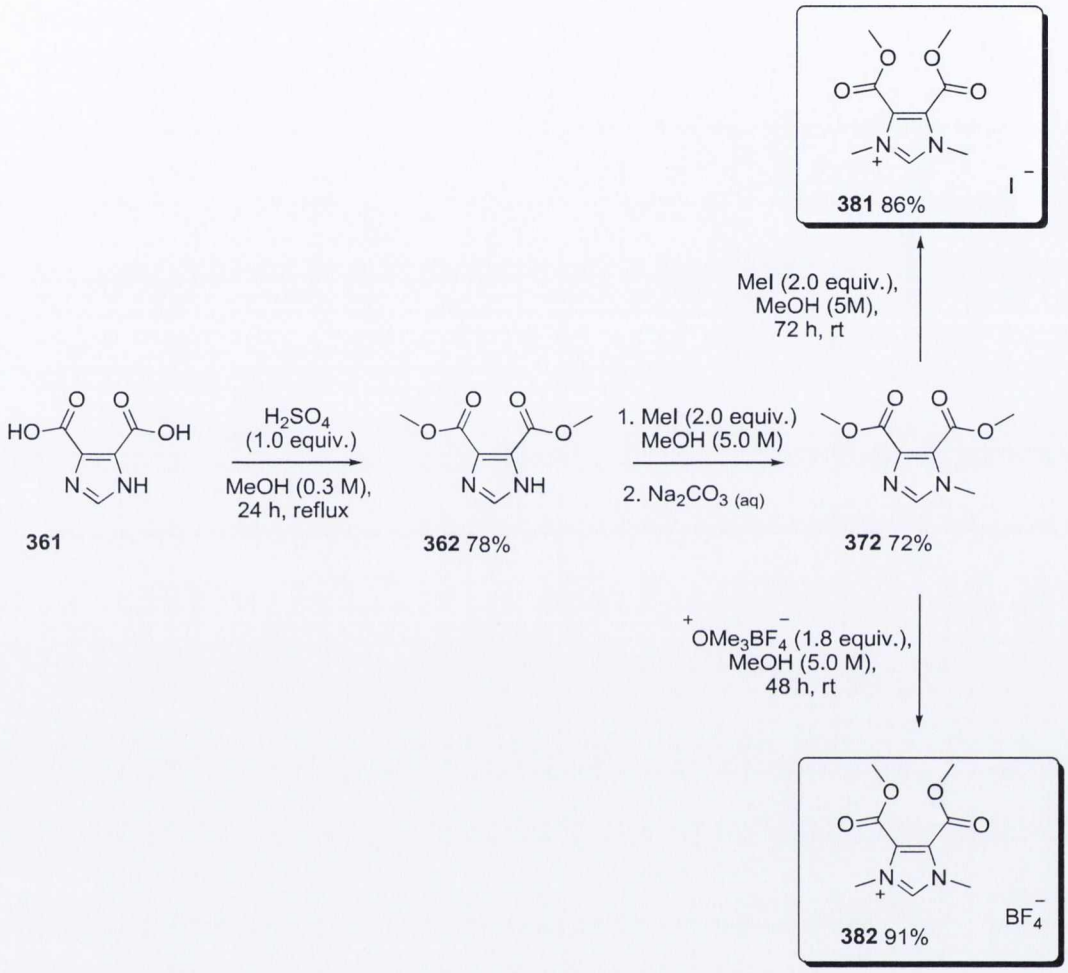
Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**120**	1	37
2	**380**	0.1	80
3	**370**	0.1	94
4	**121**	0.1	92

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

3.1.8 Synthesis and evaluation of 1,3-dimethyl substituted imidazolium ion-based catalysts: a more atom-economic design

Although the potential environmental impact of the preparation of each of the catalysts above, was taken into account during their design and synthesis (*i.e.* utilising the minimum amount of solvent, acid and alkylating agent possible), it was felt that impact of the route could further decreased. Therefore, the synthesis of catalysts **381** and **382** was re-evaluated: these

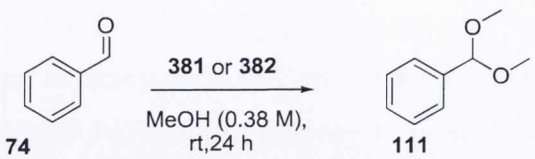
materials were again prepared from the inexpensive 4,5-imidazoledicarboxylic acid in a relatively atom-economic fashion as outlined below (Scheme 3.11).



Scheme 3.11 Synthesis of **381** and **382** from the inexpensive diacid **361**.

The performance of these simple structures was particularly gratifying as this more atom-economic synthesis led to the formation of two highly active catalyst compounds. In the presence of the tetrafluoroborate based moiety **382** the formation of the dimethyl acetal **111** was promoted in nearly quantitative yield, while a slightly inferior but nonetheless high yield of 98% was reached when **381** was employed as the catalyst (both were used at 1 mol% loading, Table 3.6). It was also satisfactory that, at 0.1 mol% loading, **382** was on a par with some of the most efficient catalysts previously evaluated, promoting the generation of **111** in excellent, with **111** afforded in 84% yield in the presence of **381** at the same loading (Table 3.6).

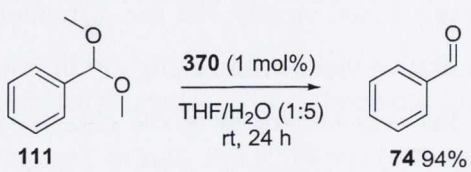
Table 3.6 Evaluation of catalysts **381** and **382** in the acetalisation of benzaldehyde with MeOH.



Entry	Catalyst	Loading (mol%)	Yield (%)[a]
1	**381**	1	98
2	**382**	1	>98
3	**381**	0.1	84
4	**382**	0.1	92

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

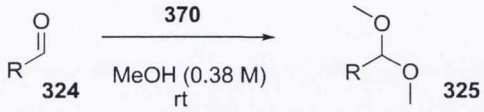
The results above show that these new imidazolium ion-based compounds are capable of acting as synthetically useful catalysts at loadings 5-50 times lower than those previously necessary using the optimal first generation material **309**. Their activity is such that one is no longer dependant on the nature of the anion to ensure high product yields (*e.g.* the iodide **381** can promote the formation of **111** in >90% yield at just 1 mol% loading). The general catalyst order of activity (*i.e.* C-2 substituted < C-4 substituted < C-4/C-5 disubstituted) and the diminished influence of the anion relative to the case with **309**, is in line with what one would expect from the mechanistic hypothesis outlined in Scheme 2.1 (Chapter 2), which provides further evidence supporting this most unusual proposed mode of action. Additionally, according to the principle of microscopic reversibility, **370** should also serve as a catalyst for the hydrolysis of acetals/ketals. This proved to be the case; in an aqueous medium, 1 mol% could catalyse the conversion of acetal **111** to benzaldehyde (**74**) under mild conditions in 94% yield (Scheme 3.12)

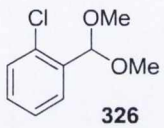
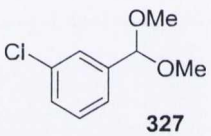
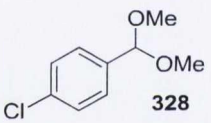
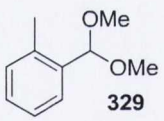
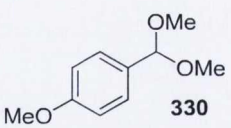
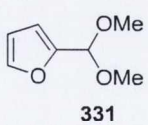
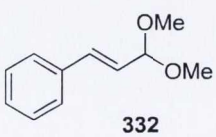


Scheme 3.12 Acetal hydrolysis under mild conditions promoted by **370**.

3.1.9 Imidazolium ion-based catalysts (2nd generation): evaluation of substrate scope

Table 3.7 Catalytic acetalisation: evaluation of substrate scope.

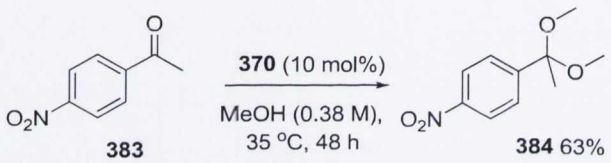


Entry	Substrate	Loading (mol%)	Time (h)	Yield (%)[a]
1	 **326**	0.1	24	95
2	 **327**	0.1	24	96
3	 **328**	0.1	24	98
4	 **329**	1	24	90
5	 **330**	1	24	92
6	 **331**	1	24	92
7	 **332**	1	24	90

[a]Isolated yield after chromatography.

With an active and easily prepared catalyst in hand, our attention next turned to the question of substrate scope (Table 3.7). Catalyst **370** could catalyse the smooth acetalisation of activated- (*i.e.* **326-328**, entries 1-3), hindered- (*i.e.* **329**, entry 4) deactivated- (*i.e.* **330**, entry 5), heterocyclic- (*i.e.* **331**, entry 6) and α,β-unsaturated aldehydes (*i.e.* **332**, entry 7) with higher (excellent) isolated product yields at 10-50 times lower catalyst loading (in shorter reaction times) than those required for the synthesis of these acetals using catalyst **309** (Table 3.7).

We also found that **370** could promote the ketalisation of *p*-nitroacetophenone (**383**) to form **384** in good yield (Scheme 3.13) – a reaction which was completely beyond the scope of catalyst **309**.



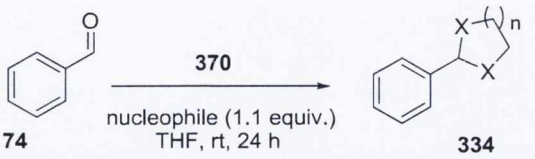
Scheme 3.13 Conversion of ketone **383** to the corresponding ketal **384** with catalyst **370**.

3.1.10 Imidazolium ion-based catalysts (2nd generation): thioacetalisation/dioxane formation

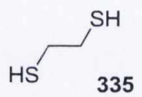
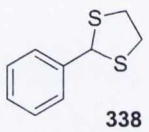
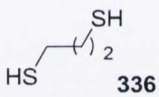
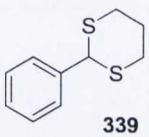
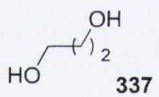
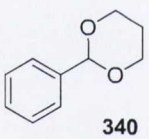
The catalytic activity of these compounds was not confined to methanolysis (as was the case with the 1st generation imidazolium ion-based catalysts), with **370** determined to be active in the promotion of protection of benzaldehyde with 1,2-ethanedithiol and 1,3-propanedithiol (entries 1 and 2, Table 3.8). The synthetically useful dithiolane **338** and dithiane **339** (a product usually formed at elevated temperatures) could be obtained, at room temperature, using remarkably low loadings when compared to those required using the 1st generation catalyst **309**, the pyridinium catalyst **121** and also conventional Lewis acid catalysts generally used to promote these reactions.[167,170,172] The catalysis of the formation of the dioxane **340** (entry 3) was also performed, affording the product in 90% yield at 5 mol% loading. Again, this synthetically useful protection was carried out at loadings lower than that previously required using **309** and **121**. However, it was noted at this time that, somewhat surprisingly, **370** proved unexpectedly more active in the formation of the dithiolane/dithaine products

relative to its performance in dioxane formation (generating similar yields of dithianes at 1 mol% loading, while the dioxane required the addition of 2 mol% catalyst).

Table 3.8 Catalysis of dithiane, dithiolane and dioxane syntheses.



74 334

Entry	Nucleophile	Product	Loading (mol %)	Yield (%)[a]
1	 **335**	 **338**	1	90
2	 **336**	 **339**	1	86
3	 **337**	 **340**	2	90

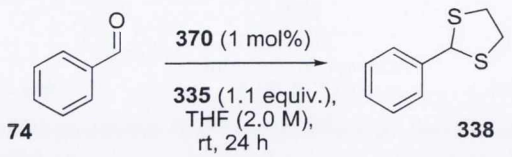
[a]Isolated yield after chromatography

3.1.11 Imidazolium ion-based catalysts (2nd generation): recyclability

The recyclability of this new highly functionalised catalyst **370** was also investigated. To do so, the protection of benzaldehyde (**74**) with 1,2-ethanedithiol (**335**) was carried out at room temperature for 24 h. Upon completion of the reaction, the catalyst was again recovered in excellent yield, by precipitation from the reaction medium using hexane, followed by decantation and drying *in vacuo*. The recovery of the pure catalyst in high yield was particularly satisfying, as the recovery of the pyridinium ion-based moiety **121** (also containing two EWGs), in high yields was more arduous. This again highlights the superiority of **370** over **121** from catalyst stability standpoint. The solid salt **370** was dried further under vacuum to remove any water and reused in 5 subsequent cycles without any loss in activity being observed (Table 3.9). While **370** was not be recycled as many times as **309** (which was

recycled in our previous study 14 times),[243] **370** was employed at considerably lower loading in this study (1 mol% *vs.* 10 mol%), and as such can be considered more recyclable than **309**, due to its significantly superior turnover number (TON) over the accumulated cycles.

Table 3.9 Catalyst recycling using 2nd generation imidazolium ion-based catalyst **370**.



Entry	Cycle	yield (%)[a]
1	1	94
2	2	94
3	3	94
4	4	95
5	5	94

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

3.1.12 Imidazolium ion-based catalysis (2nd generation): biodegradability

To evaluate the biodegradability of the test ionic liquids, the 'CO_2 Headspace' test (ISO 14593)[82] was once again implemented (by our collaborators Dr. N. Gathergood and Dr. R.Gore in DCU). The test ionic liquid, as the sole source of carbon, was added at a concentration of 40 mg L^{-1} to a mineral salt medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air. Biodegradation (mineralisation to carbon dioxide) was determined by measuring the net increase in total organic carbon (TOC) levels over time.Four representative examples of the C-2 substituted ionic liquid were selected based on catalytic activity; the amide functionalised compounds **342** and **343** and the isopropyl ester substituted catalysts **344** and **346**. The counterions compared in this study were the bromide and tetrafluoroborate counterions. As was the case with the first generation catalysts, disappointingly, none of the compounds passed the 'CO_2 Headspace' test (>60% biodegradation after 28 d = readily biodegradable). The amides **342** and **343** gave lower values of 12% and 14% respectively after 28 d (entries 1 and 2, Table 3.10), when compared to the moderate levels of biodegradation of esters **344** and **346** (30% and 35% respectively

after 28 d, entries 3 and 4, Table 3.10). The C-4 substituted examples screened, surprisingly, gave unsatisfactory results with negligible biodegradability detected with respect to compounds **353** (5%), **355** (10%) and **359** (2%) after 28 d (entries 5, 6 and 7, Table 3.10).

Table 3.10 Evaluation of the biodegradability of imidazolium ion-based ionic liquid catalysts using the 'CO_2 Headspace' Test (MIC [$mmol.L^{-1}$]).

Entry	Catalyst	*t* (6 d)[a]	*t* (14 d)[a]	*t* (21 d)[a]	*t* (28 d)[a]
1	**342**	2	7	8	12
2	**343**	7	12	11	14
3	**344**	24	31	32	30
4	**346**	26	31	30	35
5	**353**	2	4	3	5
6	**355**	6	5	8	10
7	**359**	0	0	0	2

[a]Percentage biodegradation after *t* (time) in days

The biodegradation data associated with the C-4/C-5 di-substituted IL catalysts **369**, **370**, **371** and **379** (entries1-4) are shown in Table 3.11. Again, neither ester nor amide substitution at C-4 and C-5 on imidazole ring of the ILs resulted in the compound passing the 'CO_2 Headspace' test. Catalyst **371** biodegraded to the greatest extent (31% after 28 days) of all C-4/C-5 disubstituted ILs evaluated. The 1,3-dimethyl substituted catalysts screened (*i.e.* **381** and **382**) also proved to be poorly biodegradable after 28 d (entries 5 and 6, Table 3.11).

Table 3.11 Evaluation of the biodegradability study of C-4/C-5 functionalised ionic liquids catalysts using the 'CO_2 Headspace' test (MIC [$mmol.L^{-1}$]).

Entry	Catalyst	*t* (6 d)[a]	*t* (14 d)[a]	*t* (21 d)[a]	*t* (28 d)[a]
1	**369**	12	18	22	24
2	**370**	1	2	3	6
3	**371**	15	21	30	31
4	**379**	0	0	1	2
5	**381**	0	4	5	3
6	**382**	3	9	12	12

[a]Percentage biodegradation after *t* (time) in days

3.1.13 Imidazolium ion-based catalyst (2nd generation): anti-microbial/anti-fungal activity

The toxicity of all ionic liquids evaluated for catalytic activity (C-2, C-4, C-4/C-5 functionalised imidaozlium ions) against various fungi and bacteria was also determined. A broad spectrum of organisms were selected to be screened against based on their relevance towards interesting environmental and medicinal applications.

Anti-fungal activities were evaluated *in vitro* on a panel of five clinical yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/1, *Candida lusitaniae* 2446/I, *Trichosporon beigelii* 1188), four ATCC (American Type Culture Collection) strains (*Candida parapsilosis* ATCC 22019, *Candida albicans* ATCC 90028, *Candida krusei* ATCC 6258 and *Candida albicans* ATCC 44859) and three filamentous fungi (*Aspergillus fumigatus* 231, *Asbidia corymbifera* 272 and *Trichophyton mentagrophytes* 445) Gratifyingly, antifungal activity was not observed for any of the compounds incorporating an electron withdrawing group at the C-2 or C-4 position screened at the highest concentration (2.0 mM) in 48 h.

The C-4/C-5 functionalised ionic liquids incorporating an ester group tethered to the heterocyclic nitrogen atom exhibited no anti-fungal activity (*i.e.* **369-371**, **373**, and **379**) at the highest concentration screened (0.5 mM (**371** and **373**), 1.0 mM (**379**) and 2.0 mM (**369, 370**)), depending on compound solubility in the test medium.

There was, however, antifungal activity exhibited by the iodide containing 1,3-dimethylimidazolium catalyst **381**, with an MIC value of 0.5 mM concentration against three ATCC strains, one clinical yeast and 2 filamentous fungi (entries 1, 2, 3, 9, 10 and 12, Table 3.12), 1.0 mM concentration against four clinical yeasts and one ATCC strain (entries 4-8) and 2.0 mM against the filamentous fungus *Absidio corymbifera* (entry 11, Table 3.12). Whilst the dimethyl catalyst **382** exhibited no anti-fungal activity when tested at the maximum solubilised concentration of 0.5 mM. These results show that both the cationic structure and the nature of the anion, contribute to the anti-fungal properties of the ionic liquid moiety.

Table 3.12 MIC values for anti-fungal activity of compound **381** (MIC [mmol.L^{-1}])

Entry	Organism	MIC[a]	Entry	Organism	MIC
1	*Candida albicans* ATCC 44859	0.5	7	*Candida glabarta* 20/I	1.0
2	*Candida albicans* ATCC 90028	0.5	8	*Candida lusitoniae* 2446/I	1.0
3	*Candida parapsilosis* ATCC 6258	0.5	9	*Trichosporon beigelii* 1188	0.5
4	*Candida krusei* ATCC 6258	1.0	10	*Aspergillus fumigatus* 231	0.5
5	*Candida krusei* E28	1.0	11	*Absidia corymbifera* 272	2.0
6	*Candida tropicalis* 156	1.0	12	*Trichophyton mentagrophytes* 445	0.5

[a]MIC (Minimum inhibitory concentration) after 48 h

In vitro anti-bacterial activity was also evaluated using a panel of 3 ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Kleibsiella pneumoniae* HK1175/08, *Enterococcus sp.* HK 14368/08 and *Klebsiella pneumoniae* ESBL HK14368/08). Again, as with the fungal strains no anti-microbial activity was observed for C-2 or C-4 functionalised at high concentrations (2.0 mM) over 48 h.

Anti-microbial activity was observed, for the first time with the C-4/C-5 functionalised imidazolium ions (**369-371**, **373** and **379**), however only against Gram positive strains (entries 1-4). They had no effect on Gram negative strains (entries 5-8) (Table 3.13). The gram positive strain most sensitive to these was *S. epidermus* (entry 4), this gave MIC values of 1.0 mM for **369**, 2.0 mM for **370** and just 0.25 mM for **373**. *S. aureus* H 5996/08 was affected by **369** at MIC of 2.0 mM (entry 2), whilst *S. aureus* ATCC 6538 was sensitive to **370** at 1.0 mM. Compounds **371** (at 0.5 mM) and **379** (at 1.0 mM) were non-toxic to all bacteria (Table 3.13). Additionally, the dimethyl compound **381** exhibited anti-bacterial activity against all

strains of bacteria evaluated, with the exception of *Pseudomonas aeruginosa* ATCC 9027 (entry 8). It exhibited anti-microbial activity with a MIC value of 0.5 mM for 3 Gram positive bacteria (entries 1-3) and 2.0 mM for one Gram positive and 3 Gram negative bacteria (entries 4-7) (Table 3.13). The tetrafluoroborate based catalyst **382** again exhibited no anti-bacterial activity at its maximum concentration limit of 0.05 mM (Table 3.13).

Table 3.13 Anti-bacterial activity of C-4/C-5 substituted compounds (MIC [mmol. L^{-1}])

entry	organism	MIC 369[a]	MIC 370[a]	MIC 371[a]	MIC 373[a]	MIC 379[a]	MIC 381[a]	MIC 382[a]
1	*S aureus* ATCC 6538	>2.0	2.0	>0.5	>0.5	>1.0	0.5	>0.5
2	*S aureus* HK 5996/08	2.0	>2.0	>0.5	>0.5	>1.0	0.5	>0.5
3	*S epidermidis* HK 6966/08	2.0	1.0	0.25	>0.5	>1.0	0.5	>0.5
4	*Enterococcus sp.* HK 14365/08	>2.0	>2.0	>0.5	>0.5	>1.0	2.0	>0.5
5	*E. coli* ATCC 8739	>2.0	>2.0	>0.5	>0.5	>1.0	2.0	>0.5
6	*Klebsiella pneumoniae* HK 11750/08	>2.0	>2.0	>0.5	>0.5	>1.0	2.0	>0.5
7	*Klebsiella pneumoniae ESBL* HK 14368/08	>2.0	>2.0	>0.5	>0.5	>1.0	2.0	>0.5
8	*Pseudomona aeruginosa* ATCC 9027	>2.0	>2.0	>0.5	>0.5	>1.0	>2.0	>0.5

[a]MIC (Minimum inhibitory concentration) after 48 h

3.1.14 Conclusions: second generation imidazolium catalysts

We have designed a second generation of aprotic imidazolium ion-based ionic liquid catalysts, capable of behaving as Brønsted acids in an 'on-off' fashion, controlled by the use of protic additives. These catalysts offer greatly improved catalytic efficacy compared to the first generation imidazolium ion-based ionic liquid catalysts, generally without compromising the low toxicity profile associated with the first generation series.

Analysis of the initial data associated with the 1st generation catalysts, along with the previous studies with pyridinium ions, provided mechanistic insight to the action of these catalysts. This mechanism suggested that the introduction of electron withdrawing groups on the heterocyclic ring of the imidazolium ion, would facilitate the formation of greater equilibrium concentrations of the putative acidic adduct with the nucleophilic alcohol additive, leading to faster catalysis. The first 2nd generation library prepared, comprising of compounds possessing either an ester or amide group at C-2, proved this theory was true, as they were considerably more active than the optimum first generation benchmark catalyst **309**. Installation of the activating group at the C-4 position, led to further improvements in efficacy. Gratifyingly, the installation of a second EWG at the C-5 position, led to the production of a suite of catalysts, capable of promoting the acetalisation of benzaldehdye with methanol, at catalysts loadings 50 times lower than that required to produce the acetal **111** using **309**.

The optimum catalysts are also characterised by a marked reduction in the relative contribution of the anion to catalysis, this gives the practitioner the flexibility to choose an anion based on environmental/toxicological/solubility/chemoselectivity considerations if required. It also removes the obligation to use the tetrafluoroborate anion required to bring about efficient catalysis with the 1st generation catalyst library.

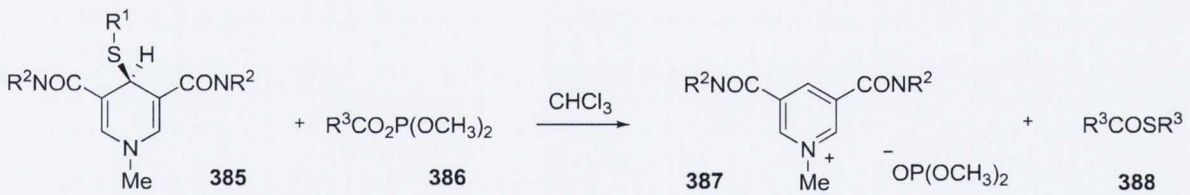
The optimum catalyst in this study (*i.e.* **370**) could promote the synthetically useful acetalisation and thioacetalisation of range of aldehydes at catalyst loadings of 0.1-1 mol%. It could also catalyse the reverse hydrolytic process and a ketalisation reaction which were beyond the scope of the first generation catalysts. Catalyst **370** not only outperformed the first generation catalyst, it also has advantages over the most effective pyridinium ion based catalyst **121**. These advantages include the ease of synthesis of **370** from the relatively inexpensive starting material 4,5-imidazoledicarboxylic acid and the stability of **370** compared to **121**, allowing for both extended catalyst shelf-life and an increase in catalyst recyclability. After the reaction the catalyst can be reused in 5 iterative cycles (at 1 mol%) without any discernible loss in activity.

As was the case with the first generation catalysts, none of the new catalyst candidates were readily biodegradable, however each of the mono-substituted catalysts screened exhibited no bacterial or fungal toxicity when tested against a range of bacteria and fungi. While, some of

the ester substituted C-4/C-5 substituted moieties exhibited some anti-microbial activity towards gram positive bacteria tested, none exhibited any anti-fungal activity. Additionally, the 1,3-dimethyl based imidazolium ion containing an iodide anion, exhibited anti-fungal and anti-microbial activity along with poor biodegradability. However, its relatively simple structure, which was designed to be efficiently synthesised, was expected to produce these results. The most efficient catalyst which was found to be of low toxicity and have moderate biodegradation after these studies was catalyst **371**. This catalysed the acetalisation of benzaldehyde with methanol in 92% yield at 0.1 mol%, whilst exhibiting moderate biodegradability (31% by CO_2 Headspace test in 28 d) and demonstrating no anti-microbial or anti-fungal capabilities.

4.1 Imidazolium ion-based catalysis: investigation of mode of action of protection reactions

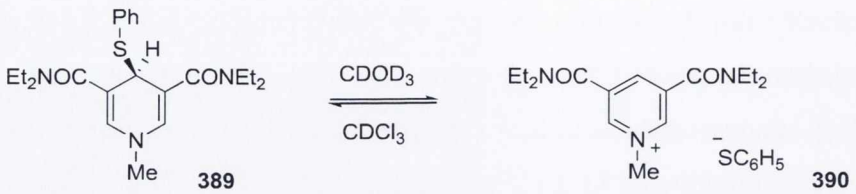
The preceding results, with respect to the activity of the imidazolium ion-based ionic liquid compounds, fortify our belief that the proposed mechanism, through which an alcohol nucleophile is adding to the C-2 position of the imidazole generating an acidic species *in situ* (Scheme 2.1), is accurate (which in turn supports the postulated mechanism with respect to the pyridinium ions functioning in the same manner). It was interesting to note that this mode of action could have implications with respect to a question, put forward by Kellogg in 1984 during an investigation into artificial hydrogenases, on the existence of an adduct derived from the addition of NAD^+ to the active site of a cysteine-derived thiol residue in biochemical processes, which involve enzymes like glyceraldehyde-3-phosphate dehydrogenases.[254] At the active site of this enzyme there is a reactive cysteine (Cys-149). This, in conjunction with catalytic action, was proposed to be involved in a yellow colour formation which is characteristic of the enzyme. It was initially observed by Racker and Krimsky[255] that the addition of a thiol based compound to NAD^+ at the C-4 position of the pyridinium ring generates the thiolate adduct **385**, this thiolate group can then be transferred, under neutral conditions, to compounds such as a phosphoester **386**, forming a thioester **388** and the pyridinium ion **387** (Scheme 4.1).[254]



Scheme 4.1 The transfer of the thiolate group from **385** to the ester **386** generating the pyridinium ion **387** and thioester **388**.

This transfer reaction, along with the fact that the maximum absorbance wavelength (λ_{max}) for thiolate addition products for either 3- or 3,5- substituted carboxamidopyridinium salts is 340-350 nm (depending on solvent),[256] may mean that addition of the thiolate to NAD^+ in the enzyme contributes to the aforementioned yellow colour formation (until this time this had generally been accounted for by charge-transfer explanations).[257] The generation of these thiolate adducts was determined to be solvent dependent (through investigations involving

both UV and ^{1}H NMR spectroscopic studies), with ionisation of the adduct occurring in solvents such as $CDCl_3$ (*e.g.* **389**). However, in more polar solvents such as $CDOD_3$ the pyridinium/thiolate ion pair (**390**) is observed (Scheme 4.2).[254]



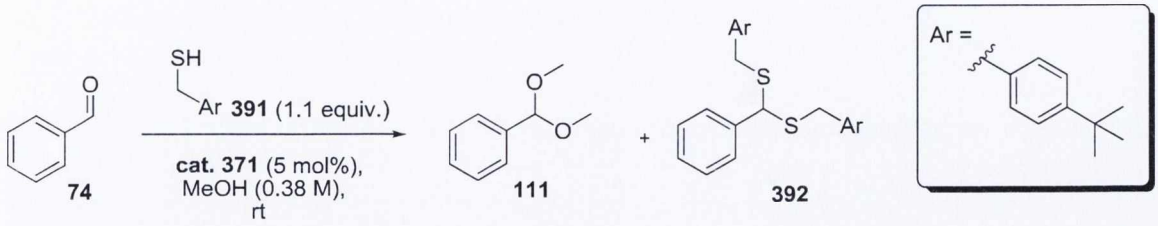
Scheme 4.2 Solvent effect on the generation of adducts **389** and **390**.

4.1.1 Preliminary investigation into the interactions between thiol derived substrates and imidazolium ion-based ionic liquids

The findings above piqued our interest in the interaction of thiols with our newly developed highly electrophilic imidazolium ion-based compounds, with a view to furthering our knowledge on the catalyst's mode of action. The preliminary investigation involved the observation of the products generated in the presence of the imidazolium ion-based compound **371**, benzaldehyde (**74**), *t*-butylbenzyl mercaptan (**391**) and MeOH.

The revelation that was to follow was extremely unexpected; the presupposed dimethyl acetal product **111** was formed after 24 h. However, the formation of the dithioacetal product also took place, affording **392** in a higher yield than the dimethyl acetal **111**, the ratio of **392** to **111** was approximately 3:1 (72:24). Due to this result the reaction was monitored, over a 24 h period, to determine the ratio of dimethyl acetal/dithioacetal formation over time, the results of this study are outlined below. The same reaction was monitored simultaneously employing *p*TSA as the acid catalyst (Table 4.1).

Table 4.1 Results of an investigation into the reactivity of **371** and *p*TSA in the presence of aldehyde **74**, thiol **391** and methanol.



Entry	Catalyst	Time (h)	Yield 111 (%)[a]	Yield 392 (%)[a]	Ratio (111: 392)
1	**371**	1	0	0	0: 0
2	*p*TSA	1	16	0	1.0:0.0
3	**371**	5	20	8	2.5:1.0
4	*p*TSA	5	58	23	2.5:1.0
5	**371**	10	22	45	1.0:2.1
6	*p*TSA	10	76	23	3.3:1.0[b]
7	**371**	24	24	73	1.0:3.0[b]
8	*p*TSA	24	76	23	3.3:1.0[b]
9	**371**	30	24	73	1.0:3.0[b]

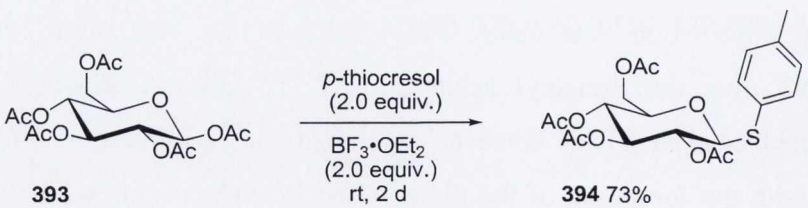
[a]Determined by ^{1}H NMR spectroscopy using an internal standard [b]Reaction had reached completion at this point.

From these studies it was found that, after 1 h no reaction took place (entry 1, Table 4.1). Nevertheless, in the presence of *p*TSA it was found that the predicted dimethyl acetal product was formed, with no formation of the dithiane **387** observed at this time (entry 2). After 5 hours, employing both catalysts it was determined that the formation of both the dimethyl acetal and the dithioacetal protected compound **392** occurs, with the protection of the aldehyde as the dimethyl acetal in both cases taking place more readily than dithioacetal formation. This resulted in a 2.5:1 ratio of **111**:**392** in the presence of both acid catalysts (with *p*TSA generating a higher overall yield of 81%, entries 3 and 4). After 10 h, an unexpected and interesting observation was made, **371** catalysed the preferential formation of the dithioacetal **392** over the dimethyl acetal in a 2.1:1 ratio of **392**:**111** (entry 5). The conventional acid catalyst *p*TSA however, promoted the reaction following the predicted reaction path, with the formation of the dimethyl acetal **111** ensuing with superior yields to the dithioacetal product formation **392** (entry 6). After 24 h, the formation of the dithioacetal product had continued in the presence of **371**, which catalysed the formation of the products **392** and **111** in a 3:1 ratio (entry 7). After the same time period, the ratio of products generated by catalysis with *p*TSA remained the same as that observed after 10 h (*i.e.* **111**:**392**,

3.3:1). The reaction involving **371** was continued for a further 24 h to determine if any supplementary change in the ratio of **111**:**371** occurred, however no change was observed. These preliminary results demonstrated an unforeseen predilection of the imidazolium ion for thiol-based compounds, a phenomenon we considered worthy of further investigation.

