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Advances in indium-catalysed organic synthesis

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ADVANCES IN INDIUM-CATALYSED ORGANIC SYNTHESIS

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CONTENTS

Abbreviations

Ac	acetate
Aq.	aqueous
$CDCl_3$	deuterated chloroform
Bn	benzyl
BTF	trifluorotoluene
d	doublet
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
dd	doublet of doublets
d.e.	diastereomeric excess
DMAP	dimethyl aminopyridine
dt	doublet of triplets
e.e.	enantiomeric excess
E	ethyl
eq	equivelant
eV	electron Volt
h	hour
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
J	coupling constant
LA	Lewis acid
LiHMDS	lithium hexamethyldisilazane
LUMO	lowest unoccupied molecular orbital
m	multiplet
NMR	nuclear magnetic resonance
o	ortho
OTf	trifluoromethanesulphonate
OTMS	trimethylsiloxy
m	meta
p	para
Ph	phenyl
PMP	para methoxy phenyl

IV

ppb	parts per billion
ppm	parts per million
pTSCL	para toluene sulfonyl chloride
Pyr	pyridine
rt	room temperature
s	singlet
Sat.	saturated
SET	single electron transfer
^{t}BuOK	potassium tertiary butoxide
t	triplet
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
TMS-	trimethyl silyl
Ts	*para* toluene sulfonyl
Tol	toluene
q	quartet

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Dedicated to Dad, Mum, Sheetal and Nina.

Abstract

Studies on the catalytic efficacy of indium complexes especially indium triflate have been investigated in various organic transformations.

Initially, the acylation of various alcohols, polyols and amines using indium triflate as a Lewis acid was investigated. The acylations were found to proceed smoothly at very low catalyst loadings. The methodology was also used for the protection of various aldehydes to form acylals.

Indium triflate was also successfully employed in the imine aldol reaction and the catalytic efficiency was compared with other Lewis acids. Excellent catalytic activity was exhibited by indium triflate in the hetero Diels-Alder reactions with lowered reaction times with respect to other traditional Lewis acids.

The imino-ene reaction was explored with the potential of creating unnatural amino acids in a facile manner. The reaction was performed in good yield however the reaction has proved to be severely substrate limited. Efforts were also made unsuccessfully to incorporate enantioselectivity into the products using indium.

Further scope for the use of indium complexes in catalytic organic transformations is also discussed.

CHAPTER 1

INTRODUCTION

1. Introduction

1.1 Catalysis

The concept of catalysis in both organic and inorganic reactions has been investigated for more than 150 years.[1] In one form or another catalytic science reaches across almost the entire field of reaction chemistry and catalytic technology has become a fundamental cornerstone of modern chemical industry.[2]

Lewis acids play an important role in catalytic organic synthesis. The idea of a Lewis acid accepting a pair of electrons from a Lewis base is not a new concept[3] however what is novel is the emergence of uninvestigated metal complexes that exhibit Lewis acid behaviour. Recent examples include lanthanide triflates such as ytterbium and scandium triflate.

1.2 Discovery of Indium

Reich and Richter working at the Freiberg School of Mines first identified indium in 1863.[4] Spectrographic examination of crude zinc chloride liquor extracted from samples of zinc blendes gave a brilliant indigo blue line and a second fainter blue line that had not been observed before. Reich and Richter isolated the oxide of the new element and subsequently reduced it to the native metal by heating in a stream of hydrogen or coal gas. The element was christened 'indium' due to its distinctive flame colouration (Latin *indicum*, indigo).

Aluminium is notable for being the most abundant metal on earth (1.5×10^7 p.p.b), however indium is significantly less abundant (4 p.p.b). Indium does not form any

minerals of its own. Instead, it is widely distributed in minute amounts in many minerals, usually concentrated in sulfide deposits.

1.3 Use of Indium[4]

Although indium was discovered in 1863, the metal was not utilised for many years and the world supply was measured in grams until well into the twentieth century. The first reported commercial application was as a minor addition to gold-based alloys in which indium served as an oxygen scavenger.

The importance of indium chemistry today is often associated with indium semiconductors. Indium combines with Group 15 (V) elements such as phosphorous and antimony to produce compounds that exhibit semiconductor characteristics. An example is the use of InSb as an infrared detector in military applications. However its use is limited because it must be cooled to liquid nitrogen temperatures (-78 °C) in order to achieve optimal performance.

A major application for indium is in the manufacture of low-pressure sodium lamps that are commonly used for outdoor lighting, where indium is applied on the inside of the glass cylinder that forms the outer envelope of the lamp.

This coating reflects infrared waves emitted by the lamp while, at the same time, transmitting the visible light. This permits the lamp to operate at a higher temperature, thereby raising its efficiency.

Indium has also found scope in the preparation of solar cells. The compounds InP and $CuInSe_2$ are relatively efficient at converting sunlight into electricity and are under active investigation for this purpose.

Another important use is in the production of nuclear control rods. Rods of composition Ag-15 % In-5 % Cd were developed in the 1950s and have a high capture cross-section for neutrons. They have been used in the majority of pressured water reactors since that time.

Indium is also used in the preparation of conductive films. Because of the high transparency of films of compounds In_2O_3 and $(InSn)_2O_3$ to visible light, they are used on glass as conductive patterns for liquid crystal displays (LCDs) and as demister strips on motor car windscreens.

1.4 Indium in Organic Synthesis

The organic chemistry community has recently witnessed an explosion of interest in the utility of indium reagents in synthesis. A substantial proportion of this work has focused on the use of stoichiometric amounts of organoindium reagents to promote organic reactions in aqueous media.

1.4.1 Allylation Reactions

Indium mediated allylation reactions are the most common reported use of indium as a reagent in organic synthesis. A wide variety of ketones and aldehydes can be allylated using indium metal to afford homoallylic alcohols in good yields (Scheme1).
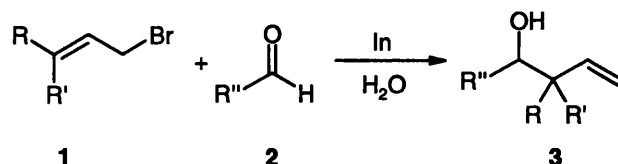
Scheme 1

Indeed, the phenomenal growth of indium mediated Barbier type reactions in water has prompted a recent detailed review of the area.[5] Indium has been found to effect allylation reaction of aldehydes and ketones in water at room temperature and without the need for an inert atmosphere (Scheme 2).

Metallic indium can promote efficient carbon-carbon bond formation in aqueous media without hydrolysis of the catalyst (Scheme 3). This property can be utilised to afford high stereoselectivities (Table 1) in indium-promoted allylations of α- and β-hydroxy aldehydes in aqueous media[6].
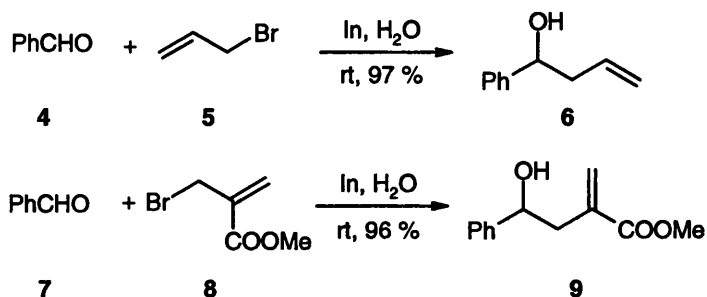
Scheme 2

The choice of solvent and Lewis acid play an important role in the diastereofacial selectivity of the reaction. This work demonstrates the utility of the Lewis acid-catalysed indium mediated allylation in aqueous media as an important synthetic tool for acyclic stereocontrol.
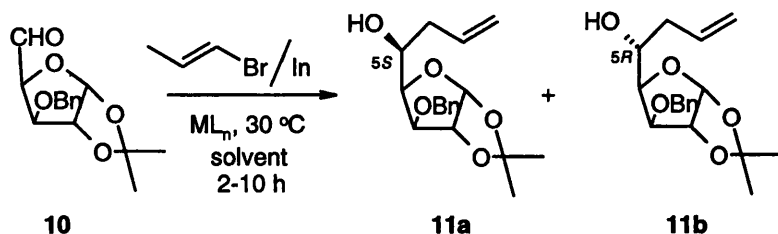
Scheme 3
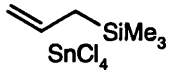
Entry	ML$_n$	Conditions	11a:11b (% yield)
1	Yb(OTf)$_3$	DMF-H$_2$O :6:4 (1 h)	6:94 (88 %)
2	SiMe$_3$ SnCl$_4$	CH$_2$Cl$_2$, -78 °C	88:12 (76 %)