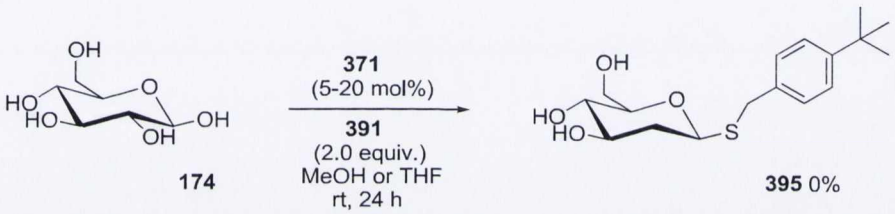
4.1.2 Investigation into the activity of 371 in the presence of thiol derived compounds: formation of thioglycosides

Glycosylation, *i.e.* the coupling of a glycoside donor and acceptor forming a glycoside, is one of the fundamental reactions employed in carbohydrate chemistry. Glycosidic linkage allows for the synthesis of polysaccharides, which are paramount in many biological processes.[258] The reaction occurs through the activation (generally by Lewis acid catalysis) of the leaving group at the anomeric position of the donor. The leaving group is eliminated *via* the formation of an oxocarbenium ion, to form an electrophilic anomeric carbon which reacts with the unprotected nucleophilic hydroxyl bond of the glycoside acceptor, thus generating a new glycosidic linkage between the two moieties.[258] The choice of leaving group at the anomeric position of the donor is therefore important. The OH group at this position (which requires activation by an acid) is the simplest form of leaving group, however more commonly employed leaving groups include halides, trichloroacetamides and thiols.[259] The formation of thioglycosides is a particularly popular method, first introduced by Fischer in 1909,[260] due to their relative stability under a number of conditions allowing for the manipulation of other PGs, a key criteria in carbohydrate chemistry. The most commonly employed method to generate these thioglycosides involves the reaction of the peracetylated sugar **393** with a thiol (*e.g. p*-thiocresol) in the presence of the Lewis acid (*e.g.* $BF_3{\cdot}OEt_2$) to generate **394** (Scheme 4.3).[261]



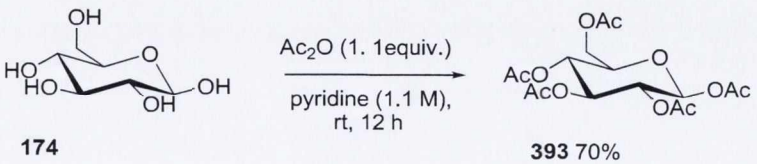
Scheme 4.3 Protection of the anomeric position of **393** with *p*-thiocresol catalysed by the Lewis acid $BF_3{\cdot}OEt_2$

Due to the activity of the imidazolium ion-based catalyst **371** in the generation of the dithioacetal **392** and, previously the cyclic dithiolane and dithianes **338** and **339** respectively, we were intrigued to find out if we could apply this catalyst activity to carbohydrate chemistry. Consequently, it was decided that we would determine if **371** could be utilised as a catalyst in the protection of the anomeric position of glucose with a thiol-based protecting group. We proposed that this would be extremely beneficial, as **371** is a more environmentally benign catalyst than the conventional Lewis acids currently employed. Our initial hypothesis involved the protection of the anomeric position of glucose (**174**) directly with **391**, without acetyl protection of the sugar, to form **395**, in either MeOH or THF at various catalytic loadings (5-20 mol%, Scheme 4.4). However, disappointingly, this reaction resulted in only starting material being recovered, due to solubility issues with the starting materials.



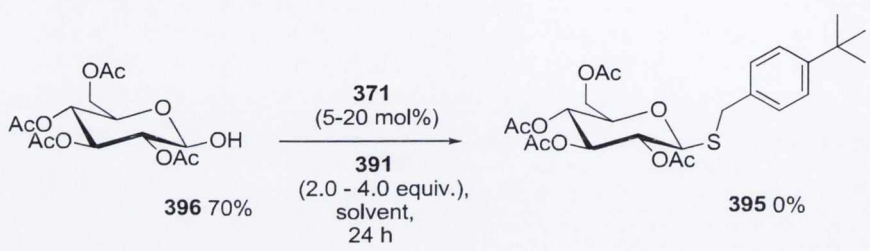
Scheme 4.4 The attempted protection of **174** with **391** catalysed by the imidazolium ion-based catalyst **371**.

We therefore carried out the acetyl protection of **174** in the presence of acetic anhydride and pyridine, generating compound **393** in 70% yield (Scheme 4.5). Whilst this circumvented the solubility issues associated with **174**, it was still found that, despite altering various parameters (*i.e.* solvent, temperature and catalyst loading), no formation of the desired thioglycoside was observed.



Scheme 4.5 Peracetylation protection of **174** with acetic anhydride.

We postulated that the fact that the anomeric position was now protected with an acetyl group, meant that the introduction of the thiol protecting group was a step too far for the mildly acidic catalyst **371**. We therefore, cleaved the acetyl protecting group at the anomeric position, using benzylamine, allowing for the more facile protection of the free anomeric OH of compound **396** with **391**, to afford the protected sugar **395** (Scheme 4.6).



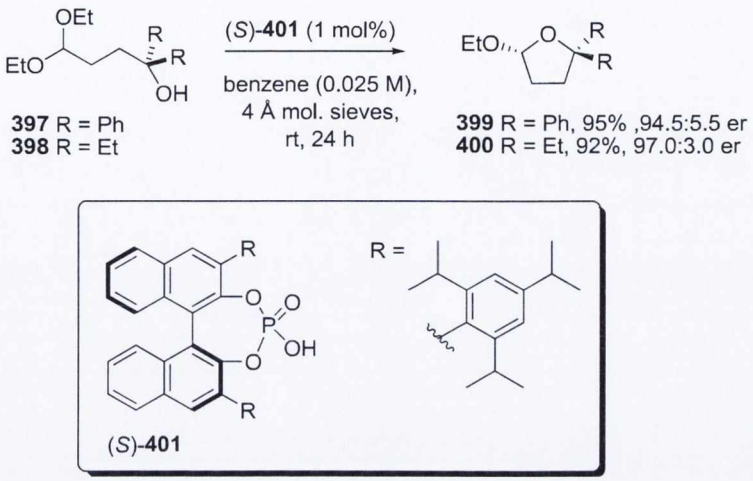
Scheme 4.6 Attempted protection of **396** with **391** in the presence of catalyst **371**.

Optimisation of the reaction conditions was undertaken including: a) the variation of solvents and solvent concentrations, (*e.g.* MeOH, THF, THF:MeOH and MeCN), b) increasing the reaction temperature/time and c) augmentation of catalyst (5-20 mol%) and thiol loadings. Disappointingly, the formation of the desired thioglycoside was once again not detected, with only starting material recovered. We postulated that the reason for the inactivity of the imidazolium ion-based catalyst may be accounted for by the stability of the cyclic glucose hemithioacetal, hence the generation of the thiol protected sugar (*i.e.* **395**) is probably beyond the limits of this mildly acidic imidazolium ion-based catalyst.

4.1.3 Transacetalisation reactions catalysed by imidazolium ion-based ionic liquids

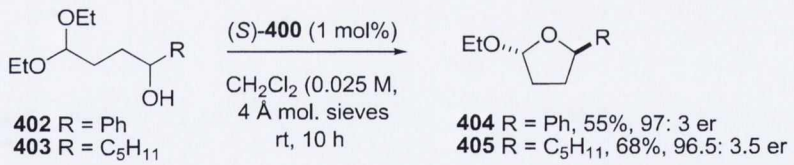
While, pondering our next step with respect to the investigation of the scope of the activity of catalyst **371** in various protection reactions, our attention was drawn to work carried out by List and co-workers in 2010.[262] They reported the use of a phosphoric acid-based Brønsted acidic catalyst in intramolecular asymmetric transacetalisation reactions. They carried out the transacetalisation reaction of various chiral alcohols in the presence of the Brønsted acidic catalyst (*S*)-**401**. Examples of these reactions include; the transacetalisation of the diphenyl functionalised alcohol **397**, yielding 95% of the cyclic product **399** with an enantiomeric ratio

(er) of 94.5:5.5. Use of the diethyl alcohol **398** afforded **400** in good yield with an enantiomeric ratio (er) of 97.5:3.5 (Scheme 4.7).[262]



Scheme 4.8 Representative examples of intramolecular transacetalisation reactions of chiral alcohols by List *et al.* employing the phosphoric acid-based catalyst (*S*)-**401**.

Later that year, the same group carried out the efficient atom-economic, kinetic resolution of achiral alcohols such as **402** and **403** in the presence of the same chiral phosphoric acid catalyst (*S*)-**401**, high enantiomeric ratios were again obtained (*e.g.* **404** and **405**, Scheme 4.9).[263]

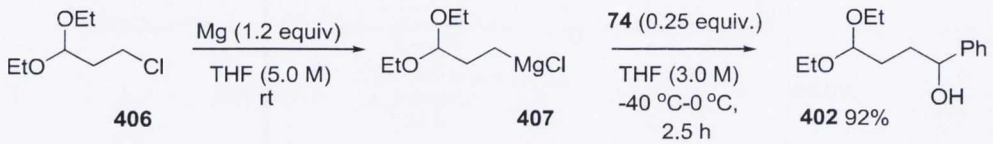


Scheme 4.9 Kinetic resolution of homoaldols *via* catalytic asymmetric transacetalisation.

4.1.4 Intramolecular transacetalisation: optimisation of reaction conditions (solvent screening)

We were interested to learn if the imidazolium ion-based catalyst **371** could catalyse a similar transacetalisation reaction employing achiral alcohols, and also potentially an unprecedented cyclisation of their thiol-derived equivalents. Transacetalisations usually require strong

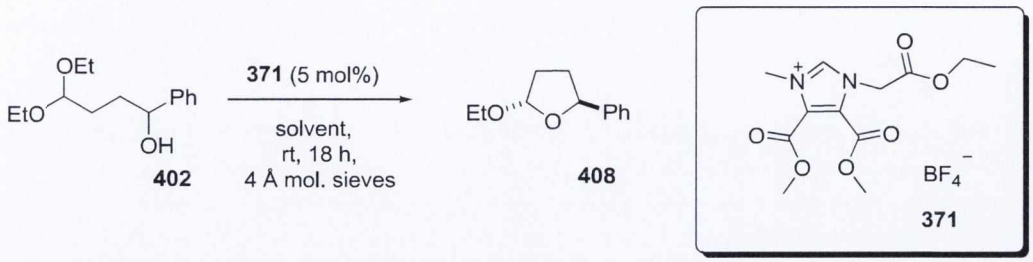
Brønsted acids, however this type of intramolecular transacetalisation should, in theory, be more amenable to a milder Brønsted acid catalyst such as **371**. Therefore, we performed the synthesis of the achiral alcohol substrate **402**, based on the procedure followed by List and co-workers.[263] The initial Grignard reagent was generated through the reaction 3-chloropropionaldehyde diethyl acetal (**406**) and Mg in THF, this was then reacted with distilled benzaldehyde (**74**) forming the desired alcohol moiety **402** in excellent yield (Scheme 4.10).



Scheme 4.10 Synthesis of alcohol **402**.

We based our preliminary reaction conditions on those previously employed by List *et al.* using 5 mol% of catalyst **339** at 25 °C for 18 h. However, the choice of solvent from the original study, (*i.e.* CH_2Cl_2), proved detrimental to the catalyst's activity, with no reaction taking place (entry 1, Table 4.2). We therefore, screened other solvents in which the catalyst is known to be active (*i.e.* MeOH, THF and MeCN) at various concentrations (entries 2-8, Table 4.2). From these preliminary studies THF was identified as the optimal solvent (entries 3, 5 and 6), while the efficacy of the reaction was also found to be highly concentration dependent with yields deteriorating at higher concentrations; (*e.g.* in THF (2 M), **408** was afforded in 79% yield (entry 3), while at 0.5 M concentration in the same solvent a yield of 93% of **408** was obtained). This trend was consistent with that reported by List and co-workers, in that higher product yields were obtained at lower reaction concentrations.[262,263]

Table 4.2 Investigation into the activity of catalyst **371** in the intramolecular transacetalisation of **402**: evaluation of optimum solvent medium.

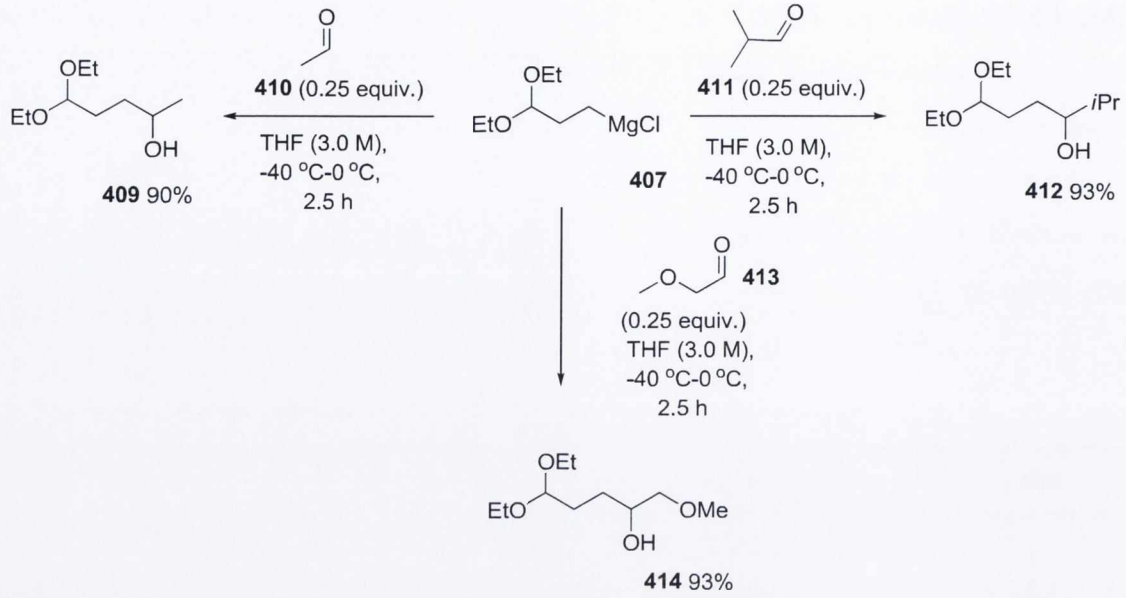


Entry	Solvent	Concentration (M)	Yield (%)[a]
1	CH_2Cl_2	2	0
2	MeOH	2	54
3	THF	2	79
4	MeCN	1	61
5	MeOH	1	56
6	THF	1	85[b]
7	MeCN	1	63
8	THF	0.5	93[b]

[a]Determined by H NMR spectroscopy using an internal standard [b]Isolated yield after chromatography

4.1.5 Intramolecular transacetalisation: substrate scope

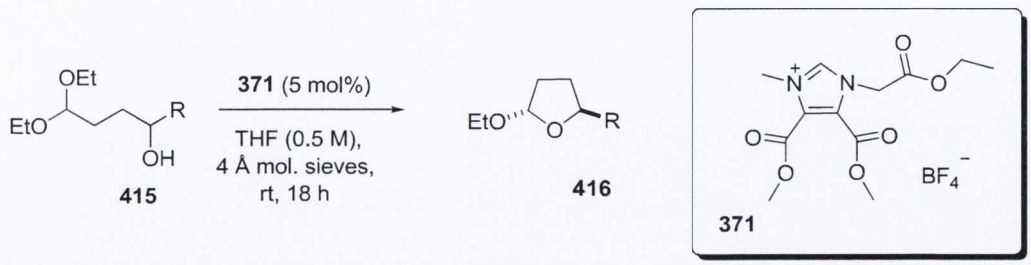
After establishing the optimum reaction conditions, an investigation into the substrate scope was undertaken. The generation of alcohols (where the phenyl group was replaced with groups such as Me, *i*Pr and CH_2OMe), was achieved following the same procedure used to prepare alcohol **402** (Scheme 4.10). The Grignard reagent **407** was reacted with aldehydes **410**, **411** and **413** to produce alcohols **409**, **412** and **414** respectively, in excellent yield (Scheme 4.11).

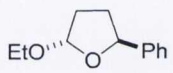
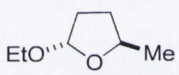
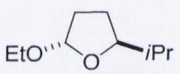
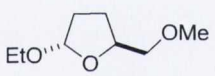


Scheme 4.11 Synthesis of alcohols (**409**, **412** and **414**) to evaluate the substrate scope of catalyst **371** in an intramolecular transacetalisation reaction.

The results of the intramolecular transacetalisation of these alcohols to generate the 2,5-substituted tetrahydrofurans in the presence of catalyst **371** are outlined in Table 4.3 below. Initially, the reaction was carried out in the absence of any catalyst where, as expected, no conversion to the cyclic product was observed. It was determined that the catalysis of the cyclisation of the alcohol possessing aromatic functionality *i.e.* Ph, was the most efficient, with the desired cyclic product **408** afforded in excellent yield (entry 1, Table 4.3). The catalysis of the formation of the cyclic aliphatic functionalised moieties also occurred, though to a lesser extent than with the aromatic alcohol, with the formation of the methyl group-containing ring structure **417** and the *i*Pr functionalised product **418** taking place, with satisfactory yields of the desired products recovered (entry 2 and 3). The reaction affording the ester containing structure **419**, also took place with a slightly lower yield (entry 4). The reaction to generate 2-ethoxy-5-phenyltetrahydrofuran (**408**) was also accomplished using *p*TSA as the acid catalyst, which catalysed the formation of the desired product in 85% yield after 18 h. This result displays the slight superiority of the imidazolium ion-based catalyst **371** in this reaction over the conventional acid catalyst *p*TSA.

Table 4.3 Imidazolium ion-based catalysis of intramolecular transacetalisation: substrate scope.

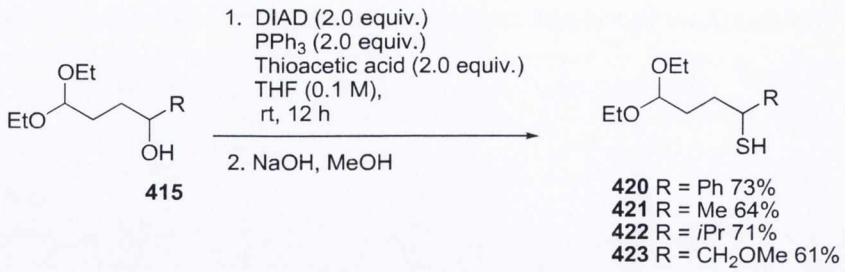


Entry	Product	Yield (%)[a]
1	 **408**	93
2	 **417**	75
3	 **418**	68
4	 **419**	59

[a]Isolated yield after chromatography

4.1.6 Intramolecular transthioacetalisations catalysed by 371

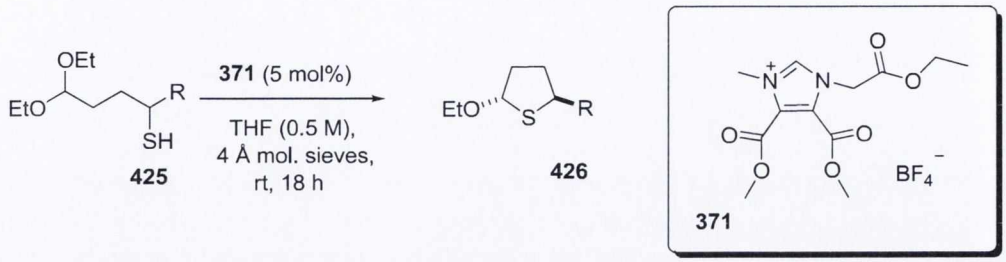
The selectivity observed in the protection of benzaldehyde as the dithioacetal in the presence of MeOH and the catalyst **371** (see Section 4.1.2), led us to postulate that, due to the activity of the imidazolium ion-based catalyst in the transacetalisation of alcohols outlined above (see Section 4.1.1), the cyclisation of thiol-based substrates should also occur in a similar fashion. We therefore synthesised the thiol-derived compounds (**420-423**) through a Mitsunobu reaction on the previously synthesised alcohols in the presence of DIAD, triphenylphosphine (PPh_3) and thioacetic acid (Scheme 4.12).

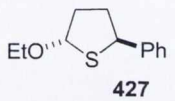
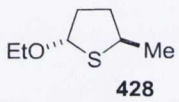
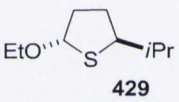
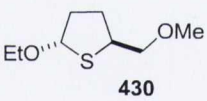


Scheme 4.12 Synthesis of thiol starting materials **420-423**.

The evaluation of catalyst **371** in the transthioacetalisation of thiols (**420-423**) was embarked upon, employing the same conditions as those used for the transacetalisation of alcohols (Table 4.3). The results of this study are outlined in Table 4.4 below. Gratifyingly it was found that the transthioacetalisation of these thiols in the presence of **371** occurred with good to excellent product yields (Table 4.4). The trend observed with the transacetalisation of alcohols, with respect to the presence of aromatic or aliphatic functionalisation, was observed again with these thiol-based compounds. The formation of the phenyl group containing tetrahydrothiophene **427** was promoted with an excellent yield (entry 1, Table 4.4), while the alkyl-substituted ring structures (*i.e.* **428** and **429**) were afforded with tolerable yields (entry 2 and 3). The most inefficient catalysis again occurred in the presence of the ester substituted thiol **423**, which afforded a moderate yield 52% of the desired compound **430** (entry 4).

Table 4.4 Evaluation of **371** in the transthioacetalisation of thiols **420-423.**



Entry	Product	Yield (%)[a]
1	 **427**	92
2	 **428**	70
3	 **429**	62
4	 **430**	52

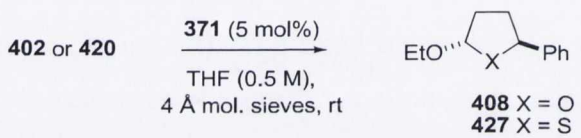
[a]Isolated yield after chromatography

It was also extremely interesting to note that, while *p*TSA catalysed the formation of the oxygen containing cyclic moieties, it was incapable of catalysing the cyclisation of these thiol-based compounds. The inability of the conventional acid to catalyse this reaction highlights that, as exhibited in the initial studies (Section 4.1.20), in the presence of thiols the mode of action of catalyst **371**, is inconsistent with that of conventional Brønsted acid catalysts. Furthermore, these results (with respect to the activity of the imidazolium ion-derived catalyst **371**) are satisfactory as they represent a new synthetic route for the production of these novel thiol-derived ring structures.

Additionally, the formation of **408** and **427** were monitored by ^{1}H NMR spectroscopy, to attempt to further elucidate the mode of action of these imidazolium ion-based catalysts. The

results of this study, in which it was observed that the rate of the reaction of the formation of the sulfur-containing compound **427** is greater than that of the oxygen-based ring structure **408**, are outlined below (entries 1-8, Table 4.5). It was observed that the majority of product formation occurs in the first 6 hours (entry 1), thereafter conversion increases more steadily until the optimal yield of 92% is reached after 18 h (entries 3, 5 and 7). Meanwhile, the catalysis of the formation of the oxygen derived moiety **408** occurs to a lesser extent (32% conversion) after 6 h (entry 2) with the product generated at a relatively steady rate over 18 h, when it reaches the optimal product yield obtained of 93% (entries 4, 6, and 8).

Table 4.5 Reaction rate investigation: monitoring the formation of **408** and **427** over 18 h.



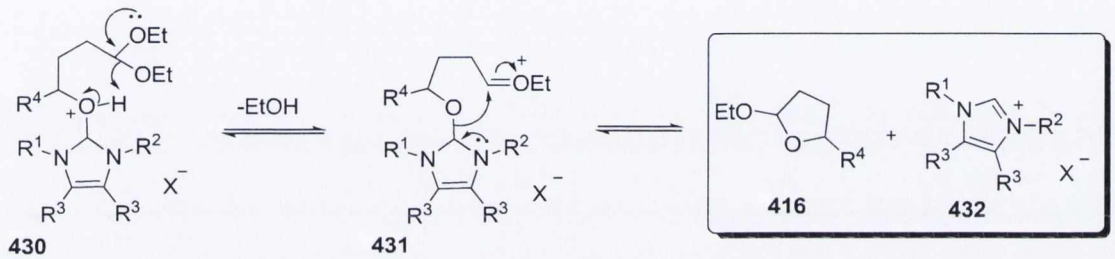
Entry	Product	Time (h)	Yield (%)[a]
1	**427**	6	63
2	**408**	6	32
3	**427**	10	75
4	**408**	10	42
5	**427**	12	88
6	**408**	12	70
7	**427**	18	92[b]
8	**408**	18	93[b]

[a]Determined by H NMR spectroscopy using an internal standard [b]Isolated yield after chromatography

4.1.7 Proposed mode of action for intramolecular transacetalisation and transthioacetalisation

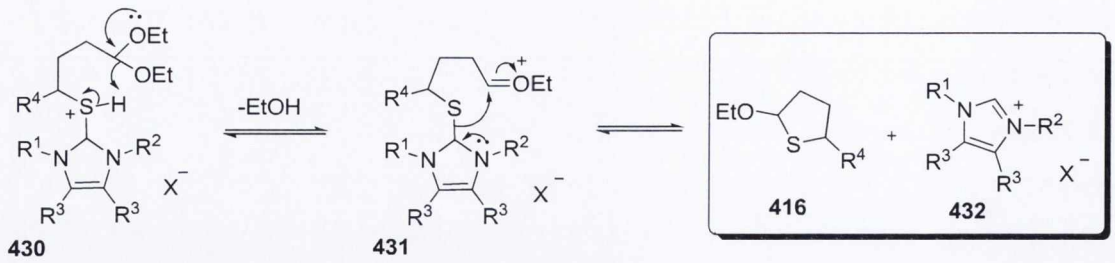
The catalysis of the dimethyl acetalisation of carbonyl compounds such as benzaldehyde has been proposed to occur through the generation of the catalytic moiety by the addition of MeOH to the C-2 position of the imidazolium core (Scheme 2.1). This addition has also been found to be facilitated by increasing the electrophilicity of the imidazolium ion core through functionalisation of the C-4/C-5 positions of the cation with electron withdrawing groups (Chapter 3).

The catalytic intramolecular transacetalisation of alcohol compounds (*e.g.* **402**, **409**, **412** and **414**) is postulated to occur through a similar mode of action to that proposed in the formation of the dimethyl acetal, with the addition of the alcohol nucleophile to the C-2 position of the electrophilic imidazolium cation (Scheme 4.13). This generates the intermediate **430**, which then forms the oxocarbenium ion intermediate **431**, the cyclisation of which is thought to be rapid, driven by the intramolecular nature of the reaction forming a 5-membered ring structure, resulting in the regeneration of the catalyst compound **432** and the generation of the desired 2,5-substituted tetrahydrofuran **416** (Scheme 4.13).



Scheme 4.13 Proposed mode of action of the imidazolium ion-based catalyst **371** in the intramolecular transacetalisation of alcohols.

With respect to the thiol-based compounds, it is suspected that the addition of the thiol occurs in a similar fashion to that of the alcohol at the C-2 position of the heterocyclic cation, allowing for the cyclisation of the moiety in the same manner as the alcohol. This addition leads to the generation of intermediate **433** which (as is the case with the alcohol derived compound) generates the oxocarbenium ion **434**, which cyclises rapidly to form **426** with the regeneration of catalyst **432** (Scheme 4.14). The result highlighting that the sulfur-containing ring structure is generated at a faster rate than the oxygen-containing ring structure, is to be expected if this mode of action is accurate- the positively charged sulfur intermediate **433** is going to be much more unstable than the equivalent oxygen-based intermediate **430**, leading to the more rapid generation of the oxocarbenium ion (which is believed to be the rate determining step).



Scheme 4.15 Proposed mode of action of catalyst **371** in the transthioacetalisation of thiol-derived compounds **420-423**.

This hypothesis, with respect to the generation of the proposed thiolate **433** is substantiated by the earlier report by Kellogg *et al.* in which a thiol will add to the C-4 position of a pyridinium moiety *i.e.* NAD^+ generating a reactive thiolate adduct (Scheme 4.1).[254] It is also supported by the results obtained with respect to imidazolium ion-based catalysis, which catalysed both the formation of dithioacetal **392** in the presence of MeOH and later in the generation of the 5-membered cyclic tetrahydrothiophenes in the presence of **371**. The activity of this imidazolium ion-based catalyst is in contrast to the conventional Brønsted acidic catalyst *p*TSA, in the presence of which no formation of the cyclic thiol-based product was observed.

4.1.7 Conclusions: imidazolium ion-based catalyst's mode of action for protection reactions

It can be demonstrated, from these studies, that the 4,5-substituted imidazolium ion-based compound **371** has the capacity to be highly active in the Brønsted acid catalysis of reactions with involving thiol-based moieties, including the dithioacetal protection of carbonyls and intramolecular ring-forming transthioacetalisation reactions. This ability is unusual, as it was also observed that these reactions, catalysed by **371**, did not take place to the same degree in the presence of the conventional BA catalyst *p*TSA. This has led to the development of a novel synthetic route, employing **371** as the catalyst, to generate cyclic 2,5-substituted tetrahydrothiophene-based compounds, along with contributing further to our understanding of the mode of action of these imidazolium ion-based ionic liquid catalysts.

This unusual reactivity was initially observed when, in the presence of MeOH and a thiol nucleophile, the dithioacetal protection of benzaldehyde took precedence over the expected, conventionally facilitated dimethyl acetal protection reaction, in the presence of catalyst **371**. This result implied that these imidazolium ion-based catalysts operate *via* a slightly alternative reaction pathway to conventional BAs in the presence of thiol-based reagents, for example, in the presence of *p*TSA the generation of the dimethyl acetal occurred to a greater degree, as expected, than the formation of the dithioacetal.

Consequently, we investigated whether this chemistry could be employed in the synthetically useful protection of the anomeric position of carbohydrate moieties to generate thioglycosides. However this reaction, disappointingly, proved beyond the scope of the catalyst, the inefficacy of which was probably contributed to by the stability of the hemithioacetal generated in these reactions.

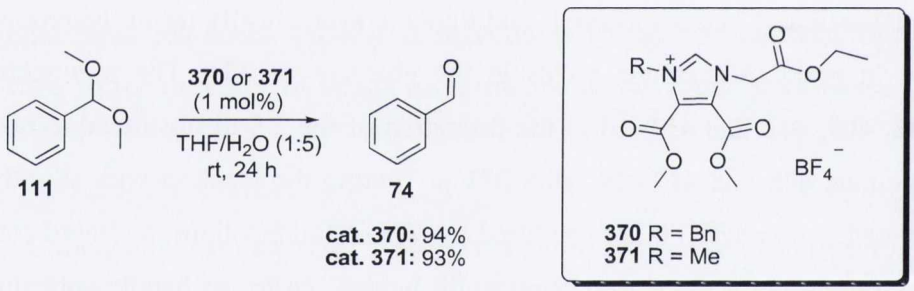
Gratifyingly, it was observed that the intramolecular transacetalisation and the transthioacetalisation of various alcohols and thiols to synthetically useful heterocycles could be achieved in good to excellent yields in the presence of **371**. The transacetalistion of alcohols **402**, **409**, **412** and **414** led to the formation of the 2,5-disubstituted tetrahydrofuran based compounds **408** and **417-419**, with **371** promoting the reaction with slightly superior yields generated compared to those catalysed by *p*TSA. Imidazolium ion-based catalyst **371**, in this case, represents a more environmentally benign, easier to handle substitute for the more corrosive, customary acid catalysts.

The most notable result from this study was however, the formation of the cyclic sulfur containing compounds **427-430**. The cyclisation of thiols **420-423** occurred in the presence of **371** in good to excellent yields, at ambient temperature. This result was particularly satisfactory as, in the presence of *p*TSA, there was no formation of the desired cyclic products observed. This led to the discovery of a new synthetic route for the formation of novel sulfur containing ring systems, as well as furthering our understanding of the activity of these imidazolium ion-based compounds as acid catalysts.

5.1 Imidazolium ion-based catalysis: acid-catalysed deprotection reactions

One of the main problems encountered in protecting group chemistry, is the identification of a reagent which can induce the selective deprotection of one protecting group in the presence of another.[108,111] Due to the mild Brønsted acidity of the imidazolium ion-based catalyst **371** (the activity of which has been demonstrated in the preceding chapters), we postulated that perhaps this catalyst could encourage the deprotection of one acid-labile protecting group in the presence of another.

We have already discovered, during our preliminary evaluation of the second generation imidazolium ion-based catalysts, that compound **370** can catalyse the hydrolysis of the benzaldehyde derived dimethyl acetal **111** in high yields. It was also determined, that employing the more environmentally benign catalyst **371**, under the same conditions, resulted in promotion of the reaction with similarly high yields of aldehyde **74** (Scheme 5.1).

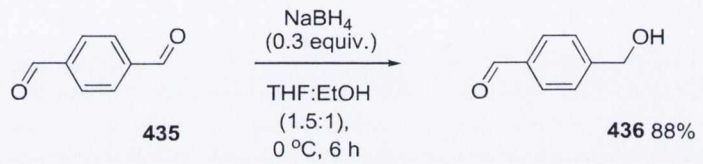


Scheme 5.1 Hydrolysis of **111** catalysed by imidazolium ion-based ionic liquids **370** and **371**.

Consequently, we decided to attempt to achieve selective deprotection, in the presence of **371**, of compounds containing a dimethyl acetal protecting group and other acid-labile protecting groups (specifically the alcohol protecting groups, trimethylsilyl (TMS), tetrahydropyran (THP) and methoxymethyl (MOM) protecting groups).

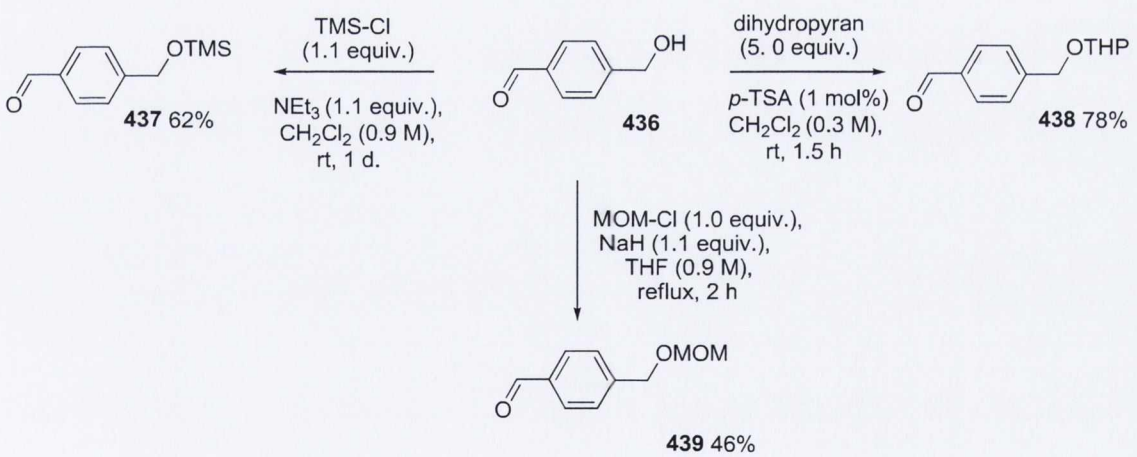
5.1.1 Selective deprotection reactions employing Brønsted acidic imidazolium ion-based catalysts: synthesis of protected moieties for catalyst evaluation

To evaluate the ability of catalyst **371** to promote the selective deprotection of acid-labile protecting groups, the initial protection of the aldehyde and alcohol-functionalised aromatic compound **436** was undertaken. The desired product was afforded through the reduction of one of the aldehyde functional groups of the commercially available starting material terephthaldehyde (**435**), following a procedure by Loim *et al.* outlined below,[264] producing **436** in good yield (Scheme 5.2).



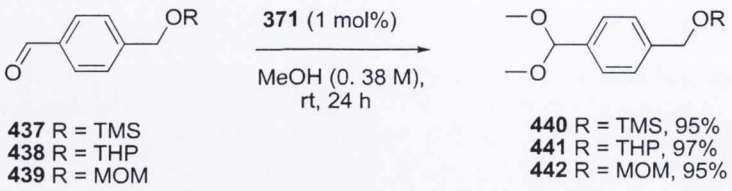
Scheme 5.2 Reduction of *bis*-aldehyde **435** to alcohol **436**.

The protection of the alcohol functionality in **436** was then undertaken using TMS (A, Scheme 5.3), THP (B, Scheme 5.3) and MOM protecting groups (C, Scheme 5.3).



Scheme 5.3 Protection of the alcohol functionality of **436**.

Following the initial protection of the alcohol, the dimethyl acetal protection of the carbonyl group of **437-439** was achieved employing imidazolium ion-based catalyst **371** in MeOH. This promoted the generation of compounds **440-442** in excellent yield (Scheme 5.4).



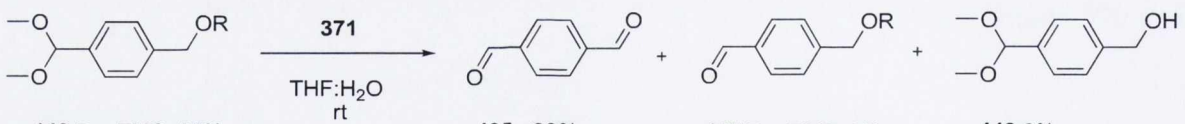
437 R = TMS
438 R = THP
439 R = MOM

440 R = TMS, 95%
441 R = THP, 97%
442 R = MOM, 95%

Scheme 5.4 Dimethyl acetal protection of carbonyl group of **437-439** catalysed by **371**.

5.1.2 Selective deprotection reactions employing Brønsted acidic imidazolium ion-based catalysts: catalyst evaluation

With the *bis*-protected compounds **440-442** in hand, the evaluation of the ability of **371** to promote the selective deprotection of either the carbonyl or alcohol protecting groups of these compounds was undertaken. The activity of acetic acid as a catalyst was also evaluated in parallel to the reactions involving **371**. Disappointingly, despite changing parameters such as catalyst loading, solvent, reaction time and temperature, the deprotection of both protecting groups occurred affording **435** as the final product, with the formation of neither **437-439** nor **443** being observed (Scheme 5.5).



440 R = TMS: 95%
441 R = THP: 97%
442 R = MOM: 95%

435 >98%

437 R = TMS, 0%
438 R = THP, 0%
439 R = MOM, 0%

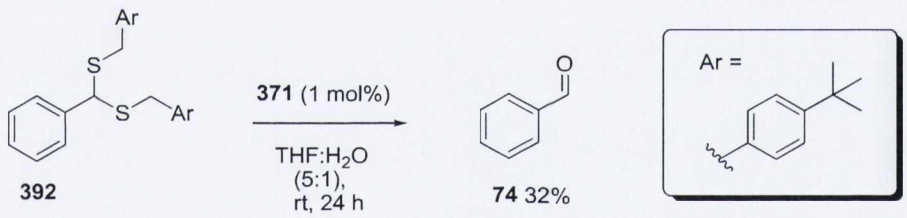
443 0%

Scheme 5.5 Deprotection of **440-442** using catalyst **371**: evaluation of catalyst activity.

Although we did not obtain the desired results from this study, it was interesting to note that the catalyst **371** is not limited to deprotection of acetal protected moieties, it can also catalyse the deprotection of other acid-labile protecting groups.

5.1.3 Deprotection chemistry employing imidazolium ion-based catalysts: the deprotection of dithioacetals

While the facile deprotection of dimethyl acetals in the presence of a mild acid catalyst in aqueous solution is widely known, the more arduous task of developing an environmentally benign, mild yet effective reagent for the deprotection of the highly stable, synthetically useful dithiane group is a major issue with respect to protecting group chemistry.[187,188,204,205] The ability of catalyst **371** to promote the deprotection of the **111** to **74**, (along with the recently discovered ability to carry out the full deprotection of compounds **440-442**) at relatively low loadings has been noted. Due to this activity, along with the discovery that these imidazolium ion-based catalysts showed a propensity (not observed with conventional catalysts such as *p*TSA), for dithioacetal formation, we were intrigued to determine if **371** could be employed to promote the deprotection of dithoacetals and dithianes. Therefore, we performed a reaction to evaluate the ability of **371** to catalyse the deprotection of the dithioacetal **392** to generate its parent aldehdye **74** (Scheme 5.6).



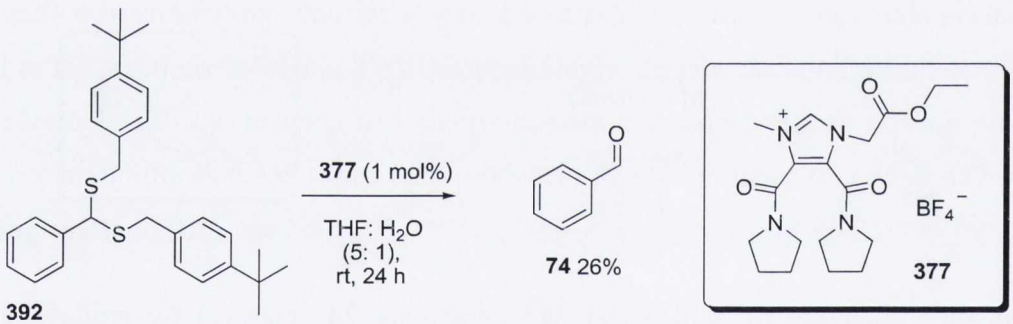
Scheme 5.6 Cleavage of dithioacetal **392** generating **74** catalysed by imidazolium ion-based ionic liquid catalyst **371**.

It was determined that the imidazolium ion-based catalyst initiated the cleavage of the dithioacetal protecting group in compound **392**, regenerating its parent aldehyde **74** in 32% yield. Despite the low yield generated by this reaction in the presence of **371**, the result was promising as it was noted that, the employment of a conventional acidic catalyst (*i.e.* *p*TSA), under the same conditions, resulted in negligible yield of the desired aldehyde product (~2%). It was also determined that the presence of the electron withdrawing groups at the C-4 and C-5 positions of the heterocyclic cation core were again important, as the unsubstituted catalyst **309** was found to be completely ineffective in promoting this reaction, with 0% aldehyde

obtained. From these results, it was decided that the use of catalyst **371** in this reaction warranted further investigation.

5.1.4 Imidazolium ion-catalysed deprotection reactions: optimisation of reaction conditions for cleavage of an acyclic dithioacetal

As a consequence of the activity exhibited by **371** in the cleavage of dithioacetal **392**, the optimisation of the reaction conditions was undertaken to determine if the reaction could be promoted with synthetically useful yields. The efficacy of the *bis*-amide substituted imidazolium ion-based catalyst **377** was established to determine if the stability/instability of the tri-ester **371** in aqueous media over time, was perhaps contributing to the generation of **74** in such a low yield. However, it was determined that **377**, although active, was less efficacious than **371** (as had previously been observed in dimethyl acetal formation reactions, Section 2.1.1 and 3.1.7), promoting the generation the desired aldehyde product in 26% yield (Scheme 5.7).

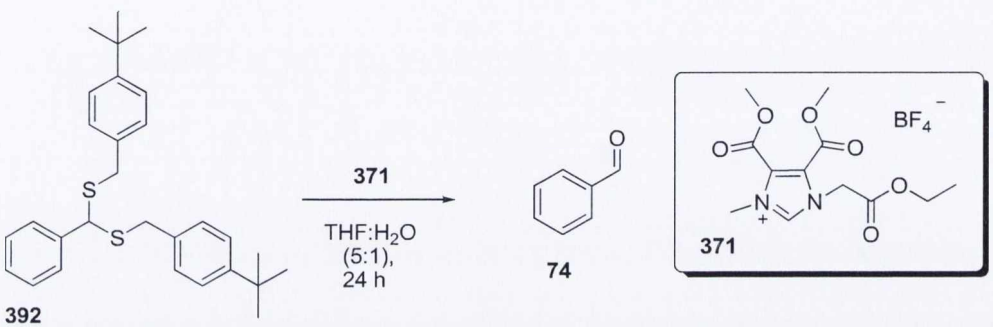


Scheme 5.7 Deprotection of **392** catalysed by the amide-substituted imidazolium ion **377**.

Focusing on the ester-based catalyst, catalyst loading was the first parameter investigated in these optimisation studies. The quantity of catalyst employed was therefore incrementally increased from 1 to 20 mol% and the catalytic activity was evaluated. The effect of elevated temperatures was also investigated at each of the loadings (entries 1-7, Table 5.1). From this investigation it was established that there was a marked increase in the amount of aldehyde generated when the catalyst loading was augmented from 1 to 5 mol% (entries 1-2) and again from 5 to 10 mol% (entries 2-4 and 3-5). It was interesting to note that doubling the catalyst loading from 10 mol% to 20 mol% (entries 4 and 6, and 5 and 7) had little effect on the

activity of product yield. It was also recognised that an increase in temperature led to an augmentation (albeit small) in product yield (*e.g.* entries 4-5, Table 5.1).

Table 5.1 Optimisation of reaction conditions for the deprotection of dithioacetal **392** catalysed by **371**: effect of an increase in catalyst loading and reaction temperature.

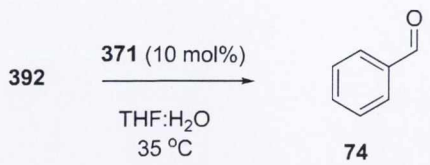


Entry	Loading (mol%)	T (°C)	Yield (%)[a]
1	**1**	25	32
2	**5**	25	40
3	**5**	35	43
4	**10**	25	59
5	**10**	35	63
6	**20**	25	61
7	**20**	35	63

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

The modification of solvent ratio (THF:H_2O) was consequently embarked upon, using the newly discovered optimal catalyst loading (10 mol%) at 35 °C. The results of these studies are outlined below (Table 5.2). It was found that, as could be expected, an increase in the amount of H_2O with respect to THF resulted in an incremental rise in the conversion of **392** to **74** (entries 1-6, Table 5.2). However, when the ratio was increased to 1:2 (THF:H_2O), it was found that a decrease in catalytic activity was observed (entries 7 and 8). This phenomenon was probably due to the degradation of the catalyst in a highly aqueous medium. The reaction time was also extended from 24 h to 48 h, however this resulted in only a slight increase in product yield (Table 5.2).

Table 5.2 Optimisation of reaction conditions for the deprotection of dithioacetal **392** catalysed by **371**: evaluation of the effect of changing the solvent ratio and reaction time.



Entry	Solvent ratio	Time (h)	Yield (%)[a]
1	5:1	24	63
2	5:1	48	65
3	2:1	24	68
4	2:1	48	71
5	1:1	24	75
6	1:1	48	79
7	1:2	24	36
8	1:2	24	37

[a]Determined by ^{1}H NMR spectroscopy using an internal standard

The optimum conditions were determined to involve 10 mol% loading of **371** in a (1:1 *v/v*) THF: H_2O solvent medium. In this solvent the catalysis of the hydrolysis of the acyclic dithioacetal molecule took place, generating benzaldehyde in high yield after 48 h (entry 6, Table 5.2). This result was gratifying in that there are no existing methods of this type deprotection, employing such a mild form of acid catalyst, to date. However, we were interested in determining if this catalyst's activity could be further exploited in the deprotection of the much more synthetically useful cyclic 5-membered dithiolanes and 6-membered dithianes.

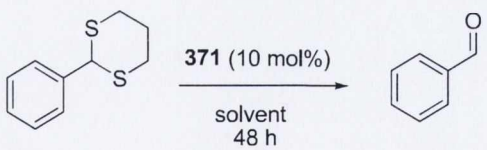
5.1.5 Imidazolium ion-catalysed deprotection reactions: optimisation of reaction conditions for the cleavage of dithianes

Dithianes are not only popular protecting groups,[167,172,179] due to their stability, they are also highly synthetically useful due to their ability to be deprotonated by *n*-BuLi or *t*-BuLi to form an anion which can react with a wide variety of reagents to form new C-C bonds as discussed in Section 1.5.[163,165,166] It has also been highlighted in the same discussion, that the removal of this group, to its detriment, proves particularly laborious, with many methods having been

developed through the years (generally requiring stoichiometric loadings and harsh reaction conditions), yet the most effective and commonly used reagents are the toxic and environmentally precarious mercury-based compounds *e.g.* $HgCl_2$ and $Hg(ClO_4)_2$. There is therefore a niche for a more environmentally sound, mild method for the catalysis of the deprotection of these moieties (see Sections 1.52-1.54). Hence, due to the relative efficacy of **371** in the deprotection of dithioacetals, we set about developing the reaction conditions necessary to cleave the dithiolane **338** and dithiane **339** in the presence of this imidazolium ion-based catalyst.

Initial optimisation was carried using dithiane **339**, which was evaluated employing the hitherto most advantageous conditions used for the hydrolysis of **392**. It was found under these circumstances that the reaction was promoted, however with a relatively low product yield (entry 1, Table 5.3). An increase in temperature from 35 °C to 65 °C, led to an increase in aldehyde formation with **74** afforded in 54% yield (entry 2). After numerous experiments in this solvent, it was decided that a change of solvent system may be beneficial, in order to allow for a further increase in temperature to 80 °C, therefore THF was replaced by 1,4-dioxane in a 2:1 ratio with water (*i.e.* dioxane:H_2O, 2:1, entry 3). Gratifyingly, it was found that in this solvent mixture (at 100 °C) compound **371** promoted the hydrolysis of dithiane **339** affording 76% of the desired aldehyde **74** (entry 4).

Table 5.3 Optimisation of conditions for the cleavage of dithiane **339** promoted by catalyst **371**.

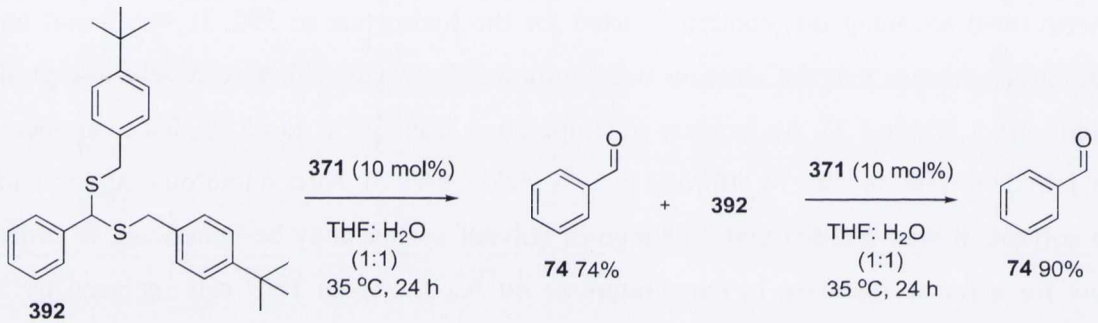


339 **74**

Entry	Solvent	Ratio	Temp (°C)	Yield (%)[a]
1	THF: H_2O	1:1	35	38
2	THF: H_2O	1:1	65	54
3	1,4-dioxane: H_2O	2:1	80	67
4	1,4-dioxane: H_2O	2:1	100	76

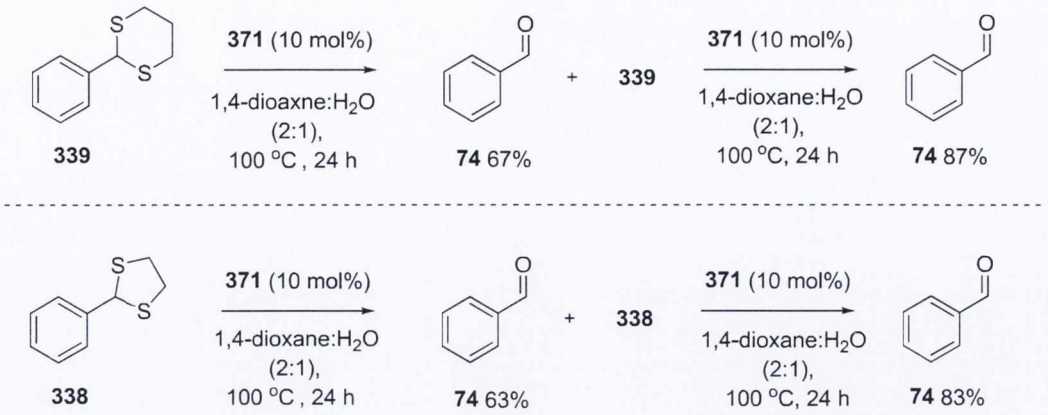
[a]Determined by ^{1}H NMR spectroscopy using an internal standard

At this point we questioned whether the fact that the catalyst was promoting the reaction with yields below 80% was due to it either the system reaching equilibrium under these conditions or the catalyst degrading due to hydrolysis/thiolysis. This would also explain the *plateau* in catalytic activity when increasing the loading from 10-20 mol% in the dithioacetal deprotection. Consequently, we evaluated the efficacy of **371** in the promotion of the hydrolysis of the acyclic moiety **392** (under similar conditions to entry 6, Table 5.2), in which we initially added 10 mol% of **371** for 24 h, after which time a further 10 mol% of the imidazolium ion-based catalyst was added (Scheme 5.8). It was found that under these conditions the yield of **74** increased from 79% to 90%.



Scheme 5.8 Hydrolysis of dithioacetal **392** in high yield through the addition of 2 x 10 mol% of **371** over 48 h.

Accordingly, the hydrolysis of dithiane **339** and dithiolane **338** in a 1,4-dioxane:H_2O (2:1) medium was carried, employing a similar procedure to that outlined in Scheme 5.8, with the catalyst promoting the cleavage of the thiol protecting groups of **339** and **338,** generating **74** in highly satisfactory, synthetically useful yields (Scheme 5.9).

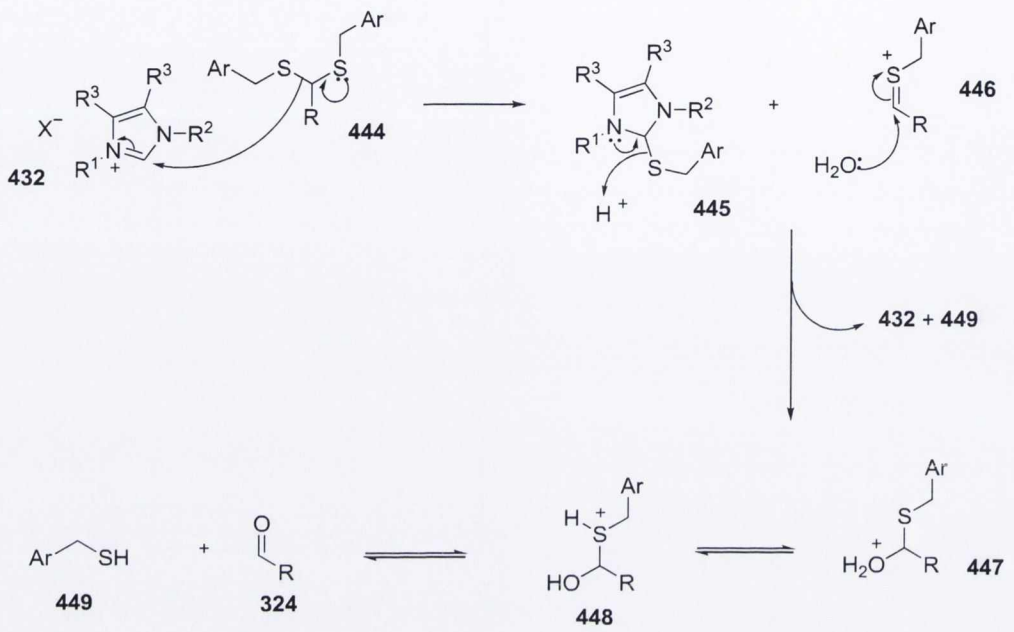


Scheme 5.9 Optimised reaction conditions for the deprotection of **339** and **338** in the presence of **371**.

5.1.6 Proposed mechanism for cleavage of dithioacetals/dithianes by imidazolium ion-based catalyst 371

From the results above we postulated that catalyst **371** promotes the cleavage of the dithioacetal/dithiane based moieties, due to an affinity of sulfur for the C-2 position of the imidazolium heterocycle **371**. The propensity for sulfur to add to this position has already been observed in the transthioacetalisation reactions discussed in Section 4.1.6. It is thought that dithioacetal **444** will cleave to form intermediates **445** and **446**, with the cleaved thiol forming a new sulfur-carbon bond at the C-2 position of the electrophilic imidazolium cation **432**. The propensity of the thiol to form this bond with the heterocyclic core (*i.e.* intermediate **445**), may be contributed to by soft-soft interactions between the sulfur nucleophile and the highly electrophilic imidazolium ion. The formation of this intermediate **445** is believed to be the rate-determining step in this reaction, it is noted that the electron withdrawing groups are extremely important in the formation of this intermediate (as was found to be the case with regards to protection chemistry, Chapters 2-4), as the unsubstituted catalyst showed no activity in preliminary studies. **445** can then react in the presence of acid (conceivably formed from the addition of water to **432**, in a similar fashion to that postulated to occur in the presence of other protic nucleophiles), cleaving the thiol functionality and regenerating the imidazolium ion-based catalyst **371** and the thiol **449**. The restoration of aromaticity to the heterocyclic core is highly likely to be the driving force behind this reaction. Meanwhile, the intermediate **446**, formed simultaneously with **445**, is extremely unstable, this will react rapidly with H_2O present in the reaction medium, generating **447** in equilibrium with **448**,

which in turn will react swiftly generating the desired parent aldehyde **324** and the thiol **449** (Scheme 5.10).



Scheme 5.10 Proposed mode of action for imidazolium ion-based catalyst **371** in the deprotection of dithioacetal protected aldehydes.

The results regarding the efficacy of this catalyst in these deprotection reactions and the proposed mode of action with respect to its catalytic activity, enables us to provide further supporting evidence for our existing theory in relation to the mechanism of this catalyst, in both protection and deprotection reactions involving aldehydes, alcohols and thiols.

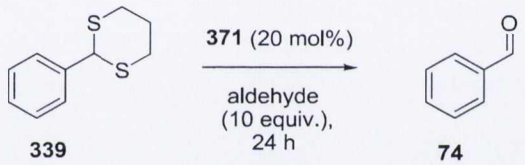
5.1.7 Imidazolium ion-catalysed dithiane deprotection reactions: an alternative method for the cleavage of dithianes

During the optimisation of reaction conditions for the hydrolysis of dithianes in aqueous media a number of obstacles were encountered and overcome. However, an alternative method was designed to facilitate the cleavage of dithiane **339** in the presence of catalyst **371**. This method involved the optimisation of a procedure in which a simple 'sacrificial' aldehyde would be added to the reaction mixture, under anhydrous conditions. The theory behind the addition of a second aliphatic aldehyde moiety (*i.e* the 'sacrificial' aldehdye) was, that this would form a new dithiane-protected compound in the presence of any dithiol (*i.e.* 1,3-

propanedithiol), generated during the cleavage of **339**. As long as the 'sacrificial' aldehyde was cheaper to be more reactive in dithiane-formation, we reasoned that clean deprotection should result.

For this reason the reaction of **339** was undertaken, in the presence of a few selected aliphatic aldehydes-chosen because of the ease of formation of their dithiane protected forms compared to aromatic aldehydes, along with the fact that they are readily available and relatively inexpensive. The optimised reaction conditions are outlined below (Table 5.4). The reactions were carried out at a temperature just below the boiling point of the respective 'sacrificial' aldehydes.

Table 5.4 Deprotection of dithiane **339**: an alternative method employing a 'sacrificial aldehdye'.



339 **74**

Entry	Aldehyde	Temp (°C)	Yield (%)[a]
1	propanal	45	81
2	butanal	72	80
4	pentanal	100	79

[a]Isolated yield after column chromatography

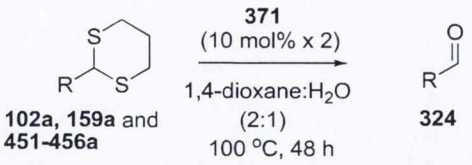
The results obtained were extremely satisfactory, in that the presence of each of the selected aliphatic aldehydes allowed for the deprotection of **339** to **74** in good yield (entry 1-3, Table 5.4). It was particularly pleasing that the reaction was most efficient in propanal at a relatively low temperature, when compared to conventional hydrolysis carried out previously (which was carried out at 100 °C), whilst still affording synthetically useful yields of the desired aldehyde (entry 1). Butanal and pentanal also proved effective in this reaction albeit at higher temperatures (entry 2 and 3). The addition of the catalyst was also required in only one portion, as the problems encountered with the conventional hydrolysis (*i.e.* the regeneration of the protected compound **339** over time) was counteracted by the generation of the aliphatic dithiane. These results are pleasing as they give the practitioner a second option when

employing catalyst **371** in the deprotection of dithianes, that does not require the use of aqueous conditions, which may be useful when removing a dithiane moiety from a molecule which contains other groups sensitive to aqueous acidic hydrolysis.

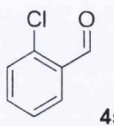
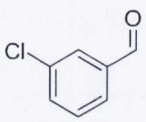
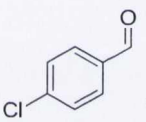
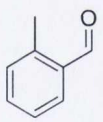
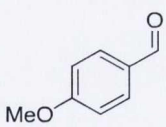
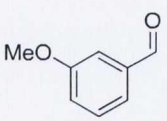
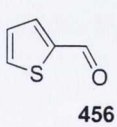
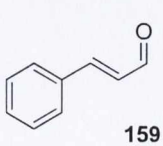
5.1.8 Imidazolium ion-catalysed dithiane deprotection reactions: evaluation of substrate scope

With an efficient procedure developed (*i.e.* that employed in Scheme 5.9), the evaluation of the activity of catalyst **371** in the deprotection of various aldehyde-derived dithianes was carried out (Table 5.5). Catalyst **371** could catalyse the cleavage of activated- (*i.e.* **451-453** and **455**, entries 1-3 and entry 6), hindered- (*i.e.* **454**, entry 4) deactivated- (*i.e.* **102**, entry 5), heterocyclic- (*i.e.* **456**, entry 7) and α, β-unsaturated dithianes (*i.e.* **159**, entry 8) with good to excellent isolated product yields (Table 5.5).

Table 5.5 Catalytic deprotection of aldehyde-derived dithianes in the presence of **371**: evaluation of substrate scope.



102a, 159a and **451-456a** → **324**

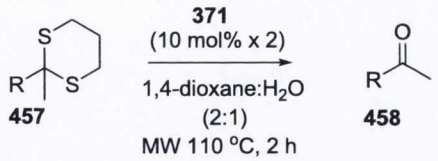
Entry	Product	Yield (%)[a]
1	 **451**	78
2	 **452**	86
3	 **453**	84
4	 **454**	65
5	 **102**	76
6	 **455**	74
7	 **456**	78
8	 **159**	85

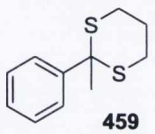
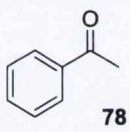
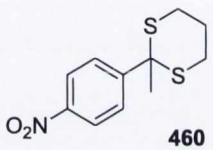
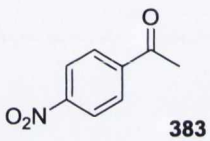
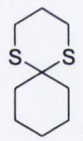
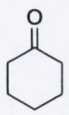
[a]Isolated yield after chromatography.

The catalytic activity of **371** in the hydrolysis of ketone-derived dithianes was also investigated. The initial evaluation was undertaken employing the optimised conditions which had proven successful in the hydrolysis of dithiane-protected aldehydes. However, under these conditions the reaction involving dithiane-protected acetophenone (**459**), *p*-nitroacetophenone (**460**) and cyclohexanone (**461**) resulted in the recovery of only starting material. This result was unsurprising, as the cleavage of dithiane protected ketones is known to be more arduous than that of their aldehyde-derived counterparts (Sections 1.52 and 1.53).

Consequently, we performed the reaction under harsher reaction conditions than those previously used *i.e.* the deprotection of the dithiane protected ketones **459** and **460** was accomplished with microwave irradiation at 110 °C for 2 h, in dioxane:H_2O solvent mixture (Table 5.6). Under these conditions, it was found that in the absence of catalyst some hydrolysis of the dithiane was observed (~15%), whilst in the presence of *p*TSA a similar amount of the ketone **78** was afforded (18%). However, in the presence of catalyst **371** a marked increase in product yields was observed; acetophenone (**78**) was isolated in 46% yield (entry 1, Table 5.6), whilst the more activated ketone *p*-nitroacetophenone (**383**) was generated in a higher but still moderate yield (entry 2) and the highest yield was observed in the synthesis of cyclohexanone (**23**, entry 3, Table 5.6).

Table 5.6 Catalytic deprotection of ketone-derived dithianes.



Entry	Substrate	Product	Yield (%)[a]
1	 **459**	 **78**	46
2	 **460**	 **383**	52
3	 **461**	 **23**	58

[a]Isolated yield after chromatography.

The lower yields (and harsher conditions required) associated with the deprotection of these ketone-based dithianes, when compared to the aldehyde-based dithianes, may be explained by the catalyst's proposed mode of action in these reactions. The proposed rate-determining step in this reaction is thought to be the attack of the dithiane at the C-2 position of the imidazolium cation. The inefficiency with respect to the cleavage of the ketone-derived dithiane may be contributed to by its larger steric bulk as outlined in Figure 5.1 below. When R^4 is H, this allows for the relatively facile addition of the thiol to the C-2 position of the heterocycle, however substitution by a methyl group (at R^4) will contribute to the more arduous formation of this intermediate due to steric hindrance, hence resulting in lower yields.

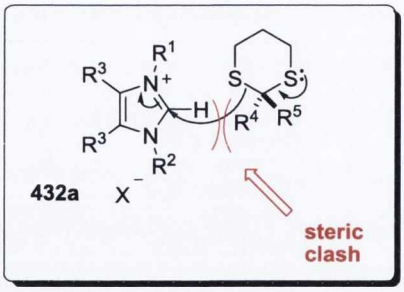


Figure 5.1 Postulated steric clash in the hydrolysis of ketones during concerted cleavage of the dithiane and addition of the thiolate to the C-2 position of the imidazolium ion-based catalyst.

5.1.9 Conclusion: imidazolium ion-catalysed dithioacetal/dithiane deprotection reactions

A new catalytic reagent for the synthetically useful deprotection of dithioacetal and dithiolane/dithiane protected moieties has been discovered, with both an aqueous and an anhydrous method developed, employing imidazolium ion-based catalyst **371**. This discovery is satisfactory as it represents a new, environmentally benign catalytic method through which the usually arduous cleavage of dithianes can be achieved. This is also particularly gratifying as existing methods (see Section 1.5.2 and 1.5.3) either involve the use of toxic, environmentally precarious mercury, iodine-based reagents or the employment of reagents in stoichiometric amounts.

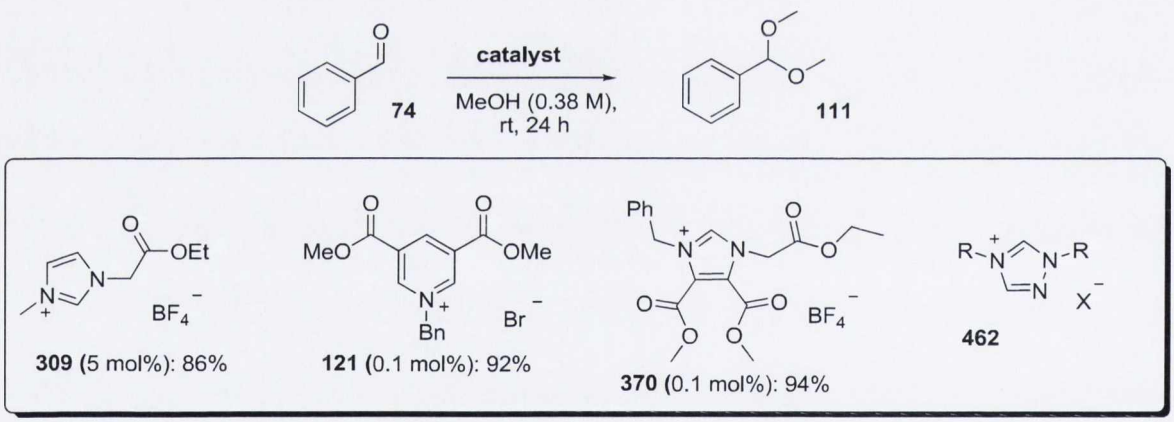
Catalyst **371** has been found to promote the deprotection of various dithiane and dithiolane protected aldehydes in good-excellent yields under relatively mild conditions, using low catalyst loadings (20 mol%). The cleavage of these thiol-based protecting groups can be accomplished through a conventional hydrolysis in the presence of catalyst and H_2O and also by an alternative anhydrous method, in which an aliphatic aldehyde is used to drive the reaction to completion, without the need for the addition of any H_2O which may be detrimental to some reactions. The hydrolysis of ketone-based dithianes can also be promoted in the presence of **371**, albeit less successfully.

As was the case with the transthioacetalisations (see Section 4.1.6), the use of *p*TSA as the acid catalyst in this reaction proved ineffective in comparison to the imidazolium ion-based

catalyst **371**. This result strengthens our conviction that these catalysts operate *via* a contrasting mode of action to conventional Brønsted acids in the presence of thiol-based compounds.

6.1 Catalytic versatility of non-toxic 1,4-dialkyltriazolium salts: *in situ* modification facilitating diametrically opposed catalysis modes in one pot

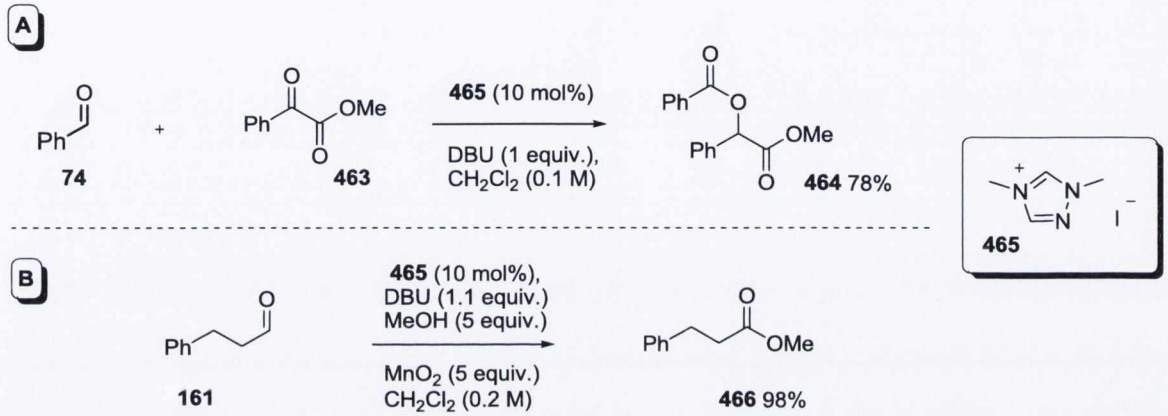
Throughout this project our goal has been to design environmentally benign materials which could serve as powerful acid catalysts in the presence of a protic additive. This has been successful in the development of the highly active C-4/C-5 substituted imidazolium ion-based catalysts such as **371**. The known activity of these compounds (along with the activity of C-3/C-5 substituted pyridinium ion-based catalysts) led us to speculate that 1,2,4-triazolium ions such as **462** (Scheme 6.1) could also act in the same way. The triazolium ion-based moiety would hold the same advantage over the imidazolium ion-based catalysts, as they had with respect to the pyridinium ion-based compounds, in that the incorporation of an additional endocyclic heteroatom would lead to a lowering of resonance stabilisation in the heterocyclic ring. These 1,2,4-triazolium ions such as **462** are also highly accessible, thus representing a compromise between the stability of **309**[243] and the activity of **121**[72] while being easier to prepare than **370** (Scheme 6.1).