Table 1

The ability of indium reagents to be tolerant of hydroxyl groups has been advantageously utilized with unprotected carbohydrates, substances that are generally insoluble in organic solvents (Scheme 4).

threo:erythro = 4:1
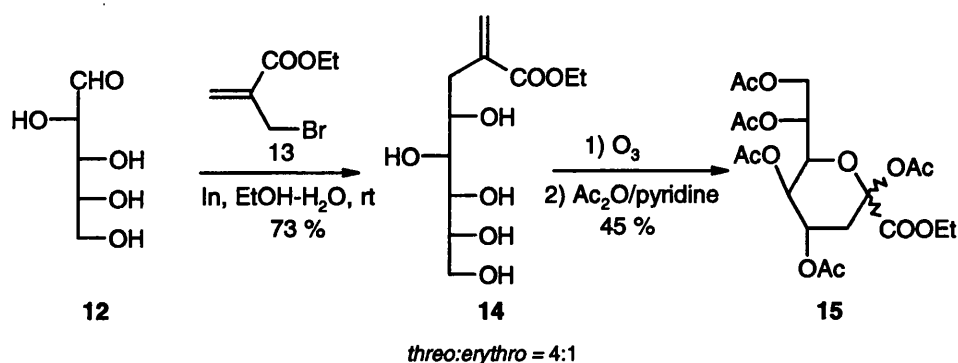
Scheme 4

Paquette and co-workers have extensively studied the stereoselectivity of indium-mediated reactions in aqueous reactions.[7,8] Initially, investigations were carried out in relation to the Cram chelate model, and the stark contrast between the Cram chelate model and indium-mediated aqueous reactions has been reported.[9]

Paquette and Lobben[10] investigated the π-facial diastereoselection in the 1,2-addition of allylindium reagents to various cyclohexanone substrates and found that the presence of water does not inhibit the operation of chelation control. They found that when the system is conformationally rigid, for example in 2-methoxy-4-*tert*-butylcyclohexanone **16**, where both methoxy and *tert*-butyl groups are both orientated equitorial, the cooperation between the α-oxygen atom and control of π-

facial nucleophillic attack reaches a maximum (> 97:3 chelate/ non-chelate ratio) (Scheme 5).

16

17
>97:3 chelate:non-chelate control

80 % yield
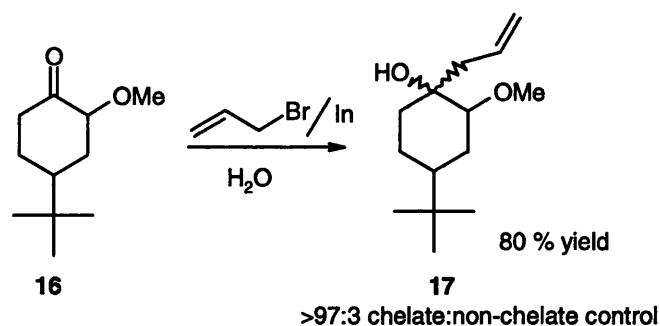
Scheme 5

Araki and co-workers[11] have reported the indium-mediated reaction of 1,3-dichloro- and 1,3-dibromopropenes with carbonyl compounds. In the presence of lithium iodide or sodium iodide, indium was found to mediate the coupling of 1,3-dichloropropene with an aldehyde. Without the iodide salts, no reaction occurred.

Various γ-heteroatom-substituted allylindium reagents have been prepared and reacted with carbonyl compounds by Araki and co-workers.[12] The reaction of 1,3-dibromopropene **18** with metallic indium gave two types of organoindium species, γ-bromoallylindium and allylic diindium reagents (Scheme 6). While the former gave 2-phenyl-3-vinyloxirane upon the coupling with benzaldehyde, the latter gave 1-phenylbut-3-en-1-ol. 1-Iodo-3-bromopropene gave the homoallylic alcohol exclusively.