Scheme 6.1 Development of aprotic heterocyclic salts employed in acid catalysed acetalisation reactions in the presence of a protic medium.

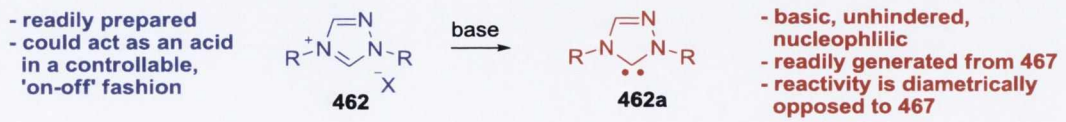
Additionally, the use of **465** as a precatalyst in NHC mediated chemistry is well precedented, with the 1,2,4-triazolium salt has been employed as precatalyst in redox reactions.[265,266,267] Representative examples of this include reports by Scheidt *et al.* who catalysed the hydroacylation of various activated ketones catalysed by NHCs, including ketone **463** which, in the presence of aldehyde **74**, a base (*i.e.* DBU) and NHC-precatalyst **465** in CH_2Cl_2, was reported to afford **464** in good yield (A, Scheme 6.2).[268] Oxidative esterifications have also

been achieved by the same group, an example of this involves the esterification of aldehyde **161** in the presence of precatalyst **465** and MnO_2 as the oxidising agent, generating excellent yields of the desired ester product **466** (B, Scheme 6.2).[269] Oxidative amidations and azidations have also been successfully achieved in recent times employing this triazolium salt-based precatalyst.[270]



Scheme 6.2 Representative examples of the employment of triazolium salt precatalyst **465** in NHC-catalysed oxidation reactions.

Consequently, we postulated that a potential advantage associated with the use of these 1,2,4-triazolium ion-derived compounds would be the development of a new paradigm for 'bifunctional catalysis'. Conventionally, this term has been used to describe the activation of two distinct reaction components simultaneously (*e.g.* general acid/base catalysis[271]). However, the use of **462** may potentially allow for *in situ* catalyst modification, by first acting as a promoter of the acid catalysed acetalisation reaction, then on addition of base, deprotonation to the corresponding carbene **462a** would allow for subsequent NHC-mediated reactions (*e.g.* the benzoin condensation- which under normal circumstances would be incompatible with acid catalysis) to occur (Scheme 6.2).



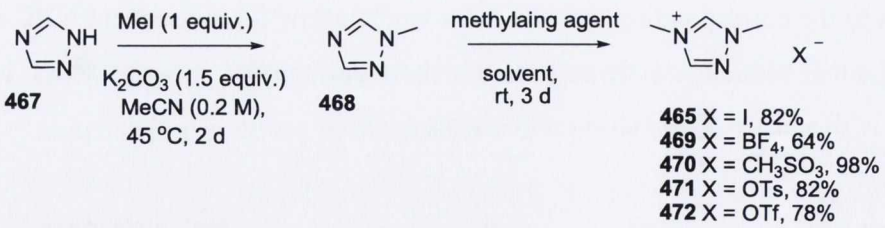
Scheme 6.3 Proposed 'bifunctional' catalytic ability of 1,4-dialklytriazolium ion.

In order to test this hypothesis, an initial evaluation of the catalytic activity of **462** in acetalisation and benzoin condensations was necessary. The acetalisation was chosen as the acid-catalysed reaction due to the knowledge gained regarding this reaction in the preceding studies, while the benzoin condensation was selected as the NHC-catalysed reaction as it was noted that, while their use is widely known in oxidation reactions, no detailed study of this catalyst in this reaction had been previously reported.

6.1.1 Triazolium salts preliminary catalyst evaluation: catalyst synthesis

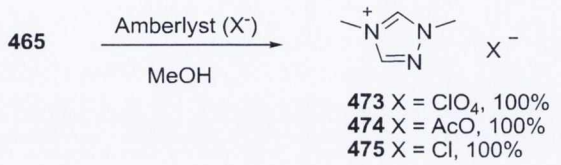
The synthesis of a number of 1,4-dimethyltriazolium salts with various counterions was undertaken, to be later evaluated in acetalisation reactions and the benzoin condensation to determine the most active triazolium ion-based compound in these reactions. The variation in the anion choice was carried out, as it had been previously found with unsubstituted imidazolium ion-based compounds such as **309** and pyridinium ion-derived compounds such as **68**, that the counterion had an effect on catalytic activity. In the case of these triazolium ions it was also found that the choice of counterion had a marked impact on the stability of the compound.

The triazolium ion-based catalysts **465** and **469-472** were synthesised from the inexpensive commercially available 1,2,4-triazole (**467**). This was methylated using MeI in acetonitrile to obtain **468** in excellent yield, which was quaternised employing various alkylating agents to afford the *bis*-methylated 1,2,4-triazolium ion incorporating the desired anions in good to excellent yield (Scheme 6.4).



Scheme 6.4 Synthesis of catalyst candidates **465** and **469-472**.

Catalysts **473-475** were then prepared from catalyst **465** *via* a counterion exchange procedure developed by Sheldon and co-workers,[272] in which the iodide catalyst was passed through Amberlyst resin which had been previously charged with the corresponding acid of the desired counterion, affording the coveted 1,2,4-triazolium salts in quantitative yields (Scheme 6.5).



Scheme 6.5 Synthesis of catalyst candidates **473-475** *via* counterion exchange with the appropriate Amberlyst resin and catalyst **465**.

The syntheses above highlight the ease with which these 1,2,4-triazolium ion-based compounds can be produced.

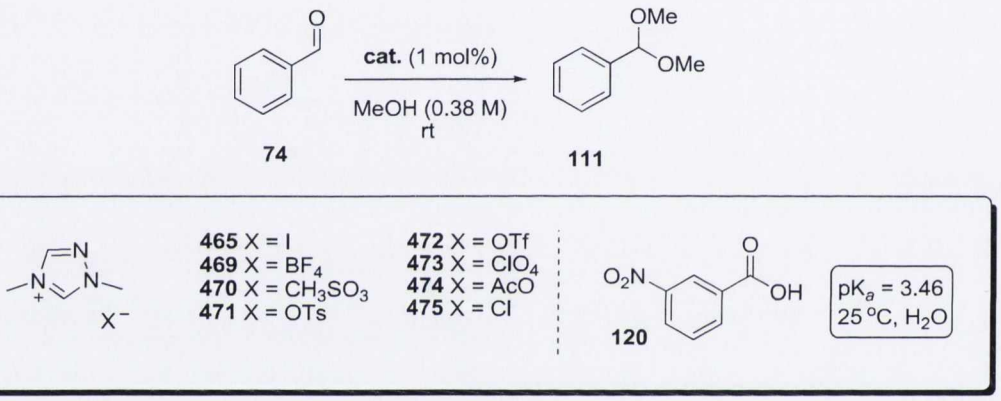
6.1.2 Triazolium salts preliminary catalyst evaluation: acetalisation

Our study began with the acetalisation of benzaldehyde (**74**) with methanol in the presence of the triazolium ion-based species prepared as described above, the results of this investigation are outlined in Table 6.1. An immediate improvement was observed in activity of these compounds relative to the unsubstituted imidazolium ions (*e.g.* **309**).[243] The employment of even the least efficient catalysts in the triazolium salt series (*i.e.* **469**, **470**, **473** and **474**, entries 1-4) at 1 mol% loading facilitated the formation of **111** in comparable yields to that obtained form catalysis by **309** at 5 mol% loading (see Section 2.1.1).[243] The relative inefficiency of the BF_4 containing salt **469** (entry 1) was somewhat surprising in that this proved to be the most effective counterion in the unsubstituted imidazolium ion-based series, however this was explained by the relative instability of this triazolium ion-based compound, which was found to be very light sensitive.

Gratifyingly, the chloride **475**, tosylate **471**, triflate **472** and iodide **465** ions all exhibited excellent activity at 1 mol% loading (entries 5-8), with **472** and **465** able to promote the formation of **111** in almost quantitative yield (entries 7 and 8). Due to this activity and also

the high activity of catalyst **471** containing the tosylate ion (entry 6) at 1 mol% loading, these 3 catalysts (*i.e.* **465**, **471** and **472**) were evaluated at 0.1 mol% loading, however at this loading it was found that the triazolium ion-based catalysts had reached the limit of their efficacy (entries 9-11) and the yields, though appreciable, were not as impressive (as was to be expected) as those obtained with the highly active pyridinium salts (*e.g.* **121**) and the 2nd generation imidazolium salts (*e.g.* **370**) at this loading. As was the case with the pyridinium ion-based and imidazolium ion-based compounds, the activity of these triazolium salts is considerably higher than that exhibited by 3-nitrobenzoic acid (**120**, entry 12).

Table 6.1 Preliminary catalyst evaluation: acetalisation of benzaldehyde

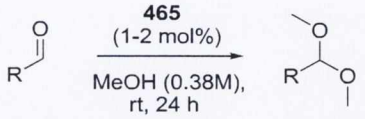


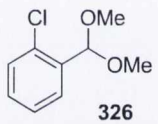
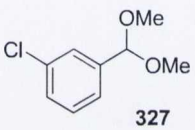
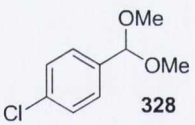
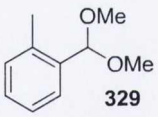
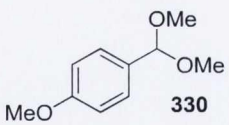
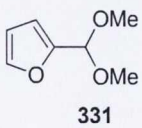
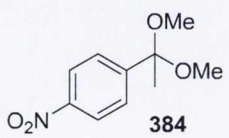
Entry	Catalyst	Yield (%)[a]
1	**469**[b]	86
2	**470**	86
3	**473**	81
4	**474**	82
5	**475**	90
6	**471**	97
7	**472**	>98
8	**465**	>98
9	**465**	68
10	**471**	62
11	**472**	65
12	**120**	37

[a]Determined by ^{1}H NMR spectroscopy using an internal standard [b]Catalyst unstable on storage (light sensitive)

6.1.3 Acetalisation catalysed by triazolium salt 465: evaluation of substrate scope

Table 6.2 Acetalisation catalysed by **465**: evaluation of substrate scope



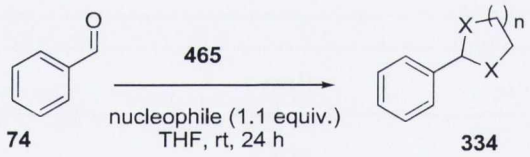
Entry	Substrate	Loading (mol%)	Time (h)	Yield (%)[a]
1	 **326**	1	24	95
2	 **327**	1	24	96
3	 **328**	1	24	98
4	 **329**	2	24	90
5	 **330**	2	24	92
6	 **331**	2	24	92
8	 **384**	10	24	32

[a]Isolated yield after chromatography

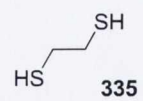
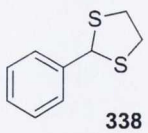
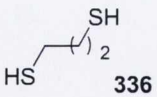
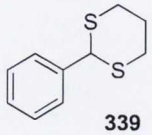
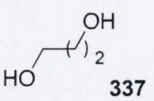
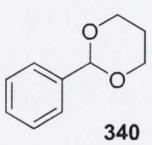
The evaluation of substrate scope was then carried out using **465**. This catalyst was chosen to continue our acetalisation study, with respect to substrate scope, as it proved the most effective at 0.1 mol% loading and it was readily obtained (through the alkylation of 1,2,4-triazole with MeI). Catalyst **465** (at 1-2% levels) performed consistently across a range of substrates – allowing the isolation of acetals derived from activated- (**326-328**, entries 1-3), hindered- (**329**, entry 4), deactivated- (**330**, entry 5), heterocyclic- (**331**, entry 6) and α,β-unsaturated (**332**, entry 7) aldehydes in uniformly excellent yields. Ketalisation of *p*-nitroacetophenone **383** to **384** (entry 8; a consistently problematic substrate) proved difficult, however an appreciable yield was obtained.

As was the case with the imidazolium ion-based compounds we also found that at low loadings **465** could promote the smooth dithiolane (*i.e.* **338**, entry 1), dithiane (*i.e.* **339**, entry 2) and dioxane (*i.e.* **340**, entry 3) protection of benzaldehyde at room temperature in excellent yields (Table 6.3). These results again highlighted the superiority of this triazolium salt when compared to the unsubstituted imidazolium salt **309**.

Table 6.3 Catalysis of dithiane, dithiolane and dioxane syntheses.



74 **334**

Entry	Nucleophile	Product	Loading (mol %)	Yield (%)[a]
1	 **335**	 **338**	2	92
2	 **336**	 **339**	2	89
3	 **337**	 **340**	5	86

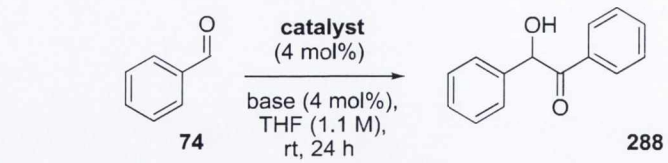
[a]Isolated yield after chromatography

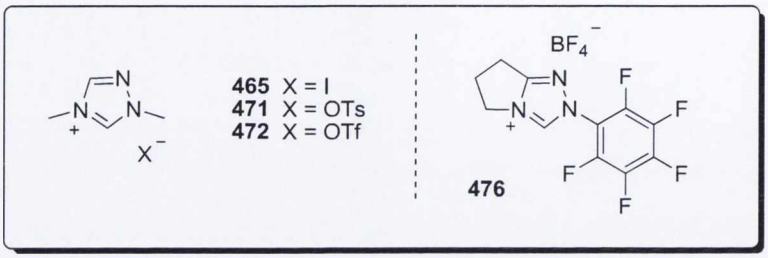
6.1.4 Benzoin condensation reactions: catalyst evaluation

With the superiority of **465** over **309** firmly established in the acid catalysed acetalisation reactions, our attention turned to the benzoin condensation. While the use of **465** as a precatalyst in NHC-mediated chemistry is well precedented with respect to oxidation reactions (see Section 6.1), we were surprised to learn that a detailed study of the use of this triazolium ion-based system in the archetypal NHC-promoted reaction, the benzoin condensation, had not been reported. Miyashita *et al.* in 1996, had evaluated its utility in the benzoin condensation of **74** under harsh conditions yielding 69% of the desired product, however this was the only reported use of this catalyst in these types of reaction.[273]

We therefore compared the performance of the optimum acetalisation-promoting catalysts **465**, **471** and **472** with the pentafluorophenyl-substituted triazolium salt **476**[240] which has been shown to exhibit excellent activity as a precatalyst in the benzoin condensation.[242,274,275] The preliminary benzoin condensations of aldehyde **74** under the literature conditions are outlined in Table 6.4.[238] Initially, K_2CO_3 was used as the base (entries 1-4, Table 6.4), however it was determined when this base was used, though the conventional catalyst **476** promoted the reaction with excellent yields (entry 4), the simple dimethyl substituted compounds were less effective in the mediation of the benzoin condensation, with lower product yields obtained of between 65-72% (entries 1-3, Table 6.4). The employment of Rb_2CO_3 (which has been widely used as a base in this type of reaction) was then evaluated in the presence of each of the triazolium salt precatalysts. Gratifyingly, **465**, **471** and **472** promoted the reaction with excellent isolated product yields comparable to that obtained using the benchmark precatalyst **476** (entries 5-8). Diazabicycloundecene (DBU) was also evaluated as a base to determine if an increase/decrease of efficacy was observed when this liquid base was employed in conjunction with the triazolium salt-based precatalysts **465** and **476**, it was observed that there was no marked difference in catalytic efficacy in the presence of this base (entries 9 and 10, Table 6.4).

Table 6.4 Benzoin condensation: preliminary catalyst evaluation





Entry	Catalyst	Base	Yield (%)[a]
1	**465**	K_2CO_3	72
2	**471**	K_2CO_3	68
3	**472**	K_2CO_3	65
4	**476**	K_2CO_3	96
5	**465**	Rb_2CO_3	96
6	**471**	Rb_2CO_3	96
7	**472**	Rb_2CO_3	97
8	**476**	Rb_2CO_3	97
9	**465**	DBU	96
10	**476**	DBU	95

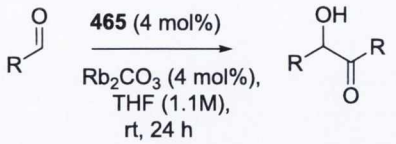
[a]Isolated yield after column chromatography

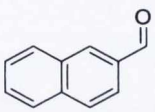
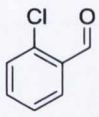
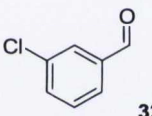
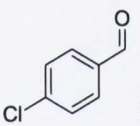
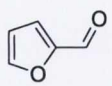
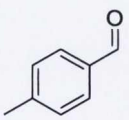
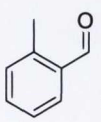
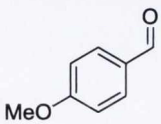
6.1.5 Benzoin condensation: evaluation of substrate scope with catalyst 465

The evaluation of substrate scope was then performed using **465**, as the other *bis*-methyl substituted precatalysts investigated (*i.e.* **471** and **472**) in the initial study did not prove more active than **465** in the benzoin condensation. Therefore, as this compound proved marginally more active (at 0.1 mol% loadings) than the other catalysts tested in the acetalisation of benzaldehyde, we decided that it would be employed in all further investigations. The carbene derived from **465** responded to changes in the steric and electronic characteristics of the substrate in the same manner as previously observed with compound **476**.[238] Excellent yields were achieved using electron neutral (**477**, entry 1, Table 6.5), activated (**326-328**, entries 2-4), heterocyclic (**331**, entry 5) and mildly deactivated-aldehydes (**478**, entry 6), and less efficient catalysis using either hindered (**329**, entry 7) or highly deactivated substrates (**330**,

entry 8, Table 6.5) which pose a serious challenge for all triazolium ion-based catalyst systems.[238,242,275]

Table 6.5 Benzoin condensation reactions with **465**: substrate scope



Entry	Substrate	Loading (mol%)	Time (h)	Yield (%)[a]
1	 **477**	4	24	91
2	 **326**	4	24	27
3	 **327**	4	24	92
4	 **328**	4	24	93
5	 **331**	4	24	93
6	 **478**	4	24	89
7	 **329**	4	24	18
8	 **330**	4	24	35

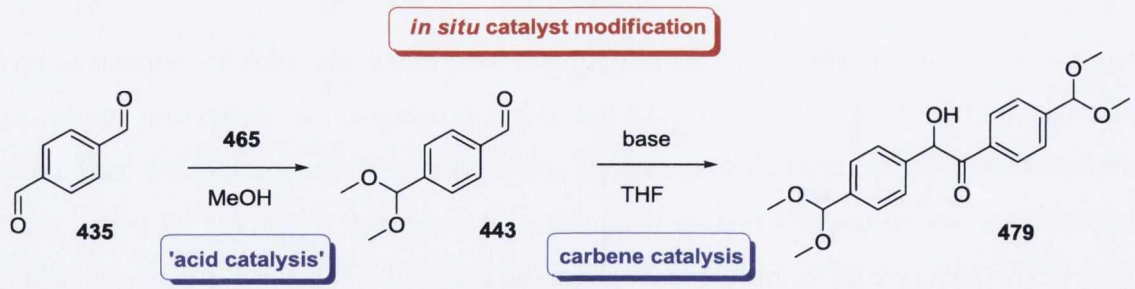
[a]Isolated yield after column chromatography

Since **465** is considerably more straightforward and less expensive to prepare than **476** (or variants thereof), we would suggest that it represents an attractive general system for use in the benzoin condensation.

6.1.6 *In situ* modification of reaction conditions facilitating diametrically opposed catalysis modes in one pot.

It had been demonstrated that the 1,4-dimethyltriazolium salt **465** was active in both the acid-catalysed acetalisation of aldehydes, as well as the base-induced carbene catalysed benzoin condensation. Therefore, we endeavoured to investigate if this activity could be exploited utilising one substrate, in which an acid-catalysed reaction (*i.e.* acetalisation) is followed by a diametrically opposed basic nucleophilic-catalysed reaction (*i.e.* benzoin condensation) in one-pot.

Bis-aldehyde **435** was selected as the substrate to demonstrate this *in situ* catalyst modification strategy. Our rationale involved the treatment of aldehyde **435** with MeOH in the presence of **465** which would, under the correct conditions, result in the quantitative formation of the mono-acetal **443**. Subsequent addition of base to generate the carbene derivative of **465** in THF solvent would then lead to the generation of the protected benzoin product **479** (Scheme 6.6).

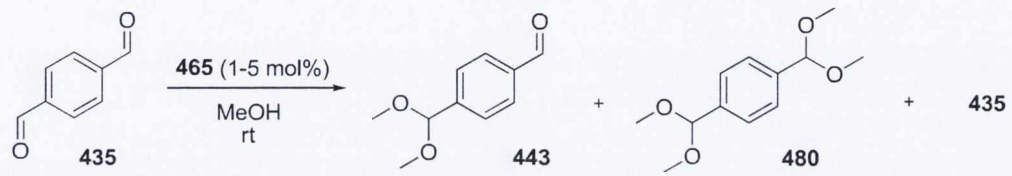


Scheme 6.6 Proposed reaction scheme for the *in situ* catalyst modification of triazolium salt **465** to afford **479** from **435** in one-pot.

The optimisation of reaction conditions to generate the mono-dimethyl acetal **443** (in the absence of the *bis*-acetalised product) in quantitative yield, was initially attempted through the

alteration of the catalyst loadings, reaction time and the amount of MeOH employed. The conditions outlined in Table 6.6 are representative examples of the considerable experimentation undertaken to optimise this reaction.

Table 6.6 Optimisation of reaction conditions for catalysis of acetalisation of **435** with **465** to generate mono-acetal **433**.



Entry	Loading (mol%)	MeOH (equiv.)	Time (h)	Yield (%)[a] of 443	Yield (%)[a] of 480	Yield (%)[a] of 435
1	0	4	18	0	0	100
2	1	4	18	76	20	3
3	1	3	18	73	10	17
4	2	3	18	76	18	6
5	2	3	24	80	19	0
6	5	3	24	82	18	0
7	5	2.5	24	90	10	0
8	5	2.0	24	96	0	3
9	5	2.2	24	>99[b]	0	0

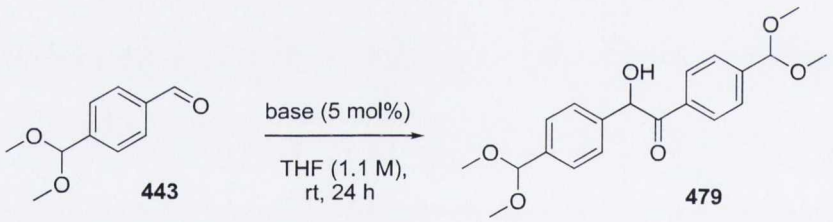
[a]Determined by ^{1}H NMR spectroscopy using an internal standard [b]Isolated yield after chromatography

In the presence of no catalyst it was found that no acetal formation occurred with only aldehyde starting material recovered (entry 1, Table 6.6). At 1 mol% loading and with 4 equivalents of methanol a yield of 76% of **443** was achieved, although the formation of the *bis*-acetal **480** also occurred. We therefore decreased the amount of alcohol present in the reaction medium to 3 equivalents, however it was found that there was a decrease in overall product yield under these conditions at 1 mol% catalyst loading (entry 3). We therefore increased catalyst loading to 2 mol%, which under the same conditions led to an increase in overall yield, however the reaction had still not reached completion (entry 4). Gratifyingly, by extending the reaction time from 18 h to 24 h, full conversion to the acetal products was observed (entry 5). However, there was still a large amount of **480** produced in the presence of 2 mol% of **465**. We therefore further increased the loading to 5 mol%. However, the ratio of **443** to **480** remained similar to that obtained at 2 mol% loading (entry 6). Hence, we decided to further decrease the amount of MeOH present initially to 2.5 equivalents which

afforded a lower amount of **480** (entry 7). A further decrease to 2 equivalents of methanol led to an increase in the yield of the mono-acetal **443**, however some starting material was also present (entry 8). The final optimisation involved increasing the quantity of MeOH to 2.2 equivalents which in the presence of **74** and **465** generated the desired mono-acetal **443** in quantitative yield (entry 9).

With the mono-acetal **443** generated in quantitative yield, the optimisation of the *in situ* generation of the carbene catalyst to promote the benzoin condensation through the addition of base and THF to the reaction medium was pursued. As Rb_2CO_3 had proven to be the most effective base in the preliminary benzoin condensation investigations, it was added to the reaction medium at 5 mol% loading, while THF (1.1 M) was also added. After 24 h, the yield of the desired benzoin product **479** was determined by ^{1}H NMR spectroscopic analysis, disappointingly this reaction afforded a surprisingly low yield of 27% (entry 1, Table 6.7). Other bases were therefore employed, however lower yields were afforded in the presence of each of these compared to that generated in the presence of Rb_2CO_3 (entries 2-5, Table 6.7).

Table 6.7 Optimisation of the *in situ* benzoin condensation of aldehyde **443**.

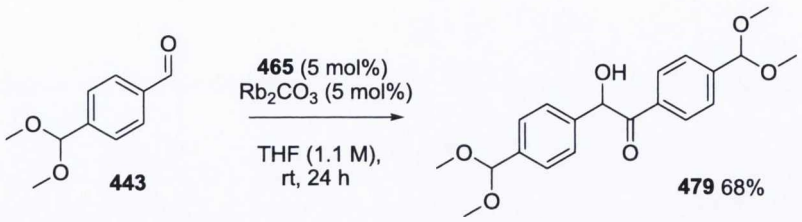


443 **479**

Entry	Base	Yield (%)[a]
1	Rb_2CO_3	27[b]
2	K_2CO_3	18[b]
3	$CsCO_3$	10
4	KHMDS	6
5	KO^{t}Bu	0

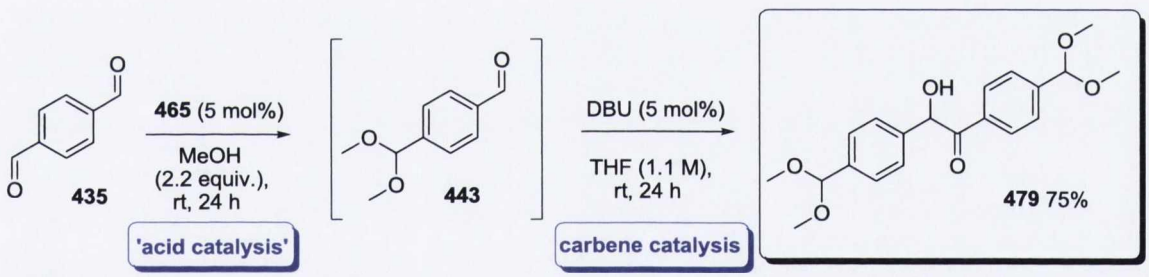
[a]Determined by ^{1}H NMR spectroscopy using an internal standard [b]Isolated yield after chromatography

Due to the unexplained low yields observed in Table 6.7 above, the pure acetal **443** was reacted, after isolation from the reaction medium, under the conditions used in Table 6.7. It was observed from this reaction that in the presence of **465** (5 mol%) and Rb_2CO_3 (5 mol%) that the desired benzoin product **479** proceeded with a improved yield of 68% (Scheme 6.7).



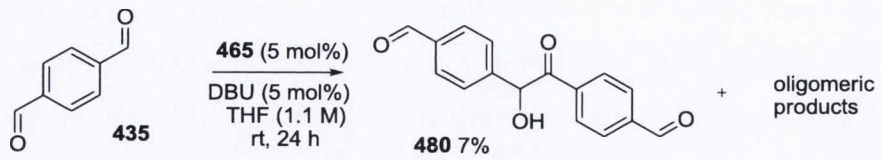
Scheme 6.7 NHC-mediated benzoin condensation of aldehyde **443** to **479**.

This result led us to further examine the reactions in Table 6.7. It was found that the resultant low yields were due to the generation of the acid derivative of aldehyde **443**. The presence of this acid was having an obvious deleterious effect on the ability of the base to generate the active carbene catalyst *in situ*. It was believed that the acid was being generated by the introduction of air to the anhydrous reaction when transferring the solid base to the reaction vessel. To counteract this problem DBU was employed as the base which pleasingly solved the problem (due to our ability to add this base *via* syringe), leading to the generation of the benzoin product in a satisfactory yield of 75% (Scheme 6.8).



Scheme 6.8 *In situ* catalyst modification of **465** allows for a one-pot synthesis of **479** from aldehdye **435**.

The reaction scheme above outlines a novel chemoselective synthesis allowed by the *in situ* modification of the 1,2,4-traizolium ion-based catalyst **465**. It should also be noted that the aldehyde **435**, when treated with **465** and base, furnishes oligiomeric products due to uncontrolled benzoin condensation chemistry, with only 7% of the dimeric benzoin **480** isolable (Scheme 6.9).



Scheme 6.9 Benzoin condensation of aldehyde **435** in the presence of precatalyst **465** and DBU.

The result of the reaction in Scheme 6.8 was therefore extremely satisfactory as it has demonstrated that these catalysts can be employed as a form of 'bifunctional' catalyst, with the ability to act as an acid or a base in one-pot depending on the nature on the additive introduced to the reaction medium.

6.1.7 Conclusions: *in situ* modification facilitating diametrically opposed catalysis modes in one pot in the presence of 1,4-dialkyltriazolium salt catalyst 465

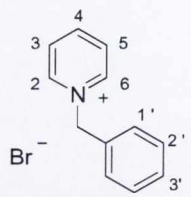
In summary, it has been shown that simple, stable, non-toxic and readily prepared triazolium salts act as highly active promoters of a specific acid-catalysed reaction – allowing the room temperature protection of a broad range of aldehydes in excellent yield at low catalyst loadings. While it was previously known that these materials are precursors to NHCs, a systematic study revealed that these materials are actually optimal for the promotion of the benzoin condensation reaction; affording the practitioner an identical activity profile to the literature benchmark system from a considerably less expensive and more readily prepared salt. The ability of **465** to serve as a precatalyst for both a strong acid and a powerful base/nucleophile (depending on the additive employed) was exploited in a unique *in situ* modification strategy in which the role played by the triazolium salt is sequentially controlled in an 'on-off' fashion

7.1 General experimental data

Proton Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 or 600 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d_6 referenced relative to residual DMSO-d_6 (δ = 2.50 ppm) or C_6D_6 referenced relative to residual C_6H_6 (δ = 7.16 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 or 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$, or anisaldehyde staining. Anhydrous THF was distilled over sodium-benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. Methanol was distilled over sodium. All reactions were carried out under a protective argon atmosphere, unless otherwise stated. Careful drying of all catalysts/ionic liquids prior to use was essential for best results-a convenient procedure for this follows: the catalysts/ionic liquids were dissolved in dry toluene under argon. The solvent was removed *in vacuo* and the procedure was repeated twice, taking care that the compound was not exposed to air. The catalysts/ionic liquids were then dried under vacuum for 2h and used in the relevant reaction. For all known compounds the spectral characteristics were in agreement with those reported in the literature.

7.2 Experimental data for Chapter 2

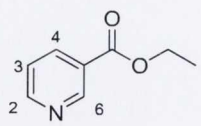
7.2.1 1-Benzylpyridinium bromide (114)



A 100 mL round bottom flask fitted with a magnetic stirring bar was charged with pyridine (10 mL, 0.124 mol) and benzyl bromide (20 mL, 0.17 mol) in toluene (50 mL). The solution was stirred at room temperature for 24 h. The solution was then filtered using a Buchner funnel and the solid was washed with ether (30 mL) giving the product **114** as a white solid (24.8g, 80%). M.p. 96-98 °C (lit.,[276] 98-100 °C). The NMR spectral data associated with **114** were consistent with those previously reported.[276]

δ_H (400 MHz, $CDCl_3$): 6.30 (s, 2H, $PhCH_2$), 7.34-7.36 (m, 3H, H-2'and H-3'), 7.66-7.79 (m, 2H, H-1'), 8.05 (app.t, 2H, H-3 and H-5), 8.45 (t, J 7.0, 1H, H-4), 9.60 (d, J 6.8, 2H, H-2 and H-6).

7.2.2 Nicotinic acid ethyl ester (321)



A 100 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with nicotinic acid (3.2 g, 30 mmol) and ethanol (50 mL) and flushed with argon. Sulfuric acid (1.2 equiv.) was then added *via* syringe and the reaction mixture was stirred under reflux for 24 h. The mixture was then cooled to room temperature and the solvent was removed *in vacuo*. The resulting residue was then dissolved in CH_2Cl_2 (25 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic layer was separated, dried with $MgSO_4$ and the solvent was removed under reduced pressure. The pure compound **321** was obtained as a yellow oil

(2.95 g, 76%) without further purification. The NMR spectral data associated with **321** were consistent with those previously reported.[277]

δ_H (400 MHz, $CDCl_3$): 1.36 (t, J 7.0, 3H, CH_3), 4.24 (q, J 7.0, 2H, CH_2), 7.31-7.34 (dd, J 7.5, 5.0, 1H, H-4), 8.25 (d, J 7.5, 1H, H-3), 8.71 (d, J 5.0, 1H, H-6), 9.20 (s, 1H, H-2).

HRMS(*m/z*-ES): $[M]^+$ calcd. for $C_8H_9NO_2$ 151.0633; found 151.0635.

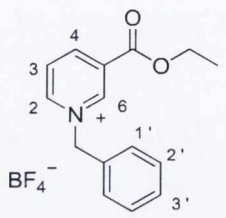
7.2.3 1-Benzyl-3-ethoxycarbonyl-pyridinium bromide (119)

A 50 mL round bottomed flask containing a stirring bar was charged with ester **321** (2.9 g, 19.4 mmol) fitted with a septum and flushed with argon. Acetone was added (15 mL) followed by benzyl bromide (2.8 mL, 24.0 mmol). The flask was then fitted with a condenser and the solution was heated under reflux for 24 h. Upon cooling to room temperature the solvent was removed *in vacuo* and the resulting oil was dissolved in a mixture of EtOAc-MeOH (9:1) (25 mL) in a conical flask. This was fitted with a septum and needle, and left open to the air for 12h, at which point the hydrobromide salt precipitated and was removed by filtration. The filtrate was then cooled to 0 °C and the pure product was precipitated by the slow addition of ether (10 mL) over 2 hours. The catalyst **119** was obtained as an off-white solid (1.2 g, 75%) and was filtered, dried under reduced pressure and stored under a protective argon atmosphere. M.p. 130-133 °C (lit.,[278] 132 °C). The NMR spectral data associated with **119** were consistent with those previously reported.[278]

δ_H (400 MHz, $CDCl_3$): 1.45 (t, J 7.0, 3H, CH_3), 4.52 (q, J 7.0, 2H, CH_2), 6.51 (s, 2H, $PhCH_2$), 7.40-7.42 (m, 3H, H-2' and H-3'), 7.72-7.73 (m, 2H, H-1'), 8.29-8.33 (dd, J 8.5, 5.7, 1H, H-3),

8.89 (d, J 8.5, 1H, H-4), 9.65 (s, 1H, H-6), 10.19 (d, J 5.7, 1H, H-2).

7.2.4 1-Benzyl-3-(ethoxycarbonyl)pyridinium tetrafluoroborate (322)



A 50 mL round bottomed flask was charged with **119** (3.22 g, 10.0 mmol) in anhydrous acetone (10 mL) under argon. To this solution $NaBF_4$ (1.32g, 12.0 mmol) was added. The flask was fitted with a condenser and the mixture was then heated under reflux for 4 d. A fine white precipitate was obtained which was removed by filtration and washed with anhydrous acetone (3 x 5 mL). The filtrate and washings were then combined and the solvent was removed *in vacuo* to afford catalyst **322** as an off-white solid (3.13 g, 95%). The product was dried under high vacuum and stored under argon. M.p. 46-48 °C.

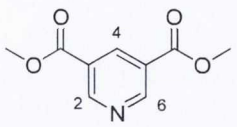
δ_H (400 MHz, DMSO-d_6): 1.39 (t, J 7.2, 3H, CH_3), 4.46 (q, J 7.2, 2H, OCH_2), 5.98 (s, 2H, $PhCH_2$) 7.44-7.50 (m, 3H, H-2' and H-3'), 7.55-7.58 (m, 2H, H-1'), 8.30 (dd, J 8.0, 6.0, 1H, H-3), 9.02 (d, J 8.0, 1H, H-4), 9.34 (d, J 6.0, 1H, H-2), 9.78 (s, 1H, H-6).

δ_C (100 MHz, DMSO-d_6): 14.5, 63.1, 64.0, 129.4, 129.7, 129.9, 130.9 (q), 134.5 (q), 146.1, 146.5, 148.3, 162.1 (q).

ν_{max} (film)/cm^{-1}: 678, 704, 747, 860, 1010, 1298, 1371, 1456, 1637, 1731, 3088.

HRMS (*m/z*-ES): $[M^+-BF_4^-]$ calcd. for $C_{15}H_{16}NO_2$ 242.1181; found 242.1173.

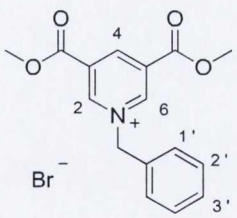
7.2.5 Dimethyl pyridine-3,5-dicarboxylate (121a)



A 50 mL round bottomed flask was fitted with a magnetic stirring bar and charged with 3,5-pyridinedicarboxylic acid (1g, 6.0 mmol). To this MeOH (10 mL) was added followed by H_2SO_4 (64 µL, 1.20 mmol). The reaction vessel was fitted with a condenser and stirred under reflux for 2 h. The reaction mixture was then added to a 100 mL separating funnel containing iced water (20 mL) and extracted using diethyl ether (2 x 10 mL). The extracts were combined and crude product was then washed with water (2 x 10 mL) and sat. $NaHCO_3$ (2 x 10 mL). The mixture was then concentrated *in vacuo* and the ester was purified by recrystallisation, filtered and dried under vacuum producing the desired compound **121a** as a white solid (1.05 g, 90%). M.p. 84-85 °C, (lit.,[279] 85-86 °C). The NMR spectral data associated with **121a** were consistent with those previously reported.[279]

δ_H (400 MHz, $CDCl_3$): 3.98 (s, 6H, OCH_3), 8.85 (s, 1H, H-4), 9.35 (s, 2H, H-2 and H-6).

7.2.6 1-Benzyl-3,5-bis(methoxycarbonyl)pyridinium bromide (121)



A 50 mL round bottomed flask containing a magnetic stirring bar, was charged with 3,5-pyridine dicarboxylic acid dimethyl ester **121a** (820 mg, 4.20 mmol), fitted with a septum and flushed with argon. Dry methanol (10 mL) was added followed by benzyl bromide (750 µL, 6.30 mmol) *via* syringe. The solution was then stirred under reflux for 36 h. After which the solvent was removed *in vacuo* and the crude product was purified by dissolution in EtOAc:MeOH (9:1) in a conical flask fitted with a septum and needle open to the air and left for 12 h. At this point unreacted starting material precipitated and was removed by filtration.

The filtrate was the cooled to 0 °C and the catalyst was precipitated by the slow addition of ether over 2-3 hours. The catalyst **121** was filtered, dried *in vacuo* and stored under argon as an off-white solid (593 mg, 39%). M.p. 131-132 ° C, (lit.,[72] 130-131 °C). The NMR spectral data associated with **121** were consistent with those previously reported.[72]

δ_H (400 MHz, $CDCl_3$): 4.07 (s, 6H, O-CH_3), 6.60 (s, 2H, $PhCH_2$), 7.47-7.49 (m, 3H, H-2' and H-3'), 7.70-7.74 (m, 2H, H-1'), 9.38 (s, 1H, H-4), 10.01 (s, 2H, H-2 and H-6).

7.2.7 1-Benzyl-3,5-bis(methoxycarbonyl)pyridinium tetrafluoroborate (323)

A 50 mL round bottomed flask was charged with **121** (500 mg, 1.40 mmol) in anhydrous acetone (2.5 mL) under argon. To this solution $NaBF_4$ (187 mg, 1.70 mmol) was added. The flask was fitted with a condenser and the mixture was then heated under reflux for 4 d. A fine white precipitate was obtained which was removed by filtration and washed with anhydrous acetone (3 x 5 mL). The filtrate and washings were then combined and the solvent was removed *in vacuo* to afford catalyst **323** as an off-white solid (496 mg, 95%). The product was dried under high vacuum and stored under argon. M.p. 56-57 °C.

δ_H (400 MHz, $CDCl_3$): 3.95 (s, 6H, O-CH_3), 6.54 (s, 2H, $PhCH_2$), 7.39-7.45 (m, 3H, H-2'and H-3'), 7.65-7.71 (m, 2H, H-1'), 9.25 (s, 1H, H-4), 9.94 (s, 2H, H-2 and H-6).

δ_C (100 MHz, $CDCl_3$): 53.8, 65.7, 129.5, 129.9, 130.1, 130.4 (q), 131.2 (q), 145.0, 148.2, 160.4(q).

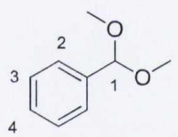
ν_{max} (film)/cm^{-1}: 624, 665, 712, 765, 878, 1055, 1265, 1298, 1385, 1456, 1501, 1666, 1795, 3067.

HRMS (*m/z*-ES): $[M^+-BF_4^-]$ calcd. For $C_{16}H_{16}NO_4$ 286.1074; found 286.1074.

7.2.8 General procedure A: acetalisation of aldehydes

A 20 mL reaction vessel was fitted with a magnetic stirring bar, charged with catalyst (0.16 mmol), fitted with a septum and flushed with argon. Benzaldehyde (340 μL, 3.34 mmol) was added followed by dry methanol (6.7 mL) *via* syringe. The solution was then stirred under argon at room temperature for 24 h. When conversion was judged to be either complete or > 95% conversion (by ^1H NMR spectroscopic analysis) the reaction was quenched with $PhNHNH_2$ and solvent was removed *in vacuo*. The crude product was purified by flash-chromatography or yield was calculated using an internal standard.

7.2.8.1 Benzaldehyde dimethyl acetal (111)

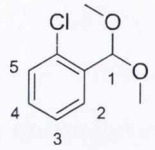


The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (40.9 mg, 0.16 mmol), methanol (6.7 mL) and benzaldehyde (340 μL, 3.34 mmol). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **111** was obtained as a pale yellow liquid (435 mg, 86%). The NMR spectral data associated with **111** were consistent with those previously reported.[280]

δ_H (400 MHz, $CDCl_3$): 3.36 (s, 6H, O-CH_3), 5.42 (s, 1H, H-1), 7.34-7.39 (m, 3H, H-3 and H-4), 7.47-7.49 (m, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 52.2, 102.7, 126.2, 127.7, 128.0, 137.5 (q).

7.2.8.2 2-Chlorobenzaldehyde dimethyl acetal (326)

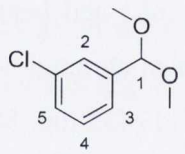


The dimethyl acetal was obtained following general procedure A using catalyst **309** (33.4 mg, 0.13 mmol), methanol (6.8 mL) and 2-chlorobenzaldehyde (400 μL, 2.56 mmol). After purification of crude material by flash chromatography (5:1, hexane:EtOAc) the product **326** was obtained as a pale yellow liquid (460 mg, 95%). The NMR spectral data associated with **326** were consistent with those previously reported.[281]

δ_H (400 MHz, $CDCl_3$): 3.32 (s, 6H, O-CH_3), 5.33 (s, 1H, H-1), 6.99-7.02 (m, 2H, H-3 and H-4), 7.07-7.09 (m, 1H, H-2) 7.30-7.32 (m, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 52.2, 101.6, 124.4, 126.5, 128.1, 129.1, 133.8 (q), 139.8 (q).

7.2.8.3 3-Chlorobenzaldehyde dimethyl acetal (327)

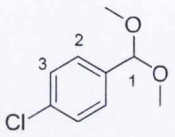


The dimethyl acetal was obtained following general procedure A using catalyst **309** (33.4 mg, 0.13 mmol), methanol (6.8 mL) and 3-chlorobenzaldehyde (400 μL, 2.56 mmol). After purification of crude material by flash chromatography (5:1, hexane:EtOAc) the product **327** was obtained as a pale yellow liquid (447 mg, 96%). The NMR spectral data associated with **327** were consistent with those previously reported.[281]

δ_H (400 MHz, $CDCl_3$): 3.41 (s, 6H, O-CH_3), 5.66 (s, 1H, H-1), 7.29-7.33 (m, 2H, H-3 and H-4), 7.38-7.40 (m, 1H, H-5), 7.63-7.65 (m, 1H, H-2).

δ_C (100 MHz, $CDCl_3$): 53.4, 100.5, 126.1, 127.6, 129.1, 129.3, 132.7 (q), 134.8 (q).

7.2.8.4 4-Chlorobenzaldehyde dimethyl acetal (328)

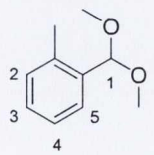


The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (46.1 mg, 0.18 mmol), methanol (7.1 mL) and 4-chlorobenzaldehyde (500 mg, 3.56 mmol). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **328** was obtained as a pale yellow liquid (633 mg, 95%). The NMR spectral data associated with **328** were consistent with those previously reported.[280]

δ_H (400 MHz, $CDCl_3$): 3.34 (s, 6H, O-CH_3), 5.39 (s, 1H, H-1), 7.32 (d, J 8.5, 2H, H-3), 7.48 (d, J 8.5, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 52.2, 101.6, 124.6, 126.4, 128.4 (q), 133.8 (q).

7.2.8.5 2-Methylbenzaldehyde dimethyl acetal (329)



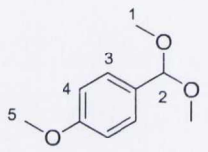
The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (22.0 mg, 0.086 mmol), methanol (2.3 mL) and 2-methylbenzaldehyde (100 μL, 0.86 mmol). After purification of the crude material by flash chromatography (15:1, hexane:EtOAc) the

product **329** was obtained as a pale yellow liquid (125 mg, 87%). The NMR spectral data associated with **329** were consistent with those previously reported.[282]

δ_H (400 MHz, $CDCl_3$): 2.42 (s, 3H, CH_3), 3.37 (s, 6H, O-CH_3), 5.51 (s, 1H, H-1) 7.14-7.16 (m, 1H, H-2), 7.25-7.30 (m, 2H, H-3 and H-4) 7.56 (dd, J 6.5, 2.0, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 18.4, 52.5, 101.3, 124.9, 126.1, 127.9, 130.1, 135.2 (q), 135.8 (q).

7.2.8.6 4-Methoxybenzaldehyde dimethyl acetal (330)

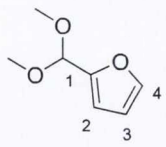


The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (21.0 mg, 0.082 mmol), methanol (2.2 mL) and 4-methoxybenzaldehyde (100 μL, 0.82 mmol). The reaction mixture was then stirred at room temperature for 24 hours. **Note:** the use of $PhNHNH_2$ was not required. After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **330** was obtained as a pale yellow liquid (133 mg, 89%). The NMR spectral data associated with **330** were consistent with those previously reported.[280]

δ_H (400 MHz, CD_3OD): 3.30 (s, 6H, H-1), 3.81 (s, 3H, H-5), 5.34 (s, 1H, H-1), 6.92 (d, J 8.9, 2H, H-3), 7.32 (d, J 8.9, 2H, H-2).

δ_C (100 MHz, CD_3OD): 51.2, 53.7, 102.7, 112.5, 127.1, 129.7 (q), 160.0 (q).

7.2.8.7 2-Dimethoxymethyl furan (331)

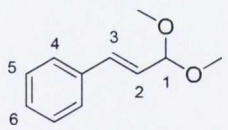


The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (20.2 mg, 0.079 mmol), methanol (2.3 mL) and furfural (100 μL, 0.79 mmol). After purification of the crude material by flash chromatography (6:1, hexane:EtOAc) the product **331** was obtained as a pale yellow liquid (93mg, 89%). The NMR spectral data associated with **331** were consistent with those previously reported.[282]

δ_H (400 MHz, $CDCl_3$): 3.30 (s, 6H, O-CH_3), 5.37 (s, 1H, H-1), 6.31 (s, 1H, H-2), 6.36 (s, 1H, H-3), 7.39 (s, 1H, H-4).

δ_C (100 MHz, $CDCl_3$): 53.3, 107.9, 109.4, 112.1, 141.9, 149.9 (q)

7.2.8.8 3,3-Dimethoxypropenyl benzene (332)

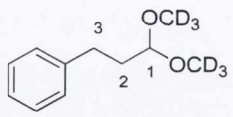


The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (20.2 mg, 0.079 mmol), methanol (2.1 mL) and cinnamaldehyde (100 μL, 0.79 mmol). **Note:** the use of $PhNHNH_2$ was not required. After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **332** was obtained as a pale yellow liquid (138 mg, 97%). The NMR spectral data associated with **332** were consistent with those previously reported.[282]

δ_H (400 MHz, $CDCl_3$): 3.41 (s, 6H, O-CH_3), 5.00 (d, J 5.1, 1H, H-1), 6.18 (dd, J 16.4, 5.1, 1H, H-2), 6.69 (d, J 16.4, 1H, H-3), 7.29-7.38 (m, 3H, H-5 and H-6), 7.44-7.45 (m, 2H, H-4).

δ_C (100 MHz, $CDCl_3$): 52.3, 102.5, 125.2, 126.3, 127.6, 128.2, 133.2, 135.6 (q).

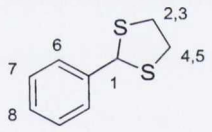
7.2.8.9 3,3-Dimethoxypropyl benzene (333)



The desired dimethyl acetal was obtained following general procedure A using catalyst **309** (9.7 mg, 0.038 mmol), deuterated methanol (1 mL) and 3-phenylpropanal (50 μL, 0.38 mmol). The reaction mixture was stirred for 1 min, then styrene (43 μL, 0.38 mmol) was added *via* syringe. The yield of **333** was determined using ^{1}H NMR spectroscopy (97%).

δ_H (400 MHz, CD_3OD): 1.84-1.93 (m, 2H, H-2), 2.59 (t, J 8.1, 2H, H-3), 4.46 (t, J 5.6, 1H, H-1), 7.17-7.38 (m, 5H, Ar).

7.2.8.10 Phenyl-1,3-dithiolane (338)

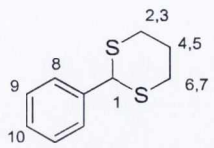


The desired dithiolane was obtained following general procedure A using catalyst **309** (25.6 mg, 0.1 mmol), 1,2-ethanethiol (100 μL, 1.19 mmol), THF (200 μL) and benzaldehyde (110 μL, 1.08 mmol). After completion of the reaction, the reaction mixture was poured onto a saturated $NaHCO_3$ solution (5 mL) and the product was extracted with ethyl acetate (2 x 10mL) and 25 mL water. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash chromatography (5:1, hexane:EtOAc) the product **338** was obtained as a colourless liquid (183 mg, 90%). The NMR spectral data associated with **338** were consistent with those previously reported.[283]

δ_H (400 MHz, $CDCl_3$): 3.34-3.40 (m, 2H, H-3 and H-5), 3.48-3.54 (m, 2H, H-2 and H-4), 5.66 (s, 1H, H-1), 7.27-7.35 (m, 3H, H-7 and H-8), 7.54-7.56 (m, 2H, H-6)

δ_C (100 MHz, $CDCl_3$): 39.8, 55.8, 127.5, 127.6, 128.1, 139.9 (q).

7.2.8.11 Phenyl-1,3-dithiane (339)

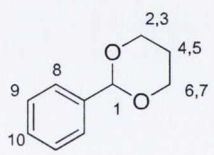


The desired dithiane was obtained following general procedure A using **309** (69.1 mg, 0.27 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and benzaldehyde (276 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography the product **339** was obtained as a white solid (344 mg, 65%). M.p. 69-71 °C (lit.,[284] 71-72 °C). The NMR spectral data associated with **339** were consistent with those previously reported.[72]

δ_H (400 MHz, $CDCl_3$): 1.99-2.19 (m, 2H, H-4 and H-5), 2.96 (ddd, J 7.5, 4.3, 3.3, 2H, H-3 and H-7), 3.07 (ddd, J 14.5, 12.2, 2.5, 2H, H-2 and H-5), 5.16 (s, 1H, H-1), 7.28-7.36 (m, 3H, H-9 and H-10), 7.46-7.48 (m, 2H, 8).

δ_C (100 MHz, $CDCl_3$): 24.9, 30.4, 51.7, 127.8, 128.5, 128.9, 139.1 (q).

7.2.8.12 Phenyl-1,3-dioxane (340)



The desired dioxane was obtained following general procedure A using catalyst **309** (33.3 mg, 0.13 mmol), 1,3-propanediol (100 μL, 1.38 mmol) and benzaldehyde (128 μL, 1.26 mmol). After purification of the crude material by flash chromatography the product **340** was

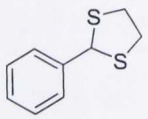
obtained as a pale yellow liquid (177 mg, 86%). The NMR spectral data associated with **340** were consistent with those previously reported.[285]

δ_H (400 MHz, $CDCl_3$): 1.40-1.51 (m, 1H, H-5), 2.15-2.28 (m, 1H, H-4), 4.04 (ddd, J 14.0, 12.3, 1.7, 2H, H-3 and H-7), 4.32 (ddd, J 11.7, 5.3, 1.2, 2H, H-2 and H-6), 5.51 (s, 1H, H-1), 7.32-7.39 (m, 3H, H-9 and H-10), 7.48-7.50 (m, 2H, H-8).

δ_C (100 MHz, $CDCl_3$): 25.1, 67.5, 102.6, 125.3, 127.9, 128.1, 138.8 (q).

7.2.9 Imidazolium recyclability study

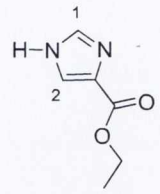
7.2.9.1 Phenyl-1,3-dithiolane (338)



The desired dithiolane was obtained following the general procedure A using catalyst **309** (25.6 mg, 0.1 mmol), 1,2-ethanethiol (100 μL, 1.19 mmol), THF (200 μL) and benzaldehyde (110 μL, 1.08 mmol). After 24 h, the yield of product **338** was obtained by ^{1}H NMR spectroscopy with the internal standard. The catalyst was precipitated using hexane, dried *in vacuo* and reused in subsequent reaction.

7.3 Experimental data for Chapter 3

7.3.1 Ethyl 1*H*-imidazole-4-carboxylate (348)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with 4-imidazoledicarboxylic acid (**347**) (250 mg, 2.2 mmol) in ethanol (5 mL). To this DMF (3 drops) was added followed by thionyl chloride (585 μL, 8 mmol). The reaction mixture was fitted with a condenser and stirred at 80 °C for 48 h. Upon completion of the reaction, the solvent was removed *in vacuo* and the residue was dissolved in water (5 mL). Aqueous sodium hydroxide was then added until the solution reached pH 9. The mixture was then extracted with EtOAc (2 x 10 mL) and the organic layer was concentrated *in vacuo* giving the pure ester **348** as an off-white solid (155 mg, 70%). M.p. 158- 160 °C

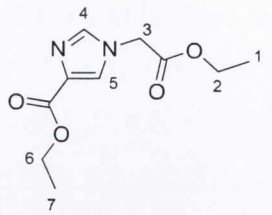
δ_H (400 MHz, $CDCl_3$): 1.39 (t, J 7.2, 3H, CH_3), 4.38 (q, J 7.2, 2H, CH_2), 7.81 (s, 1H, H-2), 7.95 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 13.9, 60.3, 125.3, 129.4, 136.5 (q), 161.7(q).

ν_{max} (film)/cm^{-1}: 684, 795, 1172, 1274, 1296, 1548, 1725, 2278, 2953, 3275.

HRMS (*m/z*-ES): [M^+] calcd. for $C_6H_8N_2O_2$ 140.0479; found 140.0479.

7.3.2 Ethyl 1-(2-ethoxy-2-oxoethyl)-1*H*-imidazole-4-carboxylate (350)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **348** (150 mg, 1.08 mmol) in acetonitrile (2 mL). To this K_2CO_3 (145 mg, 1.08 mmol) was added and the reaction mixture was stirred for 30 min under an argon atmosphere. Ethyl bromoacetate (215 μL, 1.95 mmol) was added and the reaction mixture was stirred at room temperature for 2 d. Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting residue was extracted with dichloromethane (2 x 10 mL). The extracts were combined and concentrated *in vacuo* giving a pale yellow solid. This solid was washed with ether (20 mL) after which the crude product was purified by flash column chromatography ($CHCl_3$:MeOH, 10:1) resulting in the pure product **350** as a pale yellow oil (161 mg, 70%).

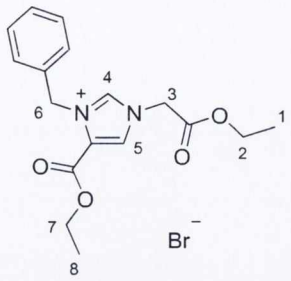
δ_H (400 MHz, $CDCl_3$): 1.34 (t, J 7.1, 6H, H-1 and H-7), 4.27 (q, J 7.1, 2H, H-2), 4.32 (q, J 7.1, 2H, H-6), 5.04 (s, 2H, H-3), 7.63 (s, 1H, H-5), 7.80 (s, 1H, H-4).

δ_C (100 MHz, $CDCl_3$): 14.1, 14.2, 48.0, 60.7, 62.0, 129.7, 137.3 (q), 142.6, 160.4 (q), 167.4 (q).

ν_{max} (film)/cm^{-1}: 668, 784, 1172, 1274, 1296, 1549, 1646, 1738, 2268.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{10}H_{14}N_2O_2$ 226.0954; found 226.0949.

7.3.3 3-Benzyl-1-(2-ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-1*H*-imidazol-3-ium bromide (351)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **350** (150 mg, 0.69 mmol) in acetonitrile (2 mL). Benzyl bromide (321 μL, 2.70 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* affording a brown oil. This oil was washed with ether (20 mL) to remove excess benzyl bromide after which the pure product **351** was obtained as a pale yellow oil (174mg, 65%).

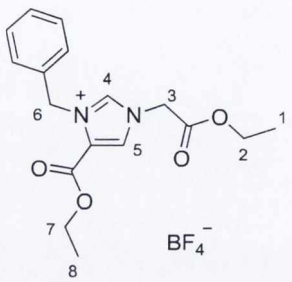
δ_H (400 MHz, DMSO-d_6): 1.36 (t, J 7.0, 6H, H-1 and H-8), 4.26 (q, J 7.0, 2H, H-2), 4.39 (q, J 7.0, 2H, H-7), 4.75 (s, 2H, H-3), 5.31 (s, 2H, H-6), 7.36-7.49 (m, 5H, Ar), 7.58 (s, 1H, H-5), 7.88 (s, 1H, H-4).

δ_C (100 MHz,DMSO-d_6): 15.1, 15.3, 49.2, 57.2, 61.1, 62.5, 126.7, 128.9, 129.7, 129.5, 134.4 (q), 137.2 (q), 145.8, 161.1 (q), 168.4 (q).

ν_{max} (film)/cm^{-1}: 674, 782, 1175, 1245, 1296, 1547, 1623, 1745, 2247, 3034.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{17}H_{21}N_2O_4^+$ 317.1416; found 317.1412.

7.3.4 3-Benzyl-1-(2-ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-1*H*-imidazol-3-ium tetrafluoroborate (352)



To a 50 mL round bottomed flask fitted with a magnetic stirring bar **351** (150 mg, 0.38mmol) was added. To this $NaBF_4$ (75 mg, 0.68 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 d, after which time a white precipitate was formed. This precipitate was filtered using a Buchner funnel under vacuum and washed with dry acetone (2 x 5 mL). The combined filtrate and washings were then concentrated *in vacuo* giving the pure product **352** as a pale yellow solid (146 mg, 96%).

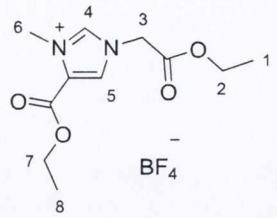
δ_H (400 MHz, DMSO-d_6): 1.32 (t, J 6.8, 6H, H-1 and H-8), 4.23 (q, J 6.8, 2H, H-2), 4.32 (q, J 6.8, 2H, H-7) 4.69 (s, 1H, H-3), 5.95 (s, 1H, H-6), 7.26-7.48 (m, 5H, Ar), 7.86 (s, 1H, H-5), 8.95 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 15.1, 15.2, 49.5, 58.1, 62.1, 62.5, 126.7, 128.9, 129.7, 130.1, 134.4 (q), 137.5 (q), 146.2, 161.2 (q), 169.0 (q).

ν_{max} (film)/cm^{-1}: 682, 795, 1236, 1158, 1287, 1535, 1645, 1747, 2258, 3026.

HRMS (*m/z*-ES): $[M^+\text{-}BF_4^-]$ calcd. for $C_{17}H_{21}N_2O_4^+$ 317.1422; found 317.1423.

7.3.5 3,5-*bis*(ethoxycarbonyl)-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate (353)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **350** (150 mg, 0.69 mmol) in acetonitrile (2 mL). Trimethyloxonium tetrafluoroborate (103 mg, 0.7 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* after which the pure product **353** was obtained as a pale yellow oil (197 mg, 90%).

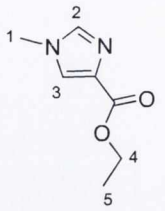
δ_H (400 MHz, DMSO-d_6): 1.30 (t, J 7.1, 6H, H-1 and H-8), 4.07 (s, 3H, H-6), 4.22 (q, J 7.1, 2H, H-2), 4.31 (q, J 7.1, 2H, H-7), 5.42 (s, 2H, H-3), 8.50 (s, 1H, H-5), 9.48 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 13.9, 14.2, 36.4, 49.9, 62.1, 62.5, 129.3, 141.1 (q), 157.2, 166.5 (q), 172.3 (q).

ν_{max} (film)/cm^{-1}: 692, 785, 1157, 1269, 1535, 1623, 1727, 2236, 2870, 3026, 3115.

HRMS (*m/z*-ES): $[M^+-BF_4^-]$ calcd. for $C_{17}H_{21}N_2O_4^+$ 241.1032; found 241.1035.

7.3.6 Ethyl 1-methyl-1*H*-imidazole-4-carboxylate (354)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **348** (120 mg, 0.86 mmol) dissolved in methanol (7.2 mL). To this methyl iodide (158 μL, 1.71 mmol) in methanol (2.7 mL) was added. The flask was fitted with a condenser and stirred under reflux for 48 h after which the solvent was removed *in vacuo* affording a dark brown oil. This crude oil was purified by flash chromatography ($CHCl_3$:MeOH (1.5%)) affording the pure compound **354** as a pale yellow oil (87 mg, 71%).

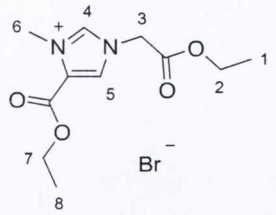
δ_H (400 MHz, DMSO-d_6): 1.28 (t, J 7.1, 3H, H-5), 3.83 (s, 3H, H-1), 4.25 (q, J 7.1, 2H, H-4), 7.62, (s, 1H, H-3), 7.91 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 14.2, 33.6, 60.4, 127.7, 133.2, 137.4 (q), 160.4 (q).

ν_{max} (film)/cm^{-1}: 675, 745, 796, 1186, 1275, 1597, 1658, 1742, 2212, 2870.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_7H_{10}N_2O_2$ 154.0742; found 154.0745.

7.3.7 3,5-*bis*(Ethoxycarbonyl)-1-methyl-1*H*-imidazol-3-ium bromide (355)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **354** (200 mg, 1.4 mmol) in acetonitrile (2 mL). Ethyl bromoacetate (320 μL, 2.9 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* affording a light brown oil. This oil was washed with ether (30 mL) to remove excess ethyl bromoacetate giving the pure product **355** as a pale yellow oil (370 mg, 85%).

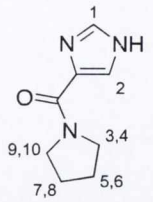
δ_H (400 MHz, DMSO-d_6): 1.34 (t, J 7.1, 6H, H-1 and H-8), 4.24 (s, 3H, H-6), 4.29 (q, J 7.1, 2H, H-2), 4.41 (q, J 7.1, 2H, H-7), 5.64 (s, 2H, H-3), 8.11 (s, 1H, H-5), 9.63 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 13.6, 14.1, 36.6, 50.4, 62.3, 62.7, 128.5, 141.3 (q), 156.8, 165.5 (q), 171.4 (q).

ν_{max} (film)/cm^{-1}: 684, 765, 1135, 1267, 1529, 1620, 1735, 2250, 2870.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{11}H_{17}N_2O_4^+$ 241.1032; found 241.1033.

7.3.8 (1*H*-imidazol-4-yl)(pyrrolidin-1-yl)methanone (357)



A 10 mL microwave reaction vial was fitted with a magnetic stirrer and to this **348** (250 mg, 1.7 mmol) was added. This was dissolved in distilled pyrrolidine (1.2 mL, 15 mmol). The reaction vessel was fitted with a lid, placed in the microwave under reduced pressure and stirred for 3 h at 110 °C. Upon completion of the reaction the pyrrolidine was removed *in vacuo* and the resulting residue was purified by flash chromatography (CH_2Cl_2:MeOH, 1:0 to 10:1) giving **357** as an off-white solid (217 mg, 77%). M.p. 92-93 °C

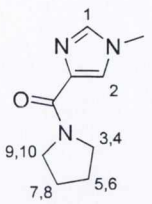
δ_H (400 MHz, DMSO-d_6): 1.93 (m, 2H, H-7 and H-8), 2.05 (m, 2H, H-5 and H-6), 3.66 (m, 2H, H-9 and H-10), 3.80 (m, 2H, H-3 and H-4), 7.49 (s, 1H, H-2), 7.70 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 23.4, 26.0, 46.6, 47.7, 126.4, 129.9 (q), 136.2, 160.4 (q).

ν_{max} (film)/cm^{-1}: 684, 765, 1123, 1226, 1269, 1535, 1623, 2236, 2870.

HRMS (*m/z*-ES): $[M^+ + H]$ calcd. for $C_8H_{11}N_3O$ 166.0980; found 166.0979.

7.3.9 (1-Methyl-1*H*-imidazol-4-yl)(pyrrolidin-1-yl)methanone (358)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **257** (150 mg, 0.91 mmol) and dissolved in methanol (7.2 mL). To this methyl iodide (186μL, 3.0 mmol) in methanol (2.7 mL) was added. The flask was fitted with a condenser and stirred under reflux for 48 h after which the solvent was removed *in vacuo* giving a dark brown oil. This crude oil was purified by flash chromatography ($CHCl_3$:MeOH (5%)) affording the pure compound **358** as an orange oil (104 mg, 64%).

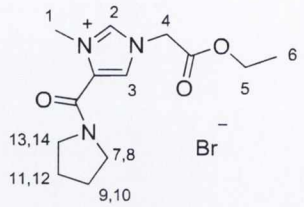
δ_H (400 MHz, DMSO-d_6): 1.93 (m, 2H, H-7 and H-8), 2.05 (m, 2H, H-5 and H-6), 3.55 (m, 2H, H-9 and H-10), 3.67 (m, 2H, H-3 and H-4), 3.95 (s, 3H, CH_3), 7.93 (s, 1H, H-2), 8.44 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 23.2, 26.5, 34.4, 45.5, 46.8, 126.7, 129.9 (q), 138.4, 161.2 (q).

ν_{max} (film)/cm^{-1}: 673, 784, 1136, 1254, 1567, 1623, 1756, 2236, 2854.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_9H_{13}N_3O$ 179.1055; found 179.1053.

7.3.10 1-(2-Ethoxy-2-oxoethyl)-3-methyl-4-(pyrrolidine-1-carbonyl)-1*H*-imidazol-3-ium bromide (359)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **358** (100 mg, 0.56 mmol) in acetonitrile (2 mL). Ethyl bromoacetate (247 μL, 2.24 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* giving a dark brown oil. This oil was washed with ether (30 mL) to remove excess ethyl bromoacetate giving the pure product **359** as an orange oil (133 mg, 69%).

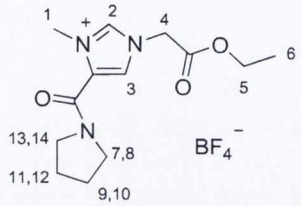
δ_H (400 MHz, DMSO-d_6): 1.31 (t, J 6.8, 3H, H-6), 1.95 (m, 2H, H-11 and H-12), 2.04 (m, 2H H-9 and H-10), 3.54 (m, 2H, H-13 and H-14), 3.66 (m, 2H, H-7 and H-8), 3.75 (s, 3H, H-1), 4.16 (q, J 6.8, 2H, H-5), 4.73 (s, 2H, H-4), 7.95 (s, 1H, H-3), 8.47 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 13.9, 23.2, 26.6, 34.4, 45.6, 46.8, 50.2, 62.0, 126.8, 130.1 (q), 138.9, 161.5 (q), 166.2 (q).

ν_{max} (film)/cm^{-1}: 673, 784, 1125, 1257, 1254, 1567, 1623, 1650, 1747, 2276, 2823.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{13}H_{20}N_3O_3^+$ 267.1539; found 267.1535.

7.3.11 1-(2-Ethoxy-2-oxoethyl)-3-methyl-4-(pyrrolidine-1-carbonyl)-1*H*-imidazol-3-ium tetrafluoroborate (360)



To a 50 mL round bottomed flask fitted with a magnetic stirring bar, **359** (100 mg, 0.3 mmol) was added. To this $NaBF_4$ (70 mg, 0.64 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 d, after which a white precipitate was formed. This precipitate was filtered using a Buchner funnel under vacuum and washed with dry acetone (2 x 5 mL). The combined filtrate and washings were then concentrated *in vacuo* giving the pure product **360** as a yellow solid (100mg, 98%). M.p 112-115 °C

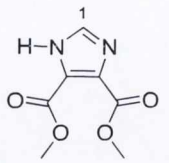
δ_H (400 MHz, DMSO-d_6): 1.36 (t, J 6.8, 3H, H-6), 1.95 (m, 2H, H-11 and H-12), 2.11 (m, 2H, H-9 and H-10), 3.65 (m, 2H, H-13 and H-14), 3.71 (m, 2H, H-7 and H-8), 3.79 (s, 3H, H-1), 4.18 (q, J 6.8, 2H, H-5), 4.77 (s, 2H, H-4), 7.96 (s, 1H, H-3), 8.97 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 13.9, 23.1, 26.6, 34.4, 45.9, 47.1, 50.6, 62.7, 126.8, 130.4 (q), 138.9, 161.6 (q), 167.3 (q).