18

$Br \longrightarrow InL_2$
19

+

InL_2
InL_2
20

PhCHO

Yield 23) 56 % cis/trans (90:10)
24) 30 %
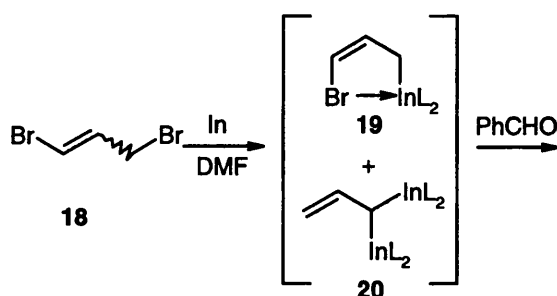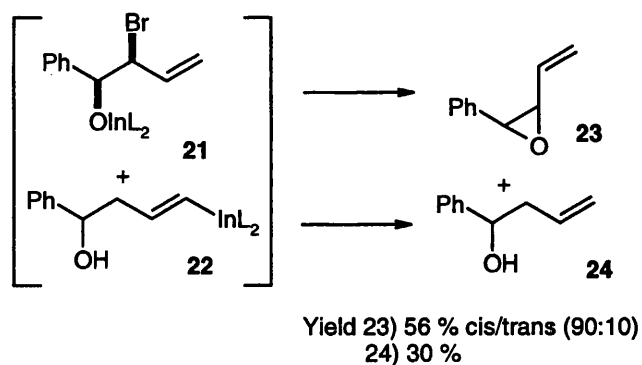
Scheme 6

Triallylindium reagents[13] have been utilised in the regioselective allylation of α,β-unsaturated nitrile and carbonyl compounds to afford 1,4 addition products. This is contrary to conventional Grignard, organolithium and allylindium sesquihalides where 1,2 addition products predominate (Scheme 7).
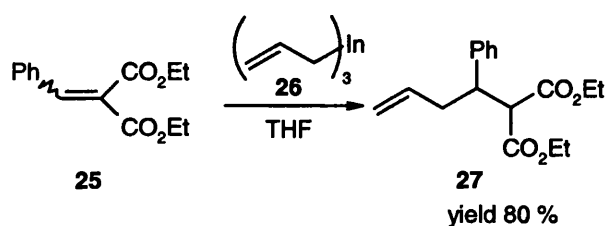
Scheme 7

Mulzer and co-workers[14] were the first to report an example of 1,4-asymmetric induction in indium-mediated allyl transfer chemistry, featuring the stereocontrolling element on the allyl bromide (Scheme 8). A series of allyl bromides bearing an ethereal stereogenic substituent at C-2 were prepared from methyl acrylate and coupled with a range of aldehydes (Table 2).

Scheme 8
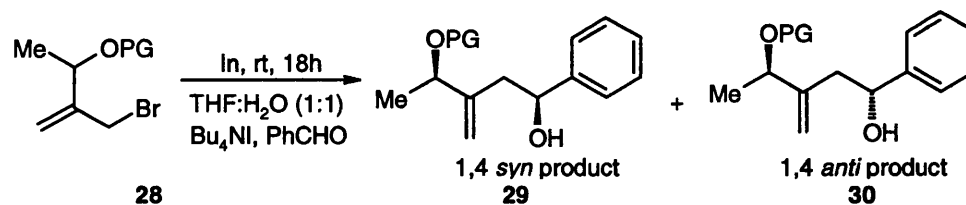
Entry	PG	% yield	*syn:anti*
1	Bn	72	86:14
2	TBDMS	67	86:14
3	MOM	89	73:27

Table 2

The use of alkynes in indium-mediated allylation chemistry has been investigated by Yamamoto and Fujiwara.[15] Allylindium reagents were reacted with both functionalised alkynes and unactivated alkynes, to give the corresponding allylation products in moderate to high yields (Scheme 9). To help clarify the mechanism of the allylindation, deuterated allylindium reagents were utilised. These results suggested that the allylation of terminal alkynes proceed *via* a double indation intermediate, containing a reactive allyl group.

Scheme 9
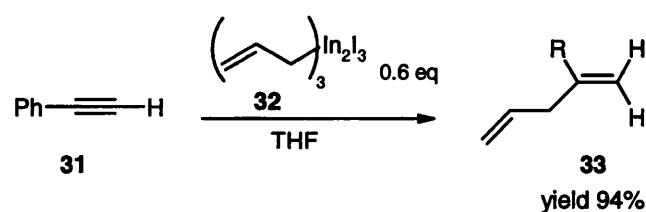
Enamines are important synthetic intermediates in organic synthesis. However, since the discovery of the Stork reaction few reactions are available for their prepartion. Recently Yammamoto and Fujiwara[16] have developed a novel enamine synthesis through the reaction of allylindium reagents with nitriles (Scheme 10).
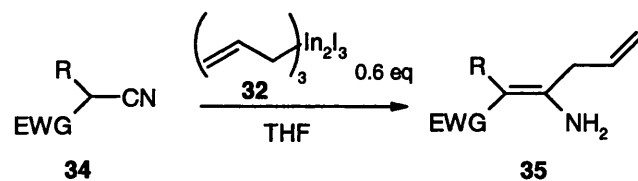
Scheme 10

Nitriles usually react with organometallic reagents (R-ML$_n$, M=Li, Mg, Zn), including allylic compounds, to give the corresponding metallated imines, which produce ketones on hydrolysis. However, reactions of allylindium reagents with certain nitriles take an entirely different route to afford the corresponding allylation-enamination products in moderate to high yields.