ν_{max} (film)/cm^{-1}: 675, 686, 1146, 1234, 1254, 1567, 1656, 1721, 2812.

HRMS (*m/z*-ES): $[M^+-BF_4^-]$ calcd. For $C_{13}H_{20}N_3O_3^+$ 267.1538; found 267.1537.

7.3.12 Dimethyl 1*H*-imidazole-4,5-dicarboxylate (362)



To a 50 mL round bottomed flask, fitted with a magnetic stirring bar, 4,5-imidazoledicarboxylic acid (500 mg, 3.20 mmol) was added. To this sulfuric acid (3.4 mL, 6.40 mmol) in methanol (10 mL) was added. The reaction mixture was fitted with a condenser and stirred under reflux for 24 h. Upon completion of the reaction the solution was brought to pH 5 with saturated $NaHCO_3$ and the product was extracted using EtOAc. The extracts were combined and concentrated under reduced pressure and the resulting ester **362** was obtained as an off-white solid (456 mg, 78%). M.p. 200-201 °C

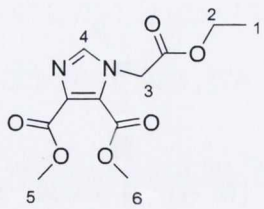
δ_H (400 MHz, DMSO-d_6): 3.80 (s, 6H, CH_3), 7.91 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 30.7, 52.0, 138.1 (q), 206.6 (q).

ν_{max} (film)/cm^{-1}: 696, 754, 1132, 1268, 1536, 1685, 1740, 3256.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_7H_8N_2O_4$ 184.0562; found 184.5065.

7.3.13 Dimethyl 1-(2-ethoxy-2-oxoethyl)-1*H*-imidazole-4,5-dicarboxylate (368)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **362** (500 mg, 2.70 mmol) in acetonitrile (2 mL). To this K_2CO_3 (383mg, 2.70 mmol) was added and the reaction mixture was stirred for 30 min under an argon atmosphere. Ethyl bromoacetate (598 µL, 5.40 mmol) was added and the reaction mixture was stirred at room temperature for 2 d.

Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting residue was extracted with dichloromethane. The extracts were combined and concentrated *in vacuo* giving a pale yellow solid. This solid was washed with ether after which the pure product **368** was obtained as an off-white solid (597 mg, 82%). M.p. 125-127 °C

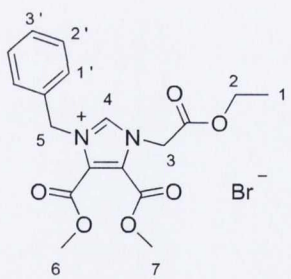
δ_H (400 MHz, $CDCl_3$): 1.21 (t, 3H, J 7.0, 3H, H-1), 3.78 (s, 3H, H-5), 3.81 (s, 3H, H-6), 4.17 (q, J 7.0, 2H, H-2), 5.14 (s, 2H, H-3), 7.98 (s, 1H, H-4).

δ_C (100 MHz, $CDCl_3$): 14.8, 31.5, 48.8, 53.1, 62.2, 124.2 (q), 138.0 (q), 142.7, 160.4 (q), 163.9 (q), 168.5 (q).

ν_{max} (film)/cm^{-1}: 685, 756, 782, 1182, 1286, 1554, 1689, 1745, 2268.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{11}H_{14}N_2O_6$ 270.0930; found 270.0923.

7.3.14 3-Benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-*bis*(methoxycarbonyl)-1*H*-imidazol-3-ium bromide (369)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with 368 (500 mg, 1.90 mmol) in acetonitrile (2 mL). Benzyl bromide (452 µL, 3.80 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* resulting in a yellow oil. This oil was washed with ether (15 mL) to remove excess benzyl bromide after which the pure catalyst **369** was obtained as a pale yellow oil (620 mg, 74%).

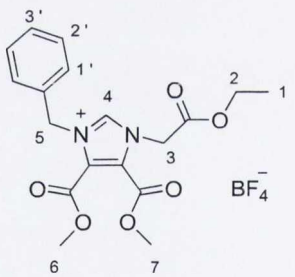
δ_H (400 MHz, DMSO-d_6): 1.22-1.25 (m, 3H, H-1), 3.86 (s, 3H, H-6), 3.88 (s, 3H, H-7), 4.23 (q, J 7.0, 2H, H-2), 5.42 (s, 2H, H-3), 5.67 (s, 2H H-5), 7.24 (t, J 7.3, 1H, H-3'), 7.37 (app.t, 2H, H-2'), 7.45 (s, J 7.3, 2H, H-1'), 9.61 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 14.0, 48.0, 50.2, 51.4, 54.1, 62.3, 123.4, 128.5, 129.1, 132.9 (q), 137.7 (q), 157.5 (q), 159.5, 163.1 (q), 166.1 (q), 167.7 (q).

ν_{max} (film)/cm^{-1}: 654, 689, 765, 805, 1240, 1295, 1568, 1645, 1798, 2258, 2879, 3032.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{18}H_{21}N_2O_6^+$ 361.1394; found 361.1390.

7.3.15 3-Benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-*bis*(methoxycarbonyl)-1*H*-imidazol-3-ium tetrafluoroborate (370)



To a 50 mL round bottomed flask fitted with a magnetic stirring bar, **369** (250 mg, 0.57 mmol) was added. To this $NaBF_4$ (74.8 mg, 0.68 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 d. After which a white precipitate was formed. This precipitate was filtered using a Buchner funnel under vacuum and washed with dry acetone (5 mL X 2). The combined filtrate and washings were then concentrated *in vacuo* giving the pure catalyst **370** as a pale yellow oil (249 mg, 98%).

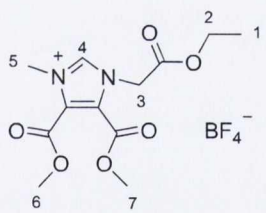
δ_H (400 MHz, DMSO-d_6): 1.23-1.26 (m, 3H, H-1), 3.78 (s, 3H, H-6), 3.81 (s, 3H, H-7), 4.25 (q, J 7.1, 2H, H-2), 5.39 (s, 2H, H-3), 5.62 (s, 2H, H-5), 7.26 (t, J 7.2, 1H, H-3'), 7.43 (app.t, 2H, H-2'), 7.64 (d, J 7.2, 2H, H-1'), 9.89 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 14.2, 47.9, 50.4, 51.5, 53.9, 62.1, 123.7, 128.9, 129.6, 133.2 (q), 138.7 (q), 157.8 (q), 159.7, 164.2 (q), 166.9 (q), 168.2 (q).

ν_{max} (film)/cm^{-1}: 679, 723, 796, 1183, 1236, 1545, 1671, 1787, 2879, 3028.

HRMS (*m/z*-ES): [M^+-BF_4^-] calcd. for $C_{18}H_{21}N_2O_6^+$ 361.1394; found 361.1392.

7.3.16 1-(2-Ethoxy-2-oxoethyl)-4,5-*bis*(methoxycarbonyl)-3-methyl-1*H*-imidazol-3-ium tetrafluoroborate (371)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **368** (250 mg, 0.93mmol) in acetonitrile (2 mL). Trimethyloxonium tetrafluoroborate (137 mg, 0.93 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* after which the pure product **371** was obtained as a pale yellow oil (318 mg, 92%).

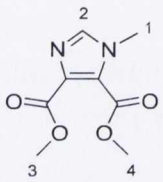
δ_H (400 MHz, DMSO-d_6): 1.24 (t, J 7.1, 3H, H-1), 3.91 (s, 3H, H-6), 3.97 (s, 3H, H-7), 4.01 (s, 3H, H-5), 4.22 (q, J 7.1, 2H, H-2), 5.39 (s, 2H, H-3), 9.45 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 14.8, 37.4, 50.7, 51.4, 54.8, 63.1, 126.5 (q), 128.4 (q), 142.6, 157.9 (q), 167.0 (q), 168.2 (q).

ν_{max} (film)/cm^{-1}: 689, 754, 1185, 2143, 1295, 1370, 1568, 1798, 2258, 2854.

HRMS (*m/z*-ES): [M^+-BF_4^-] calcd. for $C_{12}H_{17}N_2O_6^+$ 285.1081; found 285.1079.

7.3.17 Dimethyl-1-methyl-1*H*-imidazole-4,5-dicarboxylate (372)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **362** (300 mg, 1.60 mmol) in methanol (7 mL). To this methyl iodide (187 µL, 3.00 mmol) was added. The reaction mixture was stirred under argon at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting residue was extracted with CH_2Cl_2. The extracts were combined and concentrated *in vacuo* giving the pure product **372** as a pale yellow oil (273 mg, 86%).

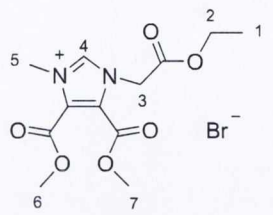
δ_H (400 MHz, $CDCl_3$): 3.77 (s, 3H, H-3), 3.78 (s, 3H, H-4), 3.83 (s, 3H, H-1), 7.92 (s, 1H, H-2).

δ_C (100 MHz, $CDCl_3$): 33.6, 51.8, 52.4, 124.7 (q), 136.1 (q), 141.2, 160.0 (q), 162.9 (q).

ν_{max} (film)/cm^{-1}: 678, 739, 801, 1194, 1248, 1386, 1597, 1742, 2201, 2870.

HRMS (*m/z*-ES): [M^+] calcd. for $C_8H_{10}N_2O_4$ 198.0719; found 198.0717.

7.3.18 1-(2-Ethoxy-2-oxoethyl)-4,5-*bis*(methoxycarbonyl)-3-methyl-1*H*-imidazol-3-ium bromide (373)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **372** (250 mg, 1.26 mmol) in acetonitrile (2 mL). Ethyl bromoacetate (277 μL, 2.50 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* giving a light brown oil. This oil was washed with diethyl ether (20 mL) to remove excess ethyl bromoacetate giving the pure product **373** as a yellow oil (408 mg, 89%).

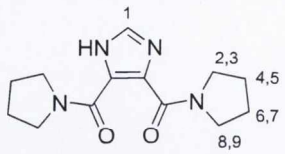
δ_H (400 MHz, DMSO-d_6): 1.25 (t, J 7.1, 3H, H-1), 3.91 (s, 3H, H-6), 3.97 (s, 3H, H-7), 4.02 (s, 3H, H-5), 4.24 (q, J 7.1, 2H, H-2), 5.40 (s, 2H, H-3), 9.45 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 13.9, 36.6, 49.9, 52.1 53.9, 62.2, 125.6 (q), 127.5 (q), 141.8, 157.0 (q), 166.1 (q), 168.4 (q).

ν_{max} (film)/cm^{-1}: 684, 745, 798, 1167, 1295, 1380, 1568, 1782, 2870.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{12}H_{17}N_2O_6^+$ 285.1081; found 285.1084.

7.3.19 (1*H*-imidazole-4,5-diyl)*bis*(pyrrolidin-1-ylmethanone) (374)



A 10 mL microwave reaction vial was fitted with a magnetic stirrer and to this dimethyl imidazole-4,5-dicarboxylate **362** (500 mg, 2.70 mmol) was added. This was dissolved in distilled pyrrolidine (1.2 mL, 14.4 mmol). The reaction was fitted with a lid, placed in the microwave under reduced pressure and stirred for 3 h at 110 °C. Upon completion of the reaction the pyrrolidine was removed *in vacuo* and the resulting residue was purified by flash chromatography (CH_2Cl_2:MeOH, 1:0-10:1) giving the pure product **374** as an off-white solid (506 mg, 72%). M.p. 145-147 °C.

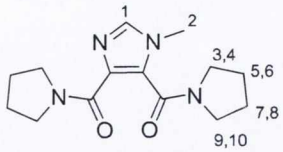
δ_H (400 MHz, DMSO-d_6): 1.95-1.98 (m, 4H, H-4 and H-5), 2.06-2.11 (m, 4H, H6 and H-7), 3.70 (m, 4H, H-2 and H-3), 3.82 (m, 4H, H-8 and H-9), 7.72 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 23.8, 26.3, 46.9, 47.8, 126.2 (q), 126.5 (q), 136.5, 159.6 (q).

ν_{max} (film)/cm^{-1}: 680, 756, 1146, 1240, 1287, 1345, 1580, 1740, 2236, 2870.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{13}H_{18}N_4O_2$ 262.1429; found 262.1432.

7.3.20 (1H-imidazole-4,5-diyl)*bis*(pyrrolidin-1-ylmethanone) (375)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **374** (250 mg, 0.95 mmol) in methanol (7 mL). To this methyl iodide (144 μL, 2.30 mmol) was added. The reaction mixture was stirred under argon at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting residue was extracted with dichloromethane (2 x 5 mL). The organic layer was concentrated *in vacuo* giving the pure product **375** as a pale yellow oil (220 mg, 84%).

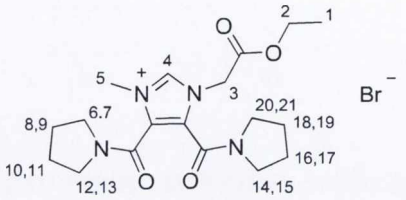
δ_H (400 MHz, DMSO-d_6): 1.91-1.98 (m, 8H, H-5, H-6, H-7 and H,8), 3.63-3.70 (m, 8H, H-3, H-4, H-9 and H-10), 3.79 (s, 3H, H-2), 7.93 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 23.9, 24.5, 26.2, 27.6, 35.2, 47.1, 48.2, 48.9, 49.5, 127.3 (q), 138.9 (q), 141.3, 161.2 (q), 167.8 (q).

ν_{max} (film)/cm^{-1}: 676, 795, 1156, 1236, 1328, 1632, 1756, 2245, 2854.

HRMS (*m/z*-ES): [M^+] calcd. for $C_{14}H_{20}N_4O_2$ 276.1431; found 276.1435.

7.3.21 3-(2-Methoxyacetyl)-1-methyl-4,5-*bis*[(pyrrolidin-1-yl)carbonyl]-1*H*-imidazol-3-ium bromide (376)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **375** (200 mg, 0.72 mmol) in acetonitrile (2 mL). Ethyl bromoacetate (320 μL, 2.90 mmol) was added and the reaction mixture was stirred at room temperature for 4 d. Upon completion of the reaction, the solvent was removed *in vacuo* giving a light brown oil. This oil was washed with ether (25 mL) to remove excess ethyl bromoacetate, giving the pure product **376** as a yellow oil (282 mg, 89%).

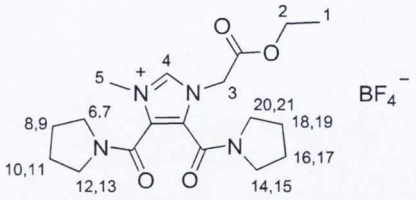
δ_H (400 MHz, DMSO-d_6): 1.36 (t, J 6.5, 3H, H-1), 1.86-1.89 (m, 8H, H-8 to H-11 and H16 to H19), 3.61-3.68 (m, 8H, H-6, H-7, H-12 to H15, H-20 and H-21), 3.65 (s, 3H, H-5), 4.25 (q, J 6.5, 2H, H-2), 4.73(s, 2H, H-3), 8.96 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 23.4, 24.2, 25.9, 27.1, 33.2, 35.4, 46.9, 47.8, 48.6, 49.5, 53.4, 61.8, 127.3 (q), 138.9 (q), 141.3, 159.5 (q), 161.2 (q), 167.8(q).

ν_{max} (film)/cm^{-1}: 656, 745, 782, 1140, 1245, 1301, 1634, 1756, 2226, 2823.

HRMS (*m/z*-ES): [M^+-Br^-] calcd. for $C_{18}H_{27}N_4O_4^+$ 363.2032; found 363.2029.

7.3.22 3-(2-Methoxyacetyl)-1-methyl-4,5-*bis*[(pyrrolidin-1-yl)carbonyl]-1*H*-imidazol-3-ium tetrafluoroborate (377)



To a 25 mL round bottomed flask fitted with a magnetic stirring bar, **376** (250 mg, 0.56mmol) was added. To this $NaBF_4$ (74.8 mg, 0.68 mmol) and acetone (10 mL) were added and the mixture was placed under an argon atmosphere. The resulting suspension was stirred at room temperature for 4 d. After which a white precipitate was formed. This precipitate was filtered using a Buchner funnel under vacuum and washed with dry acetone (2 x 5 mL). The combined filtrate and washings were then concentrated *in vacuo* giving the pure product **377** as a pale yellow oil (241 mg, 96%).

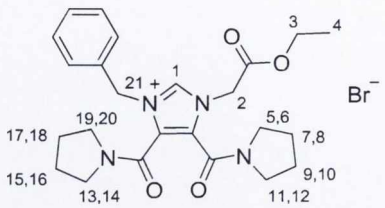
δ_H (400 MHz, DMSO-d_6): 1.29 (t, J 6.8, 3H, H-1), 1.82-1.86 (m, 8H, H-8 to H-11 and H-16 to H-19), 3.61-3.66 (m, 8H, H-6, H-7, H-12 to H-15, H-20 and H-21), 3.59 (s, 3H, H-5), 4.17 (q, J 6.8, 2H, H-2), 4.73 (s, 2H, H-3), 9.35 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 23.2, 24.5, 26.0, 27.3, 33.5, 35.7, 47.1, 47.9, 48.4, 49.1, 53.5, 62.0, 127.3 (q), 138.6 (q), 142.3, 159.6 (q), 161.2 (q), 167.7 (q).

ν_{max} (film)/cm^{-1}: 671, 795, 1136, 1254, 1298, 1546, 1651, 1743, 2235, 2824.

HRMS (*m/z*-ES): $[M^+-BF_4^-]$ calcd. for $C_{18}H_{27}N_4O_4^+$ 363.2032; found 363.2030.

7.3.23 1-Benzyl-3-(2-ethoxy-2-oxoethyl)-4,5-*bis*(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium bromide (379)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **374** (250 mg, 0.95 mmol) in acetonitrile (5 mL). To this K_2CO_3 (135 mg, 0.95 mmol) was added and the reaction mixture was stirred for 30 min under an argon atmosphere. Ethyl bromoacetate (421 µL, 3.8 mmol) was added and the reaction mixture was stirred at room temperature for 2 d. Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting residue was extracted with dichloromethane. The extracts were combined and concentrated *in vacuo* giving a pale yellow solid. This solid was washed with ether after which the pure product **378** was obtained as an off-white solid. To this benzyl bromide (452 µL, 3.80 mmol) and MeOH (5 mL) were added and the reaction mixture was stirred under reflux for 48 h. Upon completion of the reaction, the solvent was removed *in vacuo* resulting in a yellow oil. This oil was washed with ether (15 mL) to remove excess benzyl bromide after which the pure catalyst **379** was obtained as a pale yellow oil (355 mg, 72%).

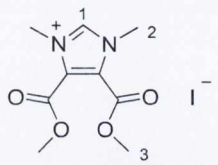
δ_H (400 MHz, DMSO-d_6): 1.25 (t, J 6.9, 3H, H-4), 1.93-1.95 (m, 4H, H-7, H-8, H-17, and H-18), 2.03-2.09 (m, 4H, H-9, H-10, H-15 and H-16), 3.59-3.69 (m, 8H, H-5, H-6, H-11 H-12, H-13, H-14, H-19 and H-20), 4.13 (m, 2H, H-3) 5.23 (s, 2H, H-2), 5.84 (s, 2H, H-21), 7.23-7.29(m, 5H, Ar),8.21 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 21.2, 23.5, 25.8, 26.2, 33.7, 45.6, 46.7, 47.9, 48.1, 52.4, 54.8, 61.6, 125.6, 126.8 (q), 127.6, 129.2, 137.3 (q), 138.3 (q), 141.2, 157.9 (q), 160.6 (q), 167.2 (q).

ν_{max} (film)/cm^{-1}: 685, 733, 804, 1146, 1265, 1532, 1674, 1723, 2232, 2834, 3034.

HRMS (*m/z*-ES): $[M^+\text{-}BF_4^-]$ calcd. for $C_{24}H_{31}N_4O_4^+$ 439.2340; found 439.2338.

7.3.24 4,5-*bis*(Methoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium iodide (381)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **372** (250 mg, 1.26 mmol) in acetonitrile (2 mL). Methyl iodide (79 μL, 1.26 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* giving the pale yellow oil **381** (368 mg, 86%).

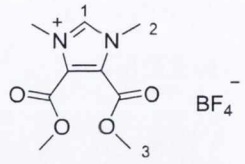
δ_H (400 MHz, DMSO-d_6): 3.91-4.02 (m, 12H, H-2 and H-3), 9.40 (s, 1H, H-1)

δ_C (100 MHz, DMSO-d_6): 36.2, 53.8, 126.6 (q), 141.2, 157.3 (q).

ν_{max} (film)/cm^{-1}: 682, 745, 796, 1193, 1245, 1381, 1624, 1785, 2225, 2868.

HRMS (*m/z*-ES): $[M^+\text{-}I^-]$ calcd. for $C_9H_{13}N_2O_4^+$ 213.0875; found 213.0877.

7.3.25 4,5-*bis*(Methoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (382)



A 25 mL round bottomed flask, fitted with a magnetic stirring bar, was charged with **372** (250 mg, 1.62 mmol) in acetonitrile (2 mL). Triemthyloxonium tetrafluoroborate (240 mg, 1.62 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. Upon completion of the reaction, the solvent was removed *in vacuo* giving the pale yellow solid **382** (344 mg, 91%). M.p. 62-64 °C

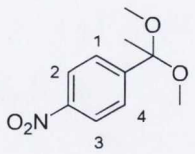
δ_H (400 MHz, DMSO-d_6): 3.92-4.02 (br.s, 12H, H-2 and H-3), 9.42 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 38.1, 53.8, 126.7 (q), 127.1 (q), 141.2, 157.4 (q).

ν_{max} (film)/cm^{-1}: 678, 742, 796, 1190, 1245, 1381, 1632, 1784, 2225, 2872.

HRMS (*m/z*-ES): [M^+-BF_4^-] calcd. for $C_9H_{13}N_2O_4^+$ 213.0875; found 213.0873.

7.3.26 4-Nitroacetophenone dimethyl ketal (384)



The desired dimethyl ketal was obtained following the general procedure A using catalyst **370** (3.7 mg, 0.01 mmol), methanol (2.6 mL) and 4-nitroacetophenone (165.2 mg, 1.00 mmol). The reaction mixture was then heated at 35 °C for 48 hours. **Note:** the use of $PhNHNH_2$ was not required. After purification of the crude material by flash chromatography (15:1 hexane;

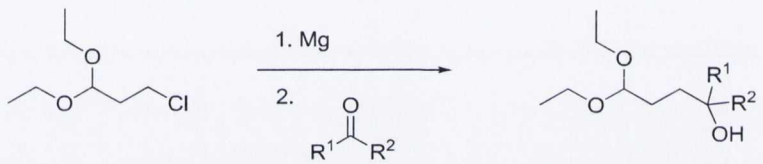
EtOAc) the product **384** was obtained as a pale yellow solid (133mg, 63%). M.p. 58-60 °C (lit.,[286] 60-61.5 °C).

δ_H (400 MHz, $CDCl_3$): 1.53 (s, 3H, CH_3), 3.78 (s, 6H, O-CH_3), 7.66 (d, J 8.9, 2H, H-1 and H-4), 8.17 (d, J 8.9, 2H, H-2 and H-3).

δ_C (100 MHz, $CDCl_3$): 26.4, 48.6, 123.1, 123.9, 129.1, 146.7 (q), 151.4 (q).

7.4 Experimental data for Chapter 4

7.4.1 General procedure B: transacetalisation alcohol substrate synthesis



7.4.1.1 Preparation of the Grignard reagent 407

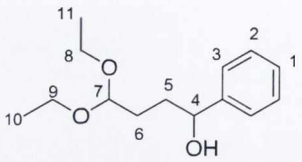
To a 100 mL round bottomed flask a solution of freshly distilled 3-chloropropionaldehyde diethylacetal **402** (8.0 g, 48.0 mmol) in THF (10 mL) was added to activated magnesium turnings (1.46 g, 60 mmol). The temperature of the exothermic reaction mixture was kept between 20-25 °C by cooling with an ice bath. After heat development ceased the mixture was diluted with THF (20 mL) and the resulting solution was used immediately.

7.4.1.2 Addition to aldehydes:

Approximately one quarter of the Grignard reagent prepared above **407** (~8 mL, 12.0 mmol) was added dropwise to a solution of the corresponding aldehyde (3.0 mmol) in THF (4 mL) at -40 °C. The mixture was stirred at -40 °C for 30 min and then allowed to cool to 0 °C over 2 h. It was then quenched at 0 °C with saturated aqueous $NaHCO_3$ (5 mL) and H_2O (5 mL). The solution was then extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated prior to purification. Flash column

chromatography on silica gel yielded the pure product. The products were used immediately in transacetalisation reaction or stored as 0.1 M solutions in Et_2O.

7.4.1.3 4,4-Diethoxy-1-phenylbutan-1-ol (402)

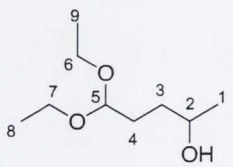


The desired alcohol was obtained following general procedure B using **407** (8 mL, 12.0 mmol) which was added dropwise to a solution of benzaldehyde (305 μL, 3.0 mmol) in THF (4 mL) at -40 °C. After purification of the crude material by flash chromatography (2:1, hexane:Et_2O) the product **402** was obtained as a pale yellow liquid (657 mg, 92%). The NMR spectral data associated with **402** were consistent with those previously reported.[263]

δ_H (400 MHz, C_6D_6): 1.05-1.70 (m, 6H, H-10 and H-11), 1.72-.1.86 (m, 4H, H-5 and H-6), 2.06 (br. s, 1H, OH), 3.44-3.51 (m, 4H, H-8 and H-9), 4.32-4.39 (m, 1H, H-4), 4.48-4.50 (m, 1H, H-7), 7.12 (t, J 7.4, 1H, H-1), 7.16-7.19 (m, 2H, H-2), 7.29 (d, J 7.2, 2H, H-3).

HRMS (*m/z*-ES): $[M^+ + Na^+]$ calcd. for $C_{14}H_{22}O_3Na$ 261.1461: found 261.1460.

7.4.1.4 5,5-Diethoxypentan-2-ol (409)



The desired alcohol was obtained following general procedure B using **407** (8 mL, 12.0 mmol) which was added dropwise to a solution of acetaldehyde (169 μL, 3.0 mmol) in THF

(4 mL) at -40 °C. After purification of the crude material by flash chromatography (3:1, hexane:Et_2O) the product **409** was obtained as a colourless oil (475 mg, 90%).

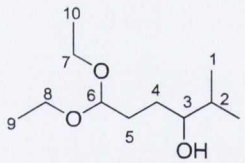
δ_H (400 MHz, C_6D_6): 1.11-1.25 (m, 9H, H-1, H-8 and H-9), 1.69-.1.82 (m, 4H, H-3 and H-4), 2.09 (br. s, 1H, OH), 3.06-3.14 (m, 1H, H-2), 3.39-3.56 (m, 4H, H-6 and H-7), 4.49 (t, J 5.1, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 15.5, 24.5, 30.6, 32.7, 60.3, 62.2, 76.9, 103.4.

ν_{max} (film)/cm^{-1}: 1120, 1185, 1350, 1376, 2864, 3580.

HRMS (*m/z*-ES): $[M^+ + Na^+]$ calcd. for $C_9H_{20}O_3Na$ 199.1312; found 199.1210.

7.4.1.5 6,6-Diethoxy-2,2-dimethylhexan-3-ol (412)



The desired alcohol was obtained following general procedure B using **407** (8 mL, 12.0 mmol) which was added dropwise to a solution of isobutyraldehyde (273 μL, 3.0 mmol) in THF (4 mL) at -40 °C. After purification of the crude material by flash chromatography (2:1, hexane:Et_2O) the product **414** was obtained as a colourless oil (570 mg, 90%).

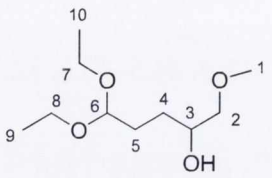
δ_H (400 MHz, C_6D_6): 0.90 (d, J 6.8, 6H, H-1), 1.10 (t, J 7.1 6H, H-9 and H-10), 1.40-1.45 (m, 2H, H-4), 1.58-1.65 (m, 2H, H-5) 1.87-1.98 (m, 1H, H-2), 2.07 (s, 1H, OH), 3.09-3.11 (m, 1H, H-3), 3.56-3.58 (m, 4H, H-7 and H-8), 4.46 (t, J 5.4, 1H, H-6).

δ_C (100 MHz, $CDCl_3$): 15.6, 26.1, 28.3, 31.2, 35.4, 61.0, 61.2, 79.5, 103.4.

ν_{max} (film)/cm^{-1}: 1124, 1165, 1260, 1353, 2864, 3598.

HRMS (*m/z*-ES): $[M^+ + Na^+]$ calcd. for $C_{11}H_{24}O_3Na$ 227.1625; found 227.1623.

7.4.1.6 5,5-Diethoxy-1-methoxypentan-2-ol (414)



The desired alcohol was obtained following the general procedure B using **407** (8 mL, 12.0 mmol) which was added dropwise to a solution of 2-methoxyacetaldehyde (221 μL, 3.0 mmol) in THF (4 mL) at -40 °C. After purification of the crude material by flash chromatography (3:1, hexane:Et_2O) the product **414** was obtained as a colourless oil (575 mg, 90%).

δ_H (400 MHz, C_6D_6): 1.10 (t, J 7.4 6H, H-9 and H-10), 1.34-1.60 (m, 2H, H-5), 1.70-1.92 (m, 2H, H-4), 2.09 (s, 1H, OH), 3.29 (s, 3H, H-1) 3.40-3.65 (m, 7H, H-2, H-3, H-7 and H-8), 4.46 (t, J 5.1, 1H, H-6).

δ_C (100 MHz, $CDCl_3$): 15.5, 26.4, 28.3, 56.9, 61.8, 62.0, 76.9, 80.4, 103.8.

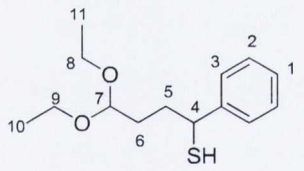
ν_{max} (film)/cm^{-1}: 1136, 1178, 1260, 1298,1353, 2820, 3545.

HRMS (*m/z*-ES): $[M^+ + Na^+]$ calcd. for $C_{10}H_{22}O_4Na$ 229.1418; found 229.1419.

7.4.2 General procedure C: transthioacetalisation substrate synthesis

To a 50 mL round bottomed flask charged with magnetic stirring bar, triphenylphosphine (1.23 g, 4.00 mmol) and THF (10 mL) were added. The solution was cooled to 0 °C and diisopropyl azodicarboxylate (DIAD) (780 mg, 4.00 mmol) was added after which the resulting solution was stirred for 30 min. A mixture of thioacetic acid (288 μL, 4.00 mmol) and the corresponding alcohol (2.00 mmol) in THF (10 mL) was added to this solution *via* syringe over 30 mins at -20 °C. The reaction mixture was warmed to 0 °C and stirred at this temperature for 1.5 h, after which it was heated to room temperature and allowed to stir overnight. The reaction mixture was poured into H_2O and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The pure thioacetate was obtained by flash column chromatography (EtOAc:hexane). The desired thiol was then afforded through saponification of the thioacetate using aq. NaOH in MeOH directly before use in the intramolecular transthioacetalisation reaction.

7.4.2.1 4,4-Diethoxy-1-phenylbutane-1-thiol (420)



The desired thiol was obtained following general procedure C using triphenylphosphine (1.23g, 4.00 mmol), DIAD (780 mg, 4.00 mmol), thioacetic acid (288 μL, 4.00 mmol) and alcohol **402** (2.00 mmol). After purification by flash column chromatography (hexane:EtOAc, 10:1), the thioacetate was treated with aqueous NaOH in MeOH generating the thiol **420** (371 mg, 73%).

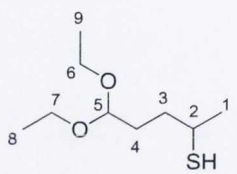
δ_H (400 MHz, C_6D_6): 1.14 (t, J 7.2, 6H, H-10 and H-11), 1.56 (br.s, 1H, SH), 1.69-1.82 (m, 4H, H-5 and H-6), 3.40-3.61 (m, 4H, H-8 and H-9), 3.78-3.81 (m, 1H, H-4), 4.47-4.51 (m, 1H, H-7), 7.14 (t, J 7.3, 1H, H-1), 7.16-7.19 (m, 2H, H-2), 7.29 (d, J 7.1, 2H, H-3).

δ_C (100 MHz, $CDCl_3$): 15.5, 30.3, 31.4 38.2, 61.5, 61.8, 104.6, 125.9, 127.1, 128.4, 143.2 (q).

ν_{max} (film)/cm^{-1}: 684, 750, 802, 1136, 1175, 1260, 1353, 2564, 2864.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{14}H_{22}O_2S$ 254.1341; found 254.1338.

7.4.2.2 5,5-Diethoxypentane-2-thiol (421)



The desired thiol was obtained following general procedure C using triphenylphosphine (1.23 g, 4.00 mmol), DIAD (780 mg, 4.00 mmol), thioacetic acid (288 μL, 4.00 mmol) and alcohol **409** (352 mg, 2.00 mmol). After purification by flash column chromatography (hexane:EtOAc, 15:1), the thioacetate was treated with aqueous NaOH in MeOH generating the thiol **421** (246 mg, 64%).

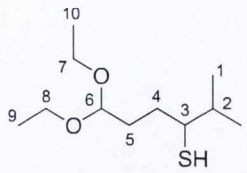
δ_H (400 MHz, C_6D_6): 1.12 (t, J 7.2, 6H, H-8 and H-9), 1.37 (d, J 7.1, 3H, H-1), 1.56 (br.s, 1H, SH),1.65-1.10 (m, 4H, H-3 and H-4), 2.75 (m, 1H, H-2), 3.45-3.50 (m, 4H, H-6 and H-7), 4.49 (m, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 15.6, 23.2, 30.1, 32.4, 35.6, 61.3, 62.1, 104.7.

ν_{max} (film)/cm^{-1}: 1123, 1178, 1286, 1345, 2567, 2864.

HRMS (*m/z*-ES): $[M^+]$ calcd. For $C_9H_{20}O_2S$ 192.1184; found 192.1183.

7.4.2.3 6,6-Diethoxy-2,2-dimethylhexane-3-thiol (422)



The desired thiol was obtained following general procedure C using triphenylphosphine (1.23 g, 4.00 mmol), DIAD (780 mg, 4.00 mmol), thioacetic acid (288 μL, 4.00 mmol) and alcohol **412** (408 mg, 2.00 mmol). After purification by flash column chromatography (hexane:EtOAc, 12:1), the thioacetate was treated with aqueous NaOH in MeOH generating the thiol **422** (312 mg, 71%).