Interest in fluorinated organic compounds in fields such as medicine, pharmaceuticals, and fluoropolymers has led to a new focus in discovering facile methods for introduction of fluorine containing groups into useful intermediates or desired substrates. Recent developements have prompted groups to investigate the preparation of fluorinated compounds using indium.

Loh and co-workers[17-20] have developed a highly stereoselective synthesis of β-trifluoromethylated homoallylic alcohols. Using aqueous indium trichloride in the presence of tin, they coupled aldehydes with trifluoromethylated allyl bromides (Scheme 11). Indium trichloride was found to be essential for the tin-mediated allylation, and *anti* products were found to be the major isomers in most allylation reactions. Commercially available trifluoroacetaldehyde ethyl hemiacetal[21] was also used to provide the α-trifluoromethylated alcohols in high yield.

36   37   38
Yield 92 %
γ:α 100: 0
anti:syn >99: <1
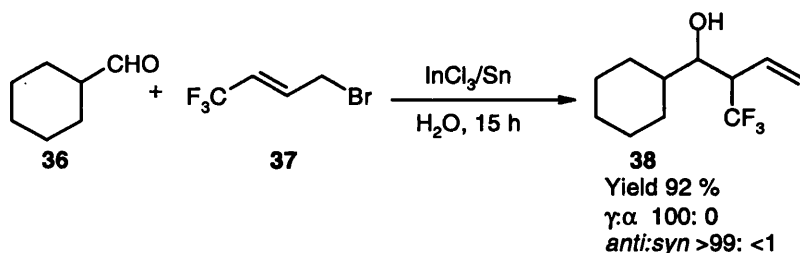
Scheme 11

Momose and co-workers[22] investigated the induction of a *gem* - difluoromethylene moiety into organic molecules. 3-Bromo-3,3-difluoropropene **39** was coupled with various aldehydes. The reactions proceeded smoothly at room temperature in the presence of indium to afford the gem-difluorinated allylic alcohols in high yield (Scheme 12).

39   40   41
yield 99 %
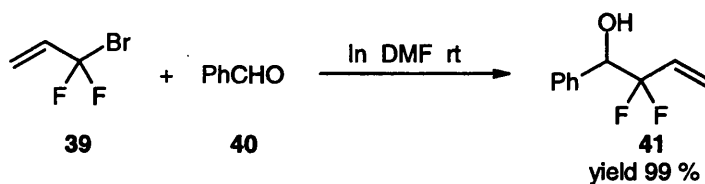
Scheme 12

Loh and co-workers[23] have also utilised indium chemistry in the diastereoselective synthesis of highly functionalized β-hydroxy carboxylates. β-Hydroxy carboxylates are of importance due to their use in the synthesis of biologically active compounds (e.g. β-lactam and β-lactone antibiotics). The group reported the indium-mediated coupling reaction of ethyl 4-bromocrotonate with carbonyl compounds in the presence of lanthanide triflate (Scheme 13). The β-hydroxy carboxylates were afforded in high yield and good diastereoselectivity (Table 3).

42   43
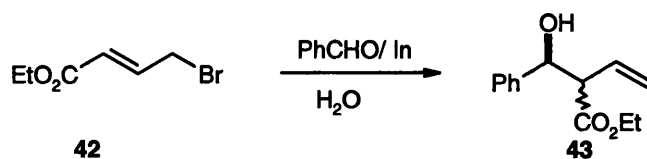
Scheme 13

Entry	ML$_n$	Solvent	Yield %	Anti:Syn
1	-	H$_2$O	59	86:14
2	La(OTf)$_3$	H$_2$O	99	90:10

Table 3

Ring expansion can prove to be a very important tool in the synthesis of biologically important natural products by avoiding entropy disfavoured medium and large size ring formation.[24] To this end, Haberman and Li[25] have reported indium mediated one-atom carbocycle ring expansions. Their method allows six-, seven- and eight-membered rings to be enlarged by one carbon-atom into seven-, eight-, nine-membered ring derivatives respectively in low to moderate yields (Scheme 14).
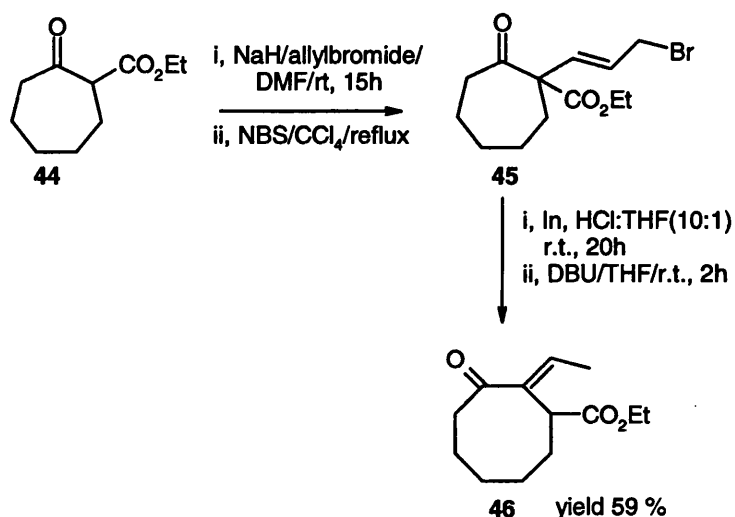
Scheme 14

Chan and Yang[26] have recently investigated the nature of the allylindium intermediate in indium-mediated organometallic reactions in aqueous media, where little is known about the intermediate that is involved in the allylation of carbonyl compounds. Three structures were considered, allylindium dibromide **47**, allylindium sesquibromide **48** and diallylindium bromide **49** (Scheme 15).

47   **48**   **49**
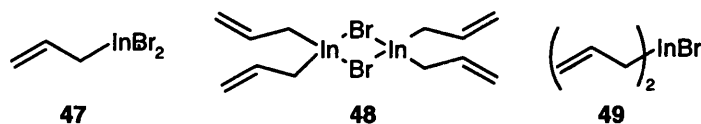
Scheme 15

The reaction between allyl bromide and indium was followed by ^{1}H NMR in D_2O. The allylindium species was found to provide a single allylic proton signal and so this ruled out the possibility of the sesquibromide structure. This was substantiated by the fact that indium has a relatively low first ionization potential, but a relatively high second and third ionization potentials. Thus experiments involving a reaction that is sensitive to the structure of the allylmetal species using organomercury compounds complexed with allyl bromides, the group concluded the allylindium species in aqueous media is the allylindium species with the structure represented by (47) (Scheme 15).

Chan and Lu have also investigated the allylation of sulphonated imines[27] in aqueous media (Scheme 16); although imines are generally regarded as unstable compounds, usually being hydrolysed to the corresponding amine and aldehyde.

50   **5**   **51**
                            yield 99%
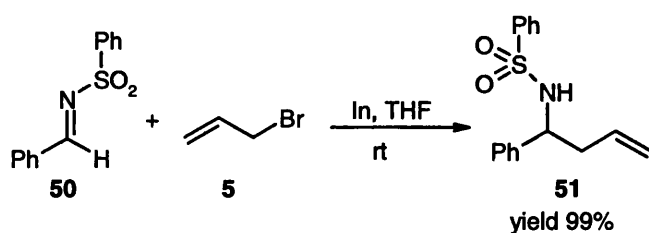
Scheme 16

Ranu and Majee[28] investigated the use of indium metal in the allylation of unactivated terminal alkynes with allyl bromide and were able to produce highly regioselective (Markovnikov addition) 1,4 dienes at room temperature (Scheme 17).

52

53

90 % Yield
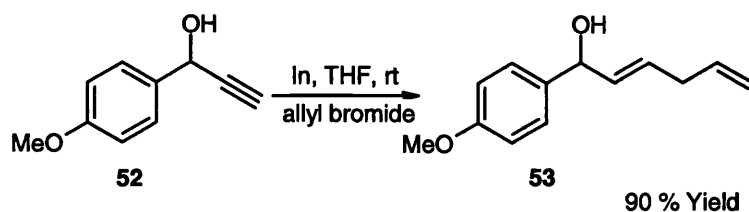
Scheme 17

Indium chemistry has recently been successfully applied to solid phase synthesis by Dolle and co-workers[29], the resin bound aldehydes were converted into the corresponding homoallylic alcohols in very high yields (Scheme 18).