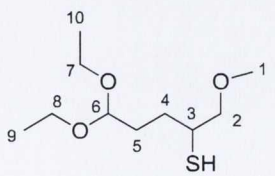
δ_H (400 MHz, C_6D_6): 0.92 (s, 6H, H-1), 1.10 (t, J 7.1 6H, H-9 and H-10), 1.34-1.54 (m, 2H, H-4), 1.58 (br.s, 1H, SH), 1.78-1.96 (m, 3H, H-2 and H-5), 2.52 (s, 1H, H-3), 3.48-3.56 (m, 4H, H-7 and H-8), 4.51 (t, J 5.4, 1H, H-6).

δ_C (100 MHz, $CDCl_3$): 15.6, 21.2, 28.3, 33.4, 35.4, 41.2, 62.4, 62.6, 104.6.

ν_{max} (film)/cm^{-1}: 1132, 1186, 1278, 1355, 2560, 2864.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{11}H_{24}O_2S$ 220.1496; found 220.1497.

7.4.2.4 5,5-Diethoxy-1-methoxypentane-2-thiol (423)



The desired thiol was obtained following general procedure C using triphenylphosphine (1.23 g, 4.00 mmol), DIAD (780 mg, 4.00 mmol), thioacetic acid (288 μL, 4.00 mmol) and alcohol **412** (412 mg, 2.00 mmol). After purification by flash column chromatography

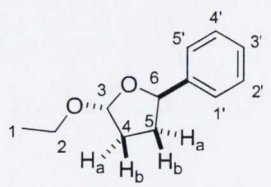
(hexane:EtOAc, 15:1), the thioacetate was treated with aqueous NaOH in MeOH generating the thiol **422** (271 mg, 61%).

δ_H (400 MHz, C_6D_6):	1.12 (t, J 7.5, 6H, H-9 and H-10), 1.35-1.50 (m, 2H, H-5), 1,58 (br.s, 1H, SH), 1.80-1.95 (m, 2H, H-4), 2.86 (s, 1H, H-3), 3.36 (s, 3H, H-1), 3.55-3.75 (m, 6H, H-2, H-7 and H-8), 4.48 (m, 1H, H-6)
δ_C (100 MHz, $CDCl_3$):	15.4, 22.6, 29.8, 36.1, 56.7, 63.1, 63.4, 78.5, 103.8.
ν_{max} (film)/cm^{-1}:	1142, 1186, 1260, 1298,1358, 2558, 2820.
HRMS (*m/z*-ES):	$[M^+]$ calcd. for $C_{10}H_{22}O_2S$ 222.1287; found 222.1290.

7.4.3 General procedure D: intramolecular cyclisation of alcohols and thiols

To a 25 mL round bottomed flask charged with a magnetic stirring bar, the corresponding alcohol/thiol (1.00 mmol) and anhydrous THF (1 mL) were added over 4 Å molecular sieves (150 mg). To this catalyst **371** (18.6 mg, 0.05 mmol) in anhydrous THF (1 mL) was added *via* syringe. The resulting solution was stirred at room temperature for 18 h. After which time NEt_3 was added to the reaction mixture and the solvent was removed *in vacuo.* The resulting crude product was then purified by column chromatography affording the desired cyclic compound. (Note: more volatile compounds such as **419** and **430** were columned directly without being concentrated under reduced pressure).

7.4.3.1 2-Ethoxy-5-phenyltetrahydrofuran (*trans*-408)



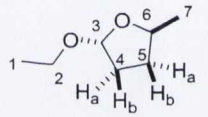
The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and alcohol **402** (238 mg, 1.00 mmol) in THF (2 mL). Purification by flash

column chromatography (hexane:EtOAc, 9:1) afforded the pure diastereomer *trans*-**408** as a colourless oil (179 mg, 93%). The NMR spectral data associated with *trans*-**408** were consistent with those previously recorded.[12]

δ_H (400 MHz, C_6D_6): 1.15 (app. t, 3H, H-1), 1.67-1.63 (m, 1H, H-4a), 1.83-1.88 (m, 1H, H-5a), 1.92-2.01 (m, 2H, H-4b and H-5b), 3.42-3.82 (m, 2H, H-2), 4.87-5.09 (m, 2H, H-3 and H-8), 7.11 (t, J 7.4, 1H, H-3'), 7.23 (dd, 7.4, 7.3 2H, H-2' and 4'), 7.44 (d, J 7.3, H-1' and 5').

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{12}H_{16}O_2$ 192.1150; found 192.1151.

7.4.3.2 2-Ethoxy-5-methyltetrahydrofuran (*trans*-417)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and alcohol **409** (176 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (hexane:EtOAc, 8:1) afforded the pure diastereomer *trans*-**417** as a colourless oil (98 mg, 75%).

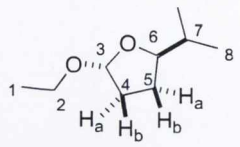
δ_H (400 MHz, C_6D_6): 1.15 (app.t, 3H, H-1), 1.32 (d, J 7.2, 3H, H-7) 1.67-1.63 (m, 1H, H-5a), 1.83-1.88 (m, 1H, H-4a), 1.92-2.01 (m, 2H, H-4b and H-5b), 3.42-3.82 (m, 2H, H-2), 3.94-4.01 (m, 1H, H-6) 5.02-5.09 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 15.7, 24.6, 33.0, 33.5, 63.6, 82.5, 104.1.

ν_{max} (film)/cm^{-1}: 786, 1135, 1185, 1240, 1350, 1486, 2861.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_7H_{14}O_2$ 130.0994; found 130.0992.

7.4.3.3 2-Ethoxy-5-isopropyltetrahydrofuran (*trans*-418)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and alcohol **414** (204 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (hexane:EtOAc, 10:1) afforded the pure diastereomer *trans*-**418** as a colourless oil (107 mg, 68%).

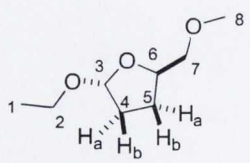
δ_H (400 MHz, C_6D_6): 0.91 (s, 6H, H-8), 1.15 (app.t, 3H, H-1), 1.32-1.35 (m, 1H, H-5a), 1.67.1.72 (m, 1H, H-4a), 1.82-1.86 (m, 2H, H-4b and H-5b), 2.14-2.16 (m, 1H, H-7), 3.36-3.75 (m, 2H, H-2), 3.94 (m, 1H, H-6), 5.06 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 15.1, 24.2, 26.1, 33.6, 33.9, 62.3, 87.9, 103.4.

ν_{max} (film)/cm^{-1}: 798, 945, 1132, 1162, 1260, 1353, 2865.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_9H_{18}O_2$ 158.1309; found 158.1309.

7.4.3.4 2-Ethoxy-5-(methoxymethyl)tetrahydrofuran (*trans*-419)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and alcohol **414** (206 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (Hexane:EtOAc, 9:1) afforded the pure diastereomer *trans*-**419** as a colourless oil (94 mg, 59%).

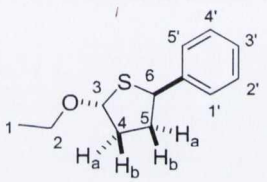
δ_H (400 MHz, C_6D_6): 1.12 (app.t, 3H, H-1), 1.35-1.40 (m, 1H, H-5a), 1.60-1.69 (m, 1H, H-4a), 1.68-1.69 (m, 2H, H-4b and H-5b), 3.30 (s, 3H, H-8), 3.36-3.38 (m, 4H, H-2 and H-7), 4.56 (m, 1H, H-6), 5.08 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 15.1, 24.6, 32.5, 59.6, 62.4, 78.1, 83.1, 105.3.

ν_{max} (film)/cm^{-1} 794, 932, 1126, 1170, 1260, 1286, 1345, 2834.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_8H_{16}O_2$ 160.1099; found 160.1095.

7.4.3.5 2-Ethoxy-5-phenyltetrahydrothiophene (*trans*-427)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and thiol **420** (254 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (hexane:EtOAc, 12:1) afforded the pure diastereomer *trans*-**427** as a colourless oil (191 mg, 92%).

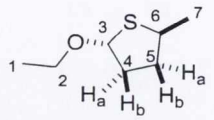
δ_H (400 MHz, C_6D_6): 1.12 (app. t, 3H, H-1), 1.78-1.88 (m, 1H, H-4a), 1.93-2.02 (m, 1H, H-5a), 2.12-2.29 (m, 2H, H-4b and H-5b), 3.65-3.82 (m, 2H, H-2), 4.10-4.21 (m, 2H, H-3 and H-6), 7.18 (t, J 7.3, 1H, H-3'), 7.21 (dd, 7.3, 7.1 2H, H-2' amd H-4'), 7.40 (d, J 7.1, 2H, H-1' and 5').

δ_C (100 MHz, $CDCl_3$): 15.7, 31.2, 32.8, 46.7, 63.6, 84.5, 126.5, 127.9, 128.2, 140.8 (q).

ν_{max} (film)/cm^{-1}: 795, 809, 871, 933, 1122, 1157, 1286, 1493, 2894, 2971, 3034.

HRMS (*m/z*-ES): [M^+] calcd. for $C_{12}H_{16}OS$ 208.0924; found 208.0922.

7.4.3.6 2-Ethoxy-5-methyltetrahydrothiophene (*trans*-428)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and thiol **421** (192 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (Hexane:EtOAc, 15:1) afforded the pure diastereomer *trans*-**428** as a colourless oil (102 mg, 70%).

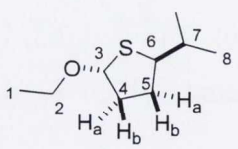
δ_H (400 MHz, C_6D_6): 1.15 (app.t, 3H, H-1), 1.29 (d, J 7.4, 3H, H-7) 1.67-1.63 (m, 1H, H-5a), 1.83-1.88 (m, 1H, H-4a), 1.92-2.01 (m, 2H, H-4b and H-5b), 2.98 (m, 1H, H-6), 3.55-3.79 (m, 2H, H-2), 4.10 (m, 1H, H-3)

δ_C (100 MHz, $CDCl_3$): 15.6, 22.4, 33.6, 34.2, 41.7, 62.1, 85.6.

ν_{max} (film)/cm^{-1}: 768, 852, 933, 1132, 1282, 1486, 2893, 2957.

HRMS (*m/z*-ES): [M^+] calcd. for $C_7H_{14}OS$ 146.0762; found 146.0765.

7.4.3.8 2-Ethoxy-5-isopropyltetrahydrothiophene (*trans*-429)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and thiol **422** (220 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (hexane:EtOAc, 12:1) afforded the pure diasteromer *trans*-**429** as a colourless oil (108 mg, 62%).

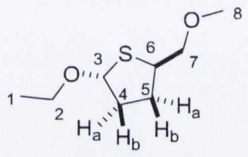
δ_H (400 MHz, C_6D_6): 0.90 (s, 6H, H-8), 1.18 (app.t, 3H, H-1), 1.67-1.85 (m, 2H, H-4a and H-5a), 1.97-2.13 (m, 2H, H-4b and H-5b), 2.12-2.16 (m, 1H, H-7), 2.74-2.79 (m, 1H, H-6) 3.55-3.75 (m, 2H, H-2), 4.29 (m, 1H, H-3).

δ_C (100 MHz, $CDCl_3$): 14.9, 22.4, 29.5, 31.6, 34.9, 42.7, 62.6, 87.9.

ν_{max} (film)/cm^{-1}: 695, 786, 849, 928, 1145, 1279, 1464, 2886, 2943.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_9H_{18}OS$ 174.1078; found 174.1078.

7.4.3.9 2-Ethoxy-5-(methoxymethyl)tetrahydrothiophene (*trans*-430)



The desired compound was obtained following general procedure D using catalyst **371** (18.6 mg, 0.05 mmol) and thiol **423** (222 mg, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (hexane:EtOAc, 15:1) afforded the pure diastereomer *trans*-**430** as a colourless oil (91 mg, 52%).

δ_H (400 MHz, C_6D_6): 1.14 (app.t, 3H, H-1), 1.70-1.78 (m, 1H, H-5a), 1.84-1.90 (m, 1H, H-4a), 1.98-2.13 (m, 2H, H-4b and H-5b), 3.30 (s, 3H, H-8), 3.09-3.14 (m, 1H, H-6), 3.49-3.75 (m, 4H, H-2 and H-7), 4.42 (m, 1H, H-3).

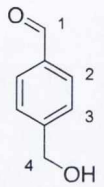
δ_C (100 MHz, $CDCl_3$): 15.5, 28.9, 34.5, 57.6, 59.2, 62.6, 77.8, 83.7.

ν_{max} (film)/cm^{-1}: 685, 786, 872, 1122, 1138, 1286, 1493, 2895, 2962.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_8H_{16}OS$ 176.0871; found 176.0868.

7.5 Experimental for Chapter 5

7.5.1 4-(Hydroxymethyl)benzaldehyde (436)

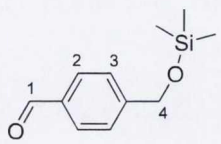


To a 50 mL round bottomed flask charged with a magnetic stirring bar, terephthaldehyde (**435,** 1 g, 7.50 mmol) in THF (17.5 mL) and EtOH (12.5 mL) was added. The reaction mixture was placed was cooled to 0 °C, to this $NaBF_4$ (85 mg, 2.20 mmol) was added and the solution was stirred at 0 °C for 6 h. The reaction mixture was then brought to pH 5 using 2M HCl and the resulting solution was concentrated *in vacuo*. The crude oil was extracted using EtOAc (2 x 10 mL) and water. The organic layers were combined and dried over $MgSO_4$. The pure product **436** was obtained as a pale yellow oil (898 mg, 88%) after flash column chromatography (1:1, EtOAc:hexane). The NMR spectral data associated with **436** were consistent with those previously reported.[264]

δ_H (400 MHz, $CDCl_3$): 4.83 (s, 2H, H-4), 7.56 (d, J 8.0 ,2H, H-3), 7.90 (d, J 8.0, 2H, H-2), 10.03 (s, 1H, H-1).

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_8H_8O_2$ 136.0524; found 136.0526.

7.5.2 4-((Trimethylsilyloxy)methyl)benzaldehyde (437)



To a 50 mL round bottomed flask charged with a magnetic stirring bar **436** (500 mg, 4.10 mmol) and triethylamine (631 µL, 4.50 mmol) were added in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and chlorotrimethylsilane (544 µL, 4.50 mmol) was added dropwise *via* syringe under argon. The reaction mixture was then heated to room temperature gradually and

stirred for 2 d after which a precipitate was formed. Hexane (20 mL) was added to the solution and the precipitates were eliminated by vacuum filtration using a Buchner funnel. The solvent was then removed from the combined organic layers under reduced pressure. A second aliquot of hexane (10 mL) was then added to the resulting residue, the mixture was filtered under vacuum again and the solvent was removed *in vacuo* affording the desired product **437** as a colourless oil (529 mg, 62%).

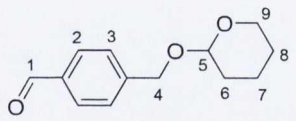
δ_H (400 MHz, $CDCl_3$): 0.17 (s, 9H, $SiCH_3$), 4.74 (s, 2H, H-4), 7.38 (d, J 7.8, 2H, H-3), 7.95 (d, J 7.8, 2H, H-2), 10.05 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 0.4, 64.1, 126.1, 128.9, 129.7 (q), 146.5 (q), 191.5.

ν_{max} (film)/cm^{-1}: 685, 765, 1120, 1253, 1354, 1728, 2726.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{11}H_{16}O_2Si$ 208.0918; found 208.0918.

7.5.3 4-((Tetrahydro-2*H*-pyran-2-yloxy)methyl)benzaldehyde (438)



A 50 mL round bottomed flask fitted with a magnetic stirring bar was charged with **436** (800 mgs, 5.90 mmol) and the reaction vessel was placed under argon. To this dihydropyran (2.3 mL, 29.60 mmol) in CH_2Cl_2 (17 mL) was added, followed by *p*TSA (11.2 mg, 0.06 mmol). The resulting mixture was stirred at rt for 1.5 h, after which the solvent was removed *in vacuo*. The resulting residue was washed with aq. $NaHCO_3$ and extracted using Et_2O (2 x 20 mL). The combined organic layers were concentrated under reduced pressure affording the desired product **438** as a colourless oil (1.01 g, 78%).

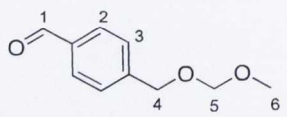
δ_H (400 MHz, $CDCl_3$): 1.54-1.90 (m, 6H, H-6, H-7 and H-8), 3.55-3.90 (m, 2H, H-9), 4.65 (app.s, 2H, H-4), 4.75 (s, 1H, H-5), 7.51-7.86 (m, 4H, H-2 and H-3), 9.96 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 19.3, 25.4, 30.5, 62.2, 68.2, 98.3, 127,7, 129.8, 135.7 (q), 145.6 (q), 191.3.

ν_{max} (film)/cm^{-1}: 745, 1030, 1120, 1205, 1600, 1685, 2860, 2930.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{13}H_{16}O_3$ 220.1096; found 220.1093.

7.5.4 4-((Methoxymethoxy)methyl)benzaldehyde (439)



A 25 mL round bottomed flask fitted with a magnetic stirring bar, was charged with alcohol **436** (260 mg, 1.84 mmol). To this a suspension of sodium hydride (49 mg, 2.02 mmol) in THF (5 mL) was added until the evolution of hydrogen subsided. The flask was then fitted with a condenser and heated under reflux for 2 h. The resulting solution was cooled to 0 °C using an ice-bath and chloromethyl methyl ether (141 μL, 1.84 mmol) was added dropwise *via* syringe under argon. The reaction mixture was then heated to room temperature and stirred for 2 h after which the solution was filtered through celite using a Hirsch funnel. The filtrate was collected and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (2:1, hexane:EtOAc) and the pure product **439** was afforded as a colourless oil (152 mg, 42%).

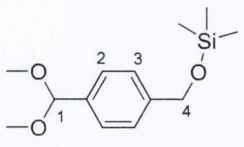
δ_H (400 MHz, $CDCl_3$): 2.25 (s, 3H, H-6), 4.45 (s, 2H, H-5), 4.71 (s, 2H, H-3), 7.53-7.56 (d, J 7.4, 2H, H-3), 7.89-7.91 (d, J 7.4, 2H, H-2), 10.04 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 55.1, 68.1, 95.6, 127.4, 129.5, 136.4 (q), 145.2 (q), 191.6.

ν_{max} (film)/cm^{-1}: 678, 730, 1040, 1100, 1162, 1385, 1684, 2800, 3100.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{10}H_{12}O_3$ 180.0786; found 180.0787.

7.5.5 (4-(Dimethoxymethyl)benzyloxy)trimethylsilane (440)



The desired dimethyl acetal was obtained following general procedure A using catalyst **371** (8.9 mg, 0.024 mmol), methanol (6.3 mL) and **437** (500 mg, 2.40 mmol). After purification of the crude material by flash chromatography (5:1 hexane:EtOAc) the product **440** was obtained as a pale yellow oil (579 mg, 95%).

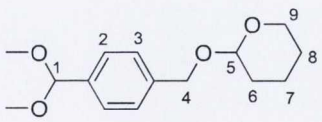
δ_H (400 MHz, $CDCl_3$): 0.17 (s, 9H, $SiCH_3$), 3.32 (s, 6H, OCH_3) 4.72 (s, 2H, H-4), 5.35 (s, 1H, H-1) 7.45 (d, J 7.8, 2H, H-3), 7.89 (d, J 7.8, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 0.4, 55.2, 64.1, 101.3, 127.3, 128.7, 135.2 (q), 147.4 (q).

ν_{max} (film)/cm^{-1}: 680, 756, 1034, 1150, 1376, 1682, 2156, 2845, 3113.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{11}H_{16}O_2Si$ 254.1348; found 254.1346.

7.5.6 2-(4-(Dimethoxymethyl)benzyloxy)tetrahydro-2*H*-pyran (441)



The desired dimethyl acetal was obtained following the general procedure A using catalyst **371** (13.4 mg, 0.036 mmol), methanol (9.4 mL) and **438** (800 mg, 3.60 mmol). After purification of the crude material by flash chromatography (3:1 hexane:EtOAc) the product **441** was obtained as a colourless oil (929 mg, 97%).

δ_H (400 MHz, $CDCl_3$): 1.51-1.89 (m, 6H, H-6, H-7 and H-8), 3.31 (s, 6H, CH_3), 3.57-3.86 (m, 2H, H-9), 4.75 (app.s, 2H, H-4), 4.86 (s,

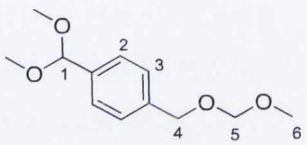
1H, H-5), 5.52 (s, 1H, H-1) 7.42-7.89 (m, 4H, H-2 and H-3).

δ_C (100 MHz, $CDCl_3$): 19.3, 25.4, 30.5, 55.6, 62.2, 68.2, 98.3, 102.1, 127,7, 129.8, 134.7 (q), 143.2 (q).

vmax (film)/cm-1: 682, 745, 1030, 1120, 1205, 1614, 1670, 2841, 2921.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{15}H_{22}O_4$ 266.1538; found 266.1535.

7.5.7 1-(Dimethoxymethyl)-4-((methoxymethoxy)methyl)benzene (442)



The desired dimethyl acetal was obtained following general procedure A using catalyst **371** (2.8 mg, 0.0075 mmol), methanol (1.9 mL) and **439** (150 mg, 0.75 mmol). After purification of the crude material by flash chromatography (3:1 hexane:EtOAc) the product **442** was obtained as a pale yellow oil (161 mg, 95 %).

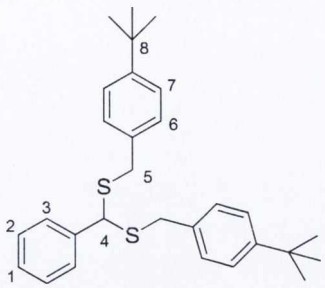
δ_H (400 MHz, $CDCl_3$): 2.18 (s, 3H, H-6), 3.32 (s, 6H, CH_3), 4.49 (s, 2H, H-5), 4.78 (s, 2H, H-3), 5.46 (s, 1H, H-1) 7.53-7.56 (m, 2H, H-3), 7.89-7.91 (m, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 54.9, 55.3, 68.1, 95.6, 101.6, 127.4, 129.5, 137.2 (q), 146.5 (q).

vmax (film)/cm-1: 680, 756, 1036, 1128, 1150, 1385, 1675, 2850, 3113.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{12}H_{18}O_4$: 226.1218; found 226.1216.

7.5.8 (Phenylmethylene)*bis*((4-*tert*-butylbenzyl)sulfane) (392)



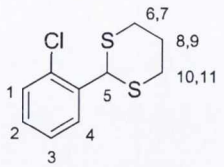
The desired dithiane was obtained following general procedure A using catalyst **371** (18.6 mg, 0.05 mmol), *t*-butylbenzyl mercaptan (421 μL, 2.26 mmol), THF (5 mL) and benzaldehyde (110 μL, 1.08 mmol). After completion of the reaction, the reaction mixture was poured onto a saturated $NaHCO_3$ solution (5 mL) and the product was extracted with ethyl acetate (2 x 10mL) 25 mL water. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash chromatography (4:1 hexane:EtOAc) the product **338** was obtained as an off-white solid (474 mg, 98%). M.p. 76-78 °C.

δ_H (400 MHz, $CDCl_3$): 1.33 (s, 18H, CH_3), 3.75 (s, 4H, H-5), 5.45 (s, 1H, H-4), 7.15 (d, J 7.8, 4H, H-6), 7.23-7.35 (m, 9H, H-1, H-2, H-3 and H-7).

δ_C (100 MHz, $CDCl_3$): 33.1, 34.9, 35.6, 51.8, 125.9, 127.1, 128.5, 128.9, 129.1, 135.6, 138.8, 149.9.

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{29}H_{36}S_2$ 448.2185; found 448.2187.

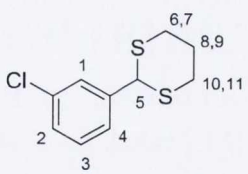
7.5.9 2-(2-Chlorophenyl)-1,3-dithiane (451a)



The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and 2-chlorobenzaldehyde (306 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (3:1 hexane:EtOAc) the product **451a** was obtained as a white solid (576 mg, 92%). M.p. 87-89 °C (lit.,[287] 89 °C).

δ_H (400 MHz, $CDCl_3$): 1.88-1.97 (m, 1H, H-9), 2.14-2.18 (m, 1H, H-8), 2.87-2.92 (m, 2H, H-7 and H-11), 3.07-3.15 (m, 2H, H-6 and H-10), 5.63 (s, 1H, H-5), 7.18-7.22 (m, 2H, H-2 and H-3), 7.34 (d, J 7.8, 1H, H-4), 7.66 (d, J 7.8, 1H, H-1).

7.5.10 2-(3-Chlorophenyl)-1,3-dithiane (452a)

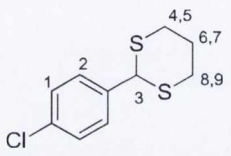


The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and 3-chlorobenzaldehyde (308 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (3:1, hexane:EtOAc) the product **452a** was obtained as a white solid (588 mg, 94%). M.p. 62-63 °C (lit.,[288] 62-63

°C). The NMR spectral data associated with **452a** were consistent with those previously reported.[288]

δ_H (400 MHz, $CDCl_3$): 1.89-1.95 (m, 1H, H-9), 2.11-2.18 (m, 1H, H-8), 2.86-2.91 (m, 2H, H-7 and H-11), 2.99-3.06 (m, 2H, H-6 and H-10), 5.10 (s, 1H, H-5), 7.24-7.25 (m, 2H, H-3 and H-4), 7.32-7.34 (m, 1H, H-2), 7.42-7.45 (m, 1H, H-1).

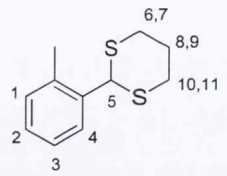
7.5.11 2-(4-Chlorophenyl)-1,3-dithiane (453a)



The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 µL, 2.98 mmol), THF (9.1 cm^3) and 4-chlorobenzaldehyde (382 mg, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (3:1, hexane:EtOAc) the product **453a** was obtained as an off-white solid (563 mg, 90%). M.p. 80-82 °C (lit.,[287] 81-82 °C). The NMR spectral data associated with **453a** were consistent with those previously reported.[289]

δ_H (400 MHz, $CDCl_3$): 1.90-1.93 (m, 1H, H-7), 2.14-2.16 (m, 1H, H-6), 2.88-2.91 (m, 2H, H-5 and H-9), 3.01-3.04 (m, 2H, H-4 and H-8), 5.13 (s, 1H, H-3), 7.30 (d, J 8.9, 2H, H-2), 7.40 (d, J 8.9, 2H, H-1).

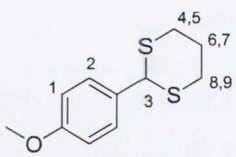
7.5.12 2.2-*o*-Tolyl-1,3-dithiane (454a)



The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and *o*-tolualdehdye (314 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (2:1, hexane:EtOAc) the product **454a** was obtained as a white crystalline solid (444 mg, 78%). M.p. 88-89 °C (lit.,[290] 90 °C).

δ_H (400 MHz, $CDCl_3$): 1.88-1.94 (m, 1H, H-9), 2.14-2.18 (m, 1H, H-8), 2.43 (s, 3H, CH_3), 2.88-2.93 (m, 2H, H-7 and H-11), 3.04-3.11 (m, 2H, H-6 and H-10), 5.31 (s, 1H, H-5), 7.14-7.19 (m, 3H, H-1, H-2 and H-3), 7.23 (d, J 6.4, 1H, H-4).

7.5.13 2-(4-Methoxyphenyl)-1,3-dithiane (102a)

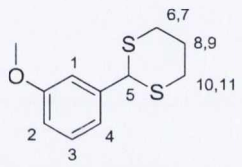


The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and 4-methoxybenzaldehyde (329 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (2:1 hexane:EtOAc) the product **102a** was obtained as a white solid (502 mg, 82%). M.p. 113-115 °C (lit.,[287] 115 °C).

The NMR spectral data associated with **102a** were consistent with those previously reported.[287]

δ_H (400 MHz, $CDCl_3$): 1.85-1.89 (m, 1H, H-7), 2.12-2.16 (m, 1H, H-6), 2.89 (ddd, J 15.1, 3.5, 3.0. 2H, H-5 and H-9), 3.05 (ddd, J 15.1, 10.4, 2.8, 2H, H-4 and H-8), 3.77 (s, 3H,O-CH_3), 5.12 (s, 1H, H-3), 6.85 (d, 2H, J 8.5, H-2), 7.37 (d, 2H, J 8.5, H-1).

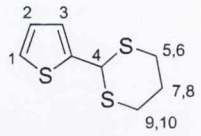
7.5.14 2-(3-Methoxyphenyl)-1,3-dithiane (455a)



The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and 2-methoxybenzaldehyde (330 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (2:1, hexane:EtOAc) the product **455a** was obtained as a white solid (484 mg, 79%). M.p. 64-65 °C (lit.,[290] 65 °C). The NMR spectral data associated with **455a** were consistent with those previously reported.[291]

δ_H (400 MHz, $CDCl_3$): 1.84-1.86 (m, 1H, H-9), 2.19-2.21 (m, 1H, H-8), 2.91 (ddd, J 12.4, 4.4, 3.4, 2H, H-7 and H-11), 3.06 (ddd, J 12.4, 9.7, 2.6, 2H, H-6 and H-10), 3.80 (s, 3H, O-CH_3), 5.15 (s, 1H, H-5), 6.84 (m, 1H, H-4), 7.02-7.28 (m, 3H, H-1, H-2 and H-3).

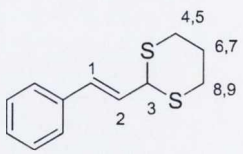
7.5.15 2-(Thiophen-2-yl)-1,3-dithiane (456a)



The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and 2-thiophenaldehyde (253 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (2:1, hexane:EtOAc) the product **456a** was obtained as a white solid (465 mg, 85%). M.p. 75-76 °C (lit.,[287] 76 °C). The NMR spectral data associated with **456a** were consistent with those previously reported.[289]

δ_H (400 MHz, $CDCl_3$): 1.92-1.98 (m, 1H, H-8), 2.10-2.17 (m, 1H, H-7), 2.87-3.02 (m, 4H, H-5, H-6, H-9 and H-10), 5.39 (s, 1H, H-4), 6.93-6.95 (m, 1H, H-3), 7.16 (m, 1H, H-2) 7.25-7.26 (m, 1H, H-1).

7.5.16 (*E*)-2-styryl-1,3-dithiane (139a)

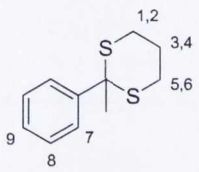


The desired dithiane was obtained following general procedure A using **371** (52 mg, 0.14 mmol), 1,3-propanedithiol (300 μL, 2.98 mmol), THF (9.1 cm^3) and cinnamaldehyde (341 μL, 2.71 mmol). Upon completion of the reaction, the reaction mixture was added to a saturated solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (2:1, Hexane:EtOAc)

the product **139a** was obtained as a white solid (523 mg, 87%). M.p. 60-62 °C (lit.,[292] 63 °C). The NMR spectral data associated with **139a** were consistent with those previously reported.[293]

δ_H (400 MHz, $CDCl_3$): 1.82-1.85 (m, 1H, H-7), 2.01-2.05 (m, 1H, H-6), 2.80-2.86 (m, 4 H, H-4, H-5, H-8 and -9), 4.75 (d, J 7.6, 1H, H-3), 6.19 (dd, J 15.6 and 7.6, 1H, H-2), 6.70 (d, J 15.6, 1H, H-1), 7.16-7.35 (m, 5H, Ar).

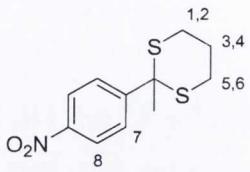
7.5.18 2-Methyl-2-phenyl-1,3-dithiane (459)



To a 100 mL round bottomed flask charged with a magnetic stirring bar, acetyl chloride (5 mL, 70.37 mmol) was added dropwise *via* a syringe to MeOH (50 mL) at 0 °C. The solution was heated to room temperature and acetophenone (1.1 mL, 9.34 mmol) was added. This was followed by the addition of 1,3-propanedithiol (1.04 mL, 10.44 mmol) and the reaction mixture was stirred at room temperature for 15 mins. The solvent was then removed *in vacuo* yielding the pure compound **459** as an off-white solid (1.92g, 98%). M.p. 33-34 °C (lit.,[294] 34-35 °C). The NMR spectral data associated with **459** were consistent with those previously reported.[289]

δ_H (400 MHz, $CDCl_3$): 1.52 (s, 3H, CH_3), 1.90-1.96 (m, 2H, H-3 and H-4), 2.69-2.73 (m, 4H, H1, H-2, H-5 and H-6), 7.24-7.26 (m, 1H, H-9), 7.34-7.38 (m, 2H, H-8), 7.93 (d, J 8.4, 2H, H-7)

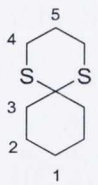
7.5.19 2-Methyl-2-(4-nitrophenyl)-1,3-dithiane (460)



To a 100 mL round bottomed flask charged with a magnetic stirring bar acetyl chloride (5 mL, 70.37 mmol) was added dropwise *via* a syringe to MeOH (50 mL) at 0 °C. The solution was heated to room temperature and 4-nitroacetophenone (1.56 g, 9.34 mmol) was added. This was followed by the addition of 1,3-propanedithiol (1.04 mL, 10.44 mmol) and the reaction mixture was stirred at room temperature for 15 mins. The solvent was then removed *in vacuo* yielding the pure compound **460** as an off-white solid (2.34 g, 97%). M.p. 120-122 °C (lit.,[295] 119-121 °C). The NMR spectral data associated with **460** were consistent with those previously reported.[289]

δ_H (400 MHz, $CDCl_3$): 1.64 (s, 3H, CH_3), 1.82-1.93 (m, 2H, H-3 and H-4), 2.51-2.66 (m, 4H, H1, H-2, H-5 and H-6), 8.02-8.04 (m, 4H, H-7 and H-8).

7.5.20 1,5-Dithiaspiro[5.5]undecane (461)



To a 100 mL round bottomed flask charged with a magnetic stirring bar acetyl chloride (5 mL, 70.37 mmol) was added dropwise *via* a syringe to MeOH (50 mL) at 0 °C. The solution was heated to room temperature and cyclohexanone (975 μL, 9.34 mmol) was added. This was followed by the addition of 1,3-propanedithiol (1.04 mL, 10.44 mmol) and the reaction mixture was stirred at room temperature for 15 mins. The solvent was then removed *in vacuo* yielding the pure compound **461** as an off-white solid (1.6 g, 92%). M.p. 39-40 °C (lit.,[287]

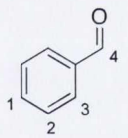
119-39-40 °C). The NMR spectral data associated with **461** were consistent with those previously reported.[296]

δ_H (400 MHz, $CDCl_3$): 1.41-1.47 (m, 2H, H-1), 1.59-1.65 (m, 4H, H-2), 1.80-1.86 (m, 4H, H-3), 1.89-1.91 (m, 2H, H-5), 2.88 (t, 4H, J 5.6, H-4).