54

= polystyrene resin

55 OH
yield 99 %
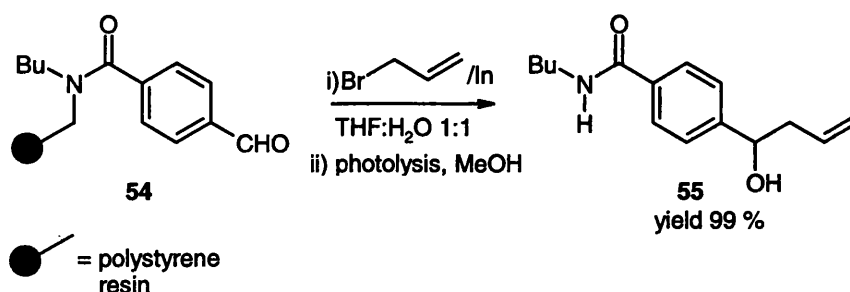
Scheme 18

Zhang and co-workers[30] have reported the synthesis of allyl and propargyl selenides by reacting α-bromoketones with diselenides using indium metal (Scheme 19). The product selenides are useful in many synthetic transformations. α-Selenoketones[31] have also been prepared under aqueuous conditions using indium, the products were obtained in moderate to good yields.

$$\text{COCH}_2\text{Br} \quad + \quad \text{PhSeSePh} \xrightarrow[\text{12h}\ \ 60\ ^\circ\text{C}]{\text{In}} \quad \text{COCH}_2\text{SeR}$$

56   **57**   THF/H$_2$O (20:1)   **58**
                                         yield 82 %
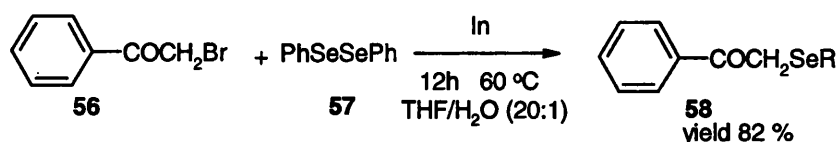
Scheme 19

Epoxides are one of the most useful and versatile substrates in organic synthesis. High reactivity and easy availability with high stereocontrol are just two of the

practical features of epoxides. The rearrangement of epoxides to carbonyl compounds was investigated by Ranu and Jana[32]. Depending on the migration pathways following Lewis acid promoted C-O bond cleavage, two types of rearrangement can occur (Scheme 20); a hydride shift will lead to ketone formation and alkyl/aryl shift will lead to aldehyde formation.
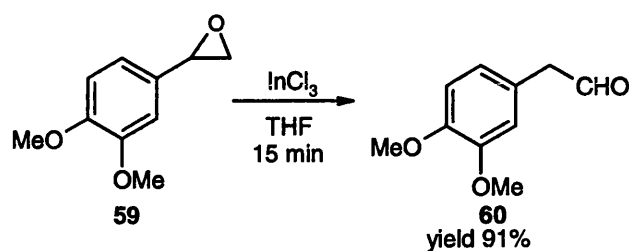
Scheme 20

Indium (III) chloride was found to be an efficient catalyst for highly regioselective isomerisation of aryl-substituted epoxides. Benzylic aldehydes and ketones were synthesised in high yield and with complete predictability under mild conditions, therefore demonstrating its practical utility in organic synthesis.

1.4.2   Reduction

Indium reagents have been exploited for their use in the reduction of organic compounds, no doubt due to its low ionisation potential (5.8 eV) with respect to other metals such as zinc (9.4 eV), tin (7.3 eV), and magnesium (7.6 eV). It was therefore postulated that indium metal should participate readily in single electron transfer (SET) processes.[5]

The first reducing indium hydride (InH$_3$) reagent was prepared by Wiberg and Schmidt[33]. Although it showed no reducing ability, it prompted the group to prepare lithium indium hydride (LiInH$_4$) from InCl$_3$ and LiH, which was found to reduce several organic compounds.

Later, Butsugan[34] and co-workers reinvestigated this work realising its potential for green chemistry and found that various aldehydes were reduced to the corresponding alcohols in high yields, although the reduction of ketones was less effective. They also confirmed that the reduction was not due to LiH.