7.5.21 General procedure E: hydrolysis of dithianes (procedure involving H_2O)

A 10 ml round bottomed flask, fitted with a magnetic stirring bar was charged with imidazolium catalyst **371** (8.9 mg, 0.024 mmol) and dithiane (0.24 mmol). To this 1,4-dioxane (5 mL) and water (2.5 mL) were added. The flask was fitted with a condenser and the reaction mixture was stirred under reflux for 24 h after which catalyst **371** was added (8.9 mg, 0.024 mmol). The reaction continued under reflux for a further 24h. The reaction mixture was then concentrated *in vacuo* and the product was extracted with ethyl acetate (2 x 10mL) and water (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The pure product was obtained by flash column chromatography.

7.5.21.1 Benzaldehyde (74)

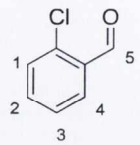


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **339** (47 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **74** was obtained as a colourless liquid (22 mg, 87%). The NMR spectral data associated with **74** were consistent with the those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 7.52-7.56 (m, 2H, H-H-2), 7.62-7.68 (m, 1H, H-1), 7.87-7.90 (m, 2H H-3), 10.01 (s, 1H, H-4).

HRMS (*m/z*-ES): $[M^+]$ calcd. for C_7H_6O 106.0419; found 106.0414.

7.5.21.2 2-Chlorobenzaldehyde (451)

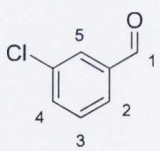


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **451a** (55 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **451** was obtained as a colourless liquid (26 mg, 86%). The NMR spectral data associated with **451** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 7.28-7.36 (m, 2H, H-2 and H-3), 7.39-7.43 (m, 1H, H-4), 7.82-7.85 (m, 1H, H-1), 10.40 (s, 1H, H-5).

HRMS (*m/z*-ES): $[M^+]$ calcd. for C_7H_5ClO 140.0029; found 140.0031.

7.5.21.3 3-Chlorobenzaldehyde (452)

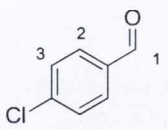


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **452a** (55 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **452** was obtained as a colourless liquid (29 mg, 86%). The NMR spectral data associated with **452** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 7.41-7.50 (m, 2H, H-2 and H-3), 7.69 (d, J 4.5, 1H, H-4), 7.78 (s, 1H, H-5), 9.91 (s, 1H, H-1).

HRMS (*m/z*-ES): $[M^+]$ calcd. for C_7H_5ClO 140.0029; found 140.0032.

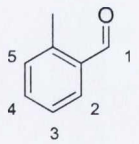
7.5.21.4 4-Chlorobenzaldehyde (453)



The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **453a** (55 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **453** was obtained as a white crystalline solid (28 mg, 84%). M.p 46-47°C (lit.,[298] 45-47 °C). The NMR spectral data associated with **453** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 7.48 (d, J 8.4, 2H, H-3), 7.72 (d, J 8.4, 2H, H-2), 9.91 (s, 1H, H-1).

7.5.21.5 2-Methylbenzaldehyde (454)

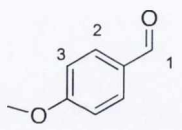


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **454a** (47 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (10:1, hexane:EtOAc) the product **454** was obtained as a colourless liquid (19 mg, 65%). The NMR spectral data associated with **454** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 2.57 (s, 3H, CH_3), 7.15 (d, J 7.4, 1H, H-5), 7.27 (t, J 7.4, 1H, H-3), 7.36 (t, J 7.4, 1H, H-4), 7.69 (d, J 7.4, 1H, H-5), 10.15 (s, 1H, H-1).

HRMS (*m/z*-ES): $[M^+]$ calcd. for C_8H_8O 120.0575; found 120.0571.

7.5.21.6 4-Methoxybenzaldehyde (102)

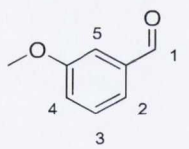


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **102a** (54 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **102** was obtained as a colourless liquid (25 mg, 76%). The NMR spectral data associated with **102** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 3.76 (s, 3H, O-CH_3), 6.89 (d, J 8.8, 2H, H-3), 7.72 (d, J 8.8, 2H, H-2), 9.77 (s, 1H, H-1).

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_8H_8O_2$ 136.0524; found 136.0525.

7.5.21.7 3-Methoxybenzaldehyde (455)

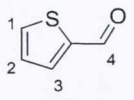


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **455a** (54 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (6:1, hexane:EtOAc) the product **455** was obtained as a colourless liquid (24 mg, 74%). The NMR spectral data associated with **455** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 3.76 (s, 3H, O-CH_3), 7.07-7.09 (m, 2H, H-2 and H-3), 7.29 (s, 1H, H-5), 7.35 (d, J 6.9, 1H, H-4), 9.88 (s, 1H, H-1).

HRMS (*m/z*-ES): [M^+] calcd. for $C_8H_8O_2$ 136.0524; found 136.0523.

7.5.21.8 2-Thiophenecarboxaldehyde (456)

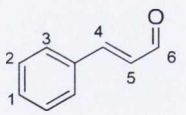


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **456a** (49 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **456** was obtained as a colourless liquid (21 mg, 78%). The NMR spectral data associated with **456** were consistent with those previously reported.[299]

δ_H (400 MHz, $CDCl_3$): 7.13 (s, 1H, H-2), 7.68-7.71 (m, 2H, H-1 and H-3), 9.86 (s, 1H, H-4).

HRMS (*m/z*-ES): [M^+] calcd. for C_5H_4OS 111.9983; found 111.9985.

7.5.21.9 Cinnamaldehyde (159)

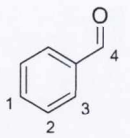


The desired aldehyde was obtained following general procedure E using catalyst **371** (8.9 mg, 0.024 mmol x 2) and dithiane **159a** (53 mg, 0.24 mmol) in dioxane (5 mL) and water (2.5 mL). After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **159** was obtained as a colourless liquid (27 mg, 85%). The NMR spectral data associated with **159** were consistent with those previously reported.[14]

δ_H (400 MHz, $CDCl_3$): 6.73 (dd, J 16.2, 7.8, 1H, H-5), 7.41-7.46 (m, 3H, H-1 and H-2), 7.48 (d, J 16.2, 1H, H-4), 7.56-7.62 (m, 2H, H-3), 9.71 (d, 7.8, 1H, H-6).

HRMS (*m/z*-ES): [M^+] calcd. for $C_9H_{10}O$, 132.0575; found 132.0574.

7.5.22 Hydrolysis of dithiane 339: anhydrous procedure yielding aldehyde 74



A 10 mL reaction vessel was fitted with a magnetic stirrer and to this **371** (37.2 mg, 0.1 mmol) and the reaction vessel was placed under argon. To this **339** (98 mg, 0.5 mmol) and propanal (358 μL, 5 mmol) were added *via* syringe. The reaction vessel was stirred at room temperature for 24 h. After purification of the crude material by flash chromatography (5:1, hexane:EtOAc) the product **74** was obtained as a colourless liquid (43 mg, 81%). The NMR spectral data associated with **74** were consistent with the those previously reported.[297]

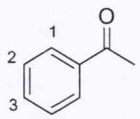
δ_H (400 MHz, $CDCl_3$): 7.52-7.56 (m, 2H, H-2), 7.62-7.68 (m, 1H, H-1), 7.87-7.90 (m, 2H H-3), 10.01 (s, 1H, H-4)

HRMS (*m/z*-ES): [M^+] calcd. for C_7H_6O 106.0419; found 106.0414.

7.5.23 General procedure F: hydrolysis of ketone derived dithianes

A 10 mL microwave reaction vial was fitted with a magnetic stirrer and to this catalyst **371** (17.9 mg, 0.048 mmol), the ketone derived dithiane (0.24 mmol), dioxane (2.5 mL) and water (1.25 mL) were added. The reaction vessel was fitted with a lid, placed in the microwave under reduced pressure and stirred for 2 h at 110 °C. Upon completion of the reaction the solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography affording the desired ketone product.

7.5.23.1 Acetophenone (78)

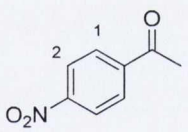


The desired aldehyde was obtained following general procedure F using catalyst **371** (17.9 mg, 0.048 mmol) and dithiane **459** (50 mg, 0.24 mmol) in dioxane (2.5 mL) and water (1.25 mL). After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **78** was obtained as a colourless liquid (13 mg, 46%). The NMR spectral data associated with **78** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 2.45 (s, 3H, CH_3), 7.31-7.33 (m, 2H, H-2), 7.42-7.44 (m, 1H, H-3), 7.83 (s, 2H, H-1).

HRMS (*m/z*-ES): $[M^+]$ calcd. for C_8H_8O 120.0575; found 120.0569.

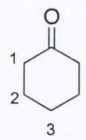
7.5.23.2 4-Nitroacetophenone (383)



The desired aldehyde was obtained following general procedure F using catalyst **371** (17.9 mg, 0.048 mmol) and dithiane **460** (61 mg, 0.24 mmol) in dioxane (2.5 mL) and water (1.25 mL). After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **383** was obtained as a colourless liquid (21 mg, 52%). M.p. 77-78 °C, (lit.,[300] 76.5-78.5). The NMR spectral data associated with **383** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 2.69 (s, 3H, CH_3), 8.12 (d, J 7.6, 2H, H-1), 8.31 (d, J 7.6, 2H, H-2).

7.5.23.3 Cyclohexanone (23)



The desired aldehyde was obtained following general procedure F using catalyst **371** (17.9 mg, 0.048 mmol) and dithiane **461** (45 mg, 0.24 mmol) in dioxane (2.5 mL) and water (1.25 mL). After purification of the crude material by flash chromatography (8:1, hexane:EtOAc) the product **23** was obtained as a colourless liquid (14 mg, 58%). The NMR spectral data associated with **23** were consistent with those previously reported.[297]

δ_H (400 MHz, $CDCl_3$): 1.77-1.91 (m, 6H, H-2 and H-3), 2.20-2.26 (m, 4H, H-1).

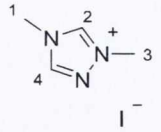
HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_6H_{10}O$, 98.0732, found 98.0732.

7.6 Experimental data for Chapter 6

7.6.1 1-Methyl-1*H*-1,2,4-triazole (468)

A 250 mL round bottomed flask containing a magnetic stirring bar, was charged with 1,2,4-triazole (2 g, 0.03 mol) in MeCN (148 mL). To this MeI (2.67 mL, 0.03 mol) was added and the reaction mixture was stirred at 45 °C for 2 d, after which a white precipitate was obtained. The mixture was filtered by vacuum filtration using a Buchner funnel. The solid was washed with CH_2Cl_2 (30 mL) and the combined organic filtrate was concentrated *in vacuo* giving **468** as a pale yellow solid (2.03 g, 82%). The compound was used directly in the following reactions to furnish **465** and **469-472** without further purification.

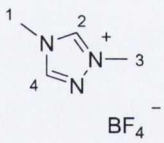
7.6.2 1,4-Dimethyl-4H-1,2,4-triazol-1-ium iodide (465)



To a 100 mL round bottomed flask containing a magnetic stirring bar, triazole **468** (2.00 g, 24.0 mmol) in DCM (8 mL) and ethanol (12 mL) was added. To this methyl iodide (6.0 mL, 0.8 mol) was added. The reaction flask was fitted with a condenser and heated at 40 °C for 3 d. Upon completion of reaction, the product was obtained by concentration of the solution *in vacuo* affording **465** as a yellow solid (4.43 g, 82%). The salt catalyst was stored under argon and kept under light free conditions. Mp 121-123 °C, (lit.,[265] 119-123 °C)

δ_H (400 MHz, DMSO-d_6): 3.88 (s, 3H, H-1), 4.06 (s, 3H, H-3), 9.10 (s, 1H, H-4), 9.96 (s, 1H, H-2).

7.6.3 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium tetrafluoroborate (469)



To a 50 mL round bottomed flask containing a magnetic stirring bar, **468** (500 mg, 6.0 mmol) in MeCN (8 mL) was added. Trimethyloxonium tetraflouroborate (1.15 g, 6.0 mmol) was added. The reaction flask was fitted with a condenser and placed under an argon atmosphere. The reaction mixture was stirred under reflux for 2 d. The solvent was removed *in vacuo,* the resulting residue was dissolved in CH_2Cl_2 and extracted using H_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure giving the pure catalyst **469** (712 mg, 64%). *Note*: catalyst was used immediately due to rapid degradation.

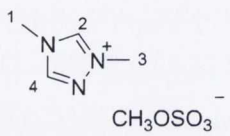
δ_H (400 MHz, DMSO-d_6): 3.87 (s, 3H, H-1), 4.18 (s, 3H, H-3), 9. 20 (s, 1H, H-4), 9.92 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 33.4, 38.6, 143.6, 145.4.

ν_{max} (film)/cm^{-1}: 609, 651, 852, 985, 1070, 1169, 1245, 1367, 1440, 1586, 1739, 1795, 2824, 3028, 3120.

HRMS (*m/z*-ES): [M^+-BF_4^-] calcd. for $C_4H_8N_3$ 98.0718; found 98.0717.

7.6.4 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium methyl sulfate (470)



To a 100 mL round bottomed flask containing a magnetic stirring bar, triazole **468** (1.00 g, 12.0 mmol) in MeCN (10 mL) was added. To this dimethyl sulfate (1.3 mL, 14.0 mmol) was added. The reaction flask was fitted with a condenser and heated under reflux for 2 d. Upon completion of reaction, the product was obtained by concentration of the solution *in vacuo* affording **470** as a colourless oil (2.52 g, 98%). The salt catalyst was stored under argon.

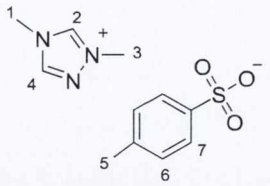
δ_H (400 MHz, DMSO-d_6): 3.38, (s, 3H, H-1), 3.89 (s, 3H, H-3), 4.06 (s, 3H, CH3-OSO_3), 9.10 (s, 1H, H-2), 9.96 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 33.9, 38.5, 52.9, 143.4, 145.3.

ν_{max} (film)/cm^{-1}: 621, 647, 736, 899, 976, 1058, 1189, 1294, 1375, 1476, 1542, 1745, 1793, 2835, 3042, 3111.

HRMS (*m/z*-ES): [M^+-$CH_3OSO_3^-$] calcd. for $C_4H_8N_3$ 98.0718; found 98.0717.

7.6.5 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium 4-methylbenzenesulfonate (471)



To a 100 mL round bottomed flask fitted with a magnetic stirring bar, **468** (1.00 g, 12.0 mmol) was added. This was dissolved in CH_2Cl_2 (4 mL), ethanol (8mL) and methyl tosylate (2.18g, 12.0 mmol) was added. The reaction flask was fitted with a condenser and the reaction was stirred at 80 °C for 2 d, after which the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and extracted using H_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. This produced **471** as an off-white solid (2.85 g, 82%). M.p. 112-114 °C

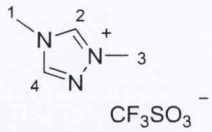
δ_H (400 MHz, DMSO-d_6): 2.29 (s, 3H, H-1), 3.88 (s, 3H, H-3), 4.05 (s, 3H, H-5), 7.12 (d, J 7.8, 2H, H-6), 7.49 (d, J 7.8, 2H, H-7), 9.11 (s, 1H, H-4), 9.99 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 20.8, 33.9, 38.5, 125.5, 128.1, 137.8 (q), 143.4, 145.3, 145.9 (q).

N_{max} (film)/cm^{-1}: 654, 767, 845, 985, 1068, 1253, 1299, 1363, 1440, 1742, 1786, 2890, 3028.

HRMS (*m/z*-ES): [M^+-OTs^-] calcd. for $C_4H_8N_3$ 98.0718; found 98.0718.

7.6.6 1,4-Dimethyl-4H-1,2,4-triazol-1-ium trifluoromethanesulfonate (472)



A 100 mL round bottomed flask fitted with a magnetic stirring bar was charged with triazole **468** (600 mg, 7.23 mmol) in MeCN (5 mL). To this distilled methyl triflate (1.6 mL, 14.50 mmol) was added and stirred at rt for 2 d. The solvent was removed under reduced pressure giving the pure compound **472** as a pale yellow oil (1.4 g, 78% yield). *Note*: Catalyst was tested immediately due to rapid degradation.

δ_H (400 MHz, DMSO-d_6): 3.78 (s, 3H, H-1), 3.93 (s, 3H, H-3), 8.97 (S, 1H, H-2), 9.79 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 34.2, 38.7, 1434.4, 145.3.

ν_{max} (film)/cm^{-1}: 621, 782, 854, 947, 1085, 1170, 1299, 1363, 1436, 1723, 1754, 2878, 3046, 3115.

HRMS (*m/z*-ES): $[M^+$-OTf] calcd. for $C_4H_8N_3$ 98.0718; found 98.0719.

7.6.7 General procedure G: counterion exchange (triazolium ions 473-475):

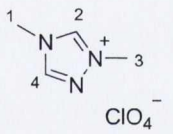
7.6.7.1 General procedure G1: preparation of anion exchange resin (AER):

A 1% acid/methanol solution was passed through a glass column packed with Amberlyst® A-26 (OH–form) until the pH of eluates reached the same value as that of the original solution, and then the resin was washed with methanol until neutral pH. The process was carried out at room temperature, using gravity as a driving force.

7.6.7.2 General procedure G2 for anion exchange:

A methanolic solution of the triazolium salt **465** (50-60 mM) was passed through a column packed with Amberlyst A-26, previously loaded with the selected anion, and then washed with 25 mL of methanol. The combined eluants were concentrated *in vacuo* removed and the oil obtained was dried under vacuum at 60 °C. The amount of halide contents in the exchanged ionic liquids was determined by a silver chromate test following a similar protocol described by Sheldon and co-workers.[2] An aqueous solution of potassium chromate (5% p/v in Milli-Q water, 0.257 M) was added to the sample. A silver nitrate aqueous solution (0.24 % p/v in Milli-Q water, 0.014 M) was added dropwise to 1 mL of the solution and the end point was reached when a red persistent suspension of silver chromate was observed. This test was carried out on each sample twice. Volumes were measured with a 1 mL syringe, and 0.1 mL contains 9 drops of the silver nitrate aqueous solution, consequently 1 drop = 0.011 mL. (0.011 mL of $AgNO_3$ was enough to react with 200 ppm (mg/L) of iodide and 6 ppm (mg/L) chloride).

7.6.7.3 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium perchlorate (473)



Catalyst **473** was prepared following general procedure G1, where Amberlyst®A-26 (OH– form) was washed with a methanolic solution of perchloric acid until the pH of the eluate was the same as the pH of the acidic solution. The resin was washed with methanol until pH was neutral. The catalyst **465** was then washed through following general procedure G2 producing compound **473** (99%).

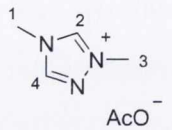
δ_H (400 MHz, DMSO-d_6): 3.89 (s, 3H, H-1), 4.07 (s, 3H, H-3), 9.12 (s, 1H, H-4), 9.98 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 34.0, 38.6, 143.3, 145.3.

ν_{max} (film)/cm^{-1}: 621, 667, 776, 843, 887, 976, 1070, 1154, 1245, 1345, 1468, 1754, 2863, 3028, 3123.

HRMS (*m/z*-ES): [M^+-ClO_4^-] calcd. for $C_4H_8N_3$ 98.0718; found 98.0719.

7.6.7.4 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium acetate (474)



Catalyst **474** was prepared as per general procedure G1, where Amberlyst®A-26 (OH–form) was washed with a methanolic solution of acetic acid until the pH of the eluate was the same as the original solution. The resin was then neutralised by washing with methanol. The catalyst **465** was then passed through the column following general procedure G2 producing the pure catalyst **474** (99%).

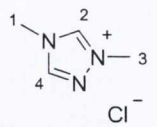
δ_H (400 MHz, DMSO-d_6): 3.89 (s, 3H, H-1), 4.07 (s, 3H, H-3), 9.11 (s, 1H, H-4), 9.98 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 34.1, 38.6, 143.3, 145.3.

ν_{max} (film)/cm^{-1}: 614, 667, 843, 878, 967, 1023, 1169, 1232, 1285, 1361, 1456, 1538, 1577, 1734, 1798, 2821, 3026, 3119.

HRMS (*m/z*-ES): [M^+-AcO^-] calcd. for $C_4H_8N_3$ 98.0718; found 98.0715.

7.6.7.5 1,4-Dimethyl-4H-1,2,4-triazol-1-ium chloride (475)



Catalyst **475** was prepared as per general procedure G1, where Amberlyst®A-26 (OH–form) was washed with a methanolic solution of hydrochloric acid until the pH of the eluate was the same as the pH of the acidic solution. The resin was washed with methanol until the pH of the eluates was neutral. The catalyst **465** was then washed through following general procedure G2 producing the pure catalyst **475** (99%).

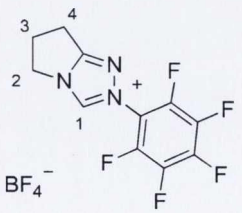
δ_H (400 MHz, DMSO-d_6): 3.90 (s, 3H, H-1), 4.07 (s, 3H, H-3), 9.15 (s, 1H, H-4), 10.06 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 34.0, 38.7, 143.4, 145.3.

ν_{max} (film)/cm^{-1}: 608, 654, 736, 857, 899, 985, 1054, 1143, 1256, 1291, 1362, 1440, 1586, 1738, 1790, 2863, 3054, 3136.

HRMS (*m/z*-ES): [M^+-Cl^-] calcd. for $C_4H_8N_3$ 98.0718; found 98.0717.

7.6.8 2-(Perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (476)



An oven dried round bottomed flask fitted with a magnetic stirring bar was charged with 2-pyrrolidinone (500 mg, 5.88 mmol) and CH_2Cl_2 (30 mL). Trimethyloxonium tetrafluoroborate (871 mg, 5.88 mmol) was added and the reaction was stirred at room temperature for 12 h. Pentafluorophenylhydrazine (1.16 g, 5.88 mmol) was added and allowed to stir for a further 2

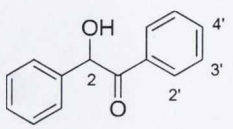
h. The solvent was removed *in vacuo* and the resulting orange solid was heated under vacuum at 110 °C for 2 h. Triethyl orthoformate (4.83 mL, 29.4 mmol) was added and heating was continued at 110 °C for 1 h. Upon cooling, toluene (60 mL) was added and the white solid product was filtered, rinsed with toluene (3 x 5 mL) and heated under vacuum at 120 °C for 6 h to provide triazolium salt **476** (1.36g, 64%). M.p. 243-244 °C (lit.,[240] 242-245 °C). The NMR spectral data associated with **476** were consistent with those previously reported.[240]

δ_H (400 MHz, acetone-d_6): 3.00 (ddd, J 15.4, 8.0, 8.0, 2H, H-3), 3.43 (t, J 8.0, 2H, H-4), 4.76 (t, J 8.0, 2H, H-2), 10.21 (s, 1H, H-1).

7.6.9 General procedure H: benzoin condensation

To a 5 mL round bottom flask, equipped with a magnetic stirring bar, Rb_2CO_3 (99.995 %, anhydrous, 0.044 mmol, 10.16 mg) that had been finely ground using a mortar and pestle, was added. The reaction vessel was put under vacuum and heated with a heat gun for one minute over two-minute intervals for a total of 4 minutes. Upon cooling, the appropriate catalyst (10 mg, 0.044 mmol) and (*E*)-stilbene (24.78 mg, 0.138 mmol) were added and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was distilled under vacuum and used directly. THF (1.1 M) was added to the reaction, followed by aldehyde (1.10 mmol). The reaction was stirred at room temperature for 24 h after which CH_2Cl_2 (3.0 mL) and deionised H_2O (3.0 mL) were added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 x 3.0 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. The product was purified using flash column chromatography.

7.6.9.1 2-Hydroxy-1,2-diphenylethanone (288)

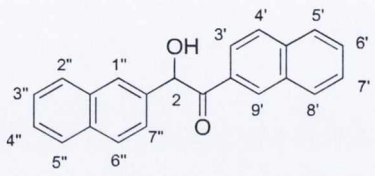


Prepared according to general procedure H using catalyst **465**. Purified by column chromatography (6:4, CH_2Cl_2:hexane) gave pure **288** (112 mg, 96%) as a white solid. M.p.

131-132 °C, (lit.,[2] 130-131 °C). The NMR spectral data associated with **288** were consistent with those previously reported.[301]

δ_H (400 MHz, $CDCl_3$): 4.56 (br.s, 1H, OH), 5.97 (s, 1H, H-2), 7.29-7.38 (m, 5H, Ar), 7.45 (app. t, 2H, H-3'), 7.56 (t, J 7.5, 1H, H-4'), 7.95 (d, J 7.5, 2H, H-2').

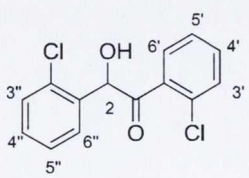
7.6.9.2 2-Hydroxy-1,2-di(naphthalen-2-yl)ethanone (477b)



Prepared according to general procedure H using catalyst **465**. Purified by column chromatography (6:4, CH_2Cl_2:hexane) gave pure **477b** (156 mg, 91%) as a white solid. M.p. 124-125 °C, (lit.,[3] 124-126 °C). The NMR spectral data associated with **477b** were consistent with those previously reported.[302]

δ_H (400 MHz, $CDCl_3$): 4.78 (br.s, 1H, OH), 6.31 (s, 1H, H-2), 7.49-7.65 (m, 5H, H-6', H-7', H-6'', H-7'' and H-8''), 7.79-7.84 (m, 5H, H-2', H-4', H-5', H-3'' and H-5''), 7.90 (d, J 8.0, 1H, H-8'), 7.98 (s, 1H, H1''), 8.02 (d, J 8.0, 1H, H-3'), 8.54 (s, 1H, H-1').

7.6.9.3 1,2-bis(2-Chlorophenyl)-2-hydroxyethanone (326b)

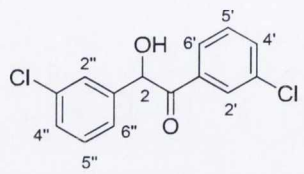


Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (6:4, CH_2Cl_2:hexane) gave **326b** (42 mg, 27%) as an off-white solid. M.p 64-

65 °C, (lit.,[4] 64 °C). The NMR spectral data associated with **326b** were consistent with those previously reported.[303]

δ_H (400 MHz, $CDCl_3$): 4.46 (br.s, 1H, OH), 6.38 (s, 1H, H-2), 7.23-7.26 (m, 5H, H-4', H-5', H-4'', H-5''and H-6''), 7.31-7.41(m, 3H, H-3', H-6' and H-3'').

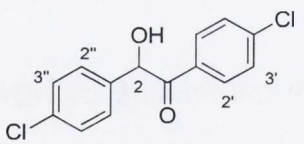
7.6.9.4 1,2-*bis*(3-Chlorophenyl)-2-hydroxyethanone (327b)



Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (6:4, CH_2Cl_2:hexane) gave **327b** (142 mg, 92%) as an off white solid. M.p 76-77 °C, (lit.,[4] 76-77 °C). The NMR spectral data associated with **327b** were consistent with those previously reported.[303]

δ_H (400 MHz, $CDCl_3$): 4.58 (br.s, 1H, OH), 5.91 (s, 1H, H-2), 7.23-7.39 (m, 5H, H-5', H-2'', H-4'' and H-6''), 7.51 (d, J 7.0, 1H, H-4'), 7.75 (d, J 8.0, 1H, H-6'), 7.92 (s, 1H, H-2').

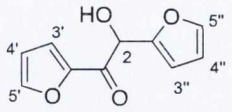
7.6.9.5 1,2-*bis*(4-Chlorophenyl)-2-hydroxyethanone (328b)



Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (6:4, CH_2Cl_2:hexane) gave **328b** (144 mg, 93%) as an off white solid. M.p. 87-88 °C, (lit.,[4] 86-87 °C). The NMR spectral data associated with **328b** were consistent with those previously reported.[303]

δ_H (400 MHz, $CDCl_3$): 4.49 (br.s, 1H, OH), 5.90 (s, 1H, H-2), 7.26-7.27 (m, 2H, H-3''), 7.32 (d, J 8.0, 2H, H-2''), 7.40 (d, J 7.8, 2H, H-3'), 7.85 (d, J 7.8, 2H, H-2').

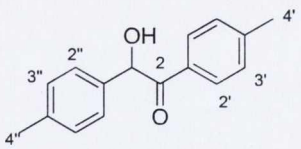
7.6.9.6 1,2-Di(furan-2-yl)-2-hydroxyethanone (331a)



Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (CH_2Cl_2) gave **331a** (98 mg, 93%) as a white solid. M.p. 136-137 °C, (lit.,[5] 136-137 °C). The NMR spectral data associated with **331a** were consistent with those previously reported.[304]

δ_H (400 MHz, $CDCl_3$): 4.22 (br.s, 1H, OH), 5.83 (br.s, 1H, H-2), 6.38 (dd, J 3.0, 1.6, 1H, H-4''), 6.45 (d, J 3.0, 1H, H-5''), 6.57 (dd, J 3.0, 1.5, 1H, H-4'), 7.27 (m, 1H, H-5'), 7.39 (d, J 1.5, 1H, H-3''), 7.56 (s, 1H, H-3').

7.6.9.7 2-Hydroxy-1,2-dip-tolylethanone (478b)

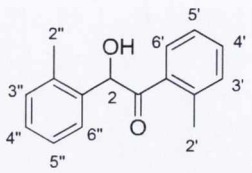


Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (6:4, CH_2Cl_2:hexane) gave **478b** (117 mg, 89%) as an off-white solid. M.p 88-89 °C, (lit.,[4] 89-90 °C). The NMR spectral data associated with **478b** were consistent with those previously reported.[304]

δ_H (400 MHz, $CDCl_3$): 2.31 (s, 3H, H-4''), 2.38 (s, 3H, H-4'), 4.57 (br.s, 1H, OH), 5.92 (s, 1H, H-2), 7.14-7.15 (d, J 7.5, 2H, H-3''),

7.20-7.28 (m, 4H, H-2'' and H-3'), 7.84 (d, J 8.5, 2H, H-2').

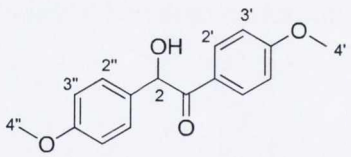
7.6.9.8 2-Hydroxy-1,2-dio-tolylethanone (329b)



Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (6:4, CH_2Cl_2:hexane) gave **329b** (24 mg, 18%) as an off white solid. M.p 76-77 °C, (lit.,[6] 76-78 °C). The NMR spectral data associated with **329b** were consistent with those previously reported.[305]

δ_H (400 MHz, $CDCl_3$): 2.39 (s, 3H, H-2''), 2.42 (S, 3H, H-2'), 4.25 (br.s, 1H, OH), 6.09 (s, 1H, H-2), 7.11-7.31 (m, 6H, H-3', H-5', H3'', H-4'', H-5'', H-6''), 7.35 (t, J 6.5, 1H, H-4'), 7.43 (d, J 7.6, 1H, H-6').

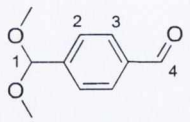
7.6.9.9 2-Hydroxy-1,2-*bis*(4-methoxyphenyl)ethanone (330b)



Prepared according to general procedure H using catalyst **465**. Purification by column chromatography (CH_2Cl_2) gave **330b** (53 mg, 35%) as an off white solid. M.p 110-111 °C, (lit.,[5] 109-110 °C). The NMR spectral data associated with **330b** were consistent with those previously reported.[304]

δ_H (400 MHz, $CDCl_3$): 3.77(s, 3H, H-4''), 3.84 (s, 3H, H-4'), 4.61 (br.s, 1H, OH), 5.87 (s, 1H, H-2), 6.84-6.91 (m, 4H, H-3' and H-3''), 7.25-7.29 (m, 2H, H-2''), 7.92 (d, J 8.8, 2H, H-2').

7.6.10 4-(Dimethoxymethyl)benzaldehyde (443)



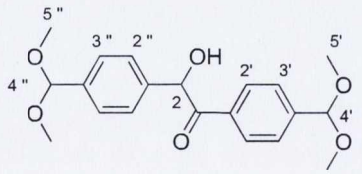
To a reaction vessel charged with terephthaldehyde (100 mg, 0.75 mmol) and catalyst **465** (9 mg, 0.04 mmol) MeOH (67 µL, 1.65 mmol) was added. The reaction vessel was fitted with a septum and place under an argon atmosphere. The mixture was stirred for 24 h after which full conversion to the pale yellow solid **443** was achieved (100 %). The NMR spectra were consistent with those previously reported.[7]

δ_H (400 MHz, $CDCl_3$): 3.34 (s, 6H, CH_3), 5.47 (s, 1H, H-1), 7.62-7.69 (m, 2H, H-2), 7.87-7.94 (m, 2H, H-3), 10.04 (s, 1H, H-4).

HRMS (*m/z*-ES): $[M^+]$ calcd. for $C_{10}H_{12}O_3$ 180.0785; found 180.0786.

7.6.11 *In situ* catalyst modification: procedure

7.6.11.1 1,2-*bis*(4-(Dimethoxymethyl)phenyl)-2-hydroxyethanone (479)



To a reaction vessel, containing a magnetic stirring bar, terephthaldehyde (100 mg, 0.75 mmol) and catalyst **465** (9 mg, 0.04 mmol) was added. The reaction vessel was placed under argon and anhydrous MeOH (67 µL, 1.65 mmol) was added. The reaction mixture was stirred under argon for 24 h, after which time full conversion to the monoacetal **443** occurred, this

was then followed by the addition of DBU (6.6 μL, 0.04 mmol) and dry THF (600 μL) *via* syringe to the reaction vessel to generate basic conditions. The mixture was stirred under argon for a further 24 h, after which time the solvent was removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2 (3.0 mL). This was extracted using H_2O (3.0 mL x2) and the combined organic layers were concentrated under vacuum. The resulting crude compound was purified by flash column chromatography (6:4, CH_2Cl_2:hexane) giving the pure product **479** as a pale yellow solid (102mg, 75%). Mp 122-125 °C

δ_H (400 MHz, $CDCl_3$):	3.30 (s, 12H, H-5' and H-5''), 4.59 (bs, 1H, OH), 5.43 (s, 2H, H-4' and H-4''), 5.95 (s, 1H, H-2), 6.82-6.84 (m, 2H, H-2''), 7.27-7.29 (m, 2H, H-3''), 7.45 (d, J 8.6, 2H, H-3'), 7.89 (d, J 8.6, 2H, H-2').
δ_C (100 MHz, $CDCl_3$):	52.4, 78.6, 103.5, 126.6, 127.3, 127.9 128.9, 135.6 (q), 135.8 (q), 136.2 (q), 145.1 (q), 172.9 (q).
ν_{max} (film)/cm^{-1}:	745, 806, 1145, 1260, 1685, 3350.
HRMS (*m/z*-ES):	$[M^+]$ calcd. for $C_{20}H_{24}O_6$ 360.1573; found 360.1575.

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