The reducing ability of lithium indium hydride was improved by the introduction of phenyl groups to the indium atom. $LiPhInH_3$ and $LiPh_2InH_2$ were prepared by the addition of PhLi to suspensions of $InCl_3$ and LiH. The ability of $LiPh_2InH_2$ to reduce organic compounds appeared to be more successful in comparison with $LiPhInH_3$, except in the case of ketones where the results were reversed (Table 4).
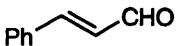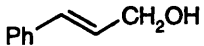
Substrate	Product	Yields (%)		
		$LiInH_4$	$LiPhInH_3$	$LiPh_2InH_2$
Ph⌒⌒CHO **61**	Ph⌒⌒CH_2OH **62**	92	62	81

Table 4

The work of Araki[35] and co-workers complemented the groups earlier work by carrying out highly diastereoselective reductions of acyclic hydroxy ketones and diketones with lithium indium hydride, in comparison with $NaBH_4$ and $LiAlH_4$ reductions (Scheme 21).

100 : 0 *meso : dl*
yield 100 %
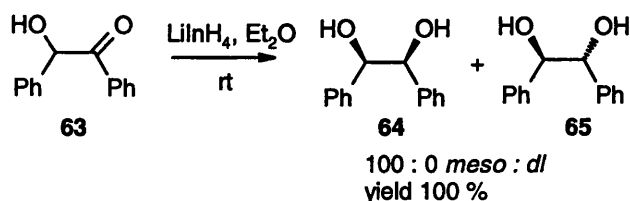
Scheme 21

Dichloroindium hydrides[36] have been generated using a transmetallation reaction between indium trichloride and tributyl stannane. The hydride was found to be stable even at ambient temperature and is able to perform a practical reduction of carbonyls and halides.

Indium metal has also been found to reduce α-halocarbonyl compounds[37] and benzyl iodides to the corresponding dehalogenated products in excellent yields under sonication (Scheme 22). However simple alkyl and aryl iodides remain inert to these conditions.
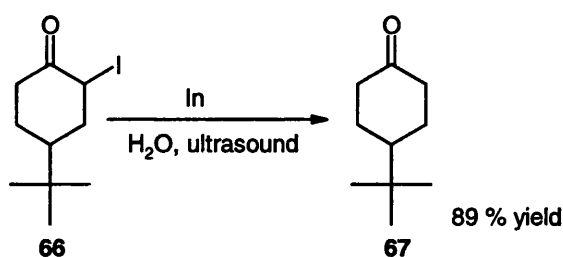
Scheme 22

Recently Moody and Pitts[38] have reported the facile reduction of nitro-groups with the use of indium. The reductions were carried using indium metal in aqueous ethanolic ammonium chloride and the corresponding anilines were produced in good yields (Scheme 23). The group furthered the use of this system by carrying out the regioselective reduction of the heterocyclic rings in quinolines, isoquinolines and quinoxalines (Scheme 24).[39]
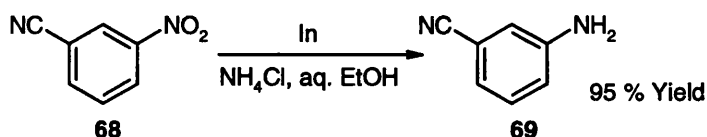
Scheme 23
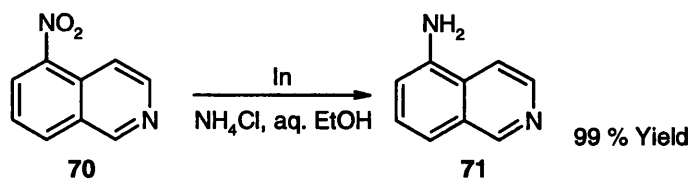
Scheme 24

The protection-deprotection of olefins *via* bromination-debromination is an important tool in organic synthesis. Debrominations are difficult for two reasons. Firstly, stereoselectivity in the debromination step and secondly compatibility of the reagent with the carbon-carbon double bond formed and other functionalities present in the substrate. However, aryl substituted *vic*-dibromides have been found to undergo smooth debromination to produce the corresponding (*E*)-alkenes when treated with indium metal in methanol.[40]

Interestingly, only *trans* olefins are obtained whether they are *meso/erythro* or *dl/threo* (Scheme 25). If debromination occurs by the usual *trans*-elimination, *meso/erythro*- or *dl/threo*-vic-dibromides would give *trans*- or *cis*-alkenes, respectively. It is therefore suggested that the reaction occurs *via* a common relatively stable radical or anion intermediate, which directly collapses to the (*E*)-alkene.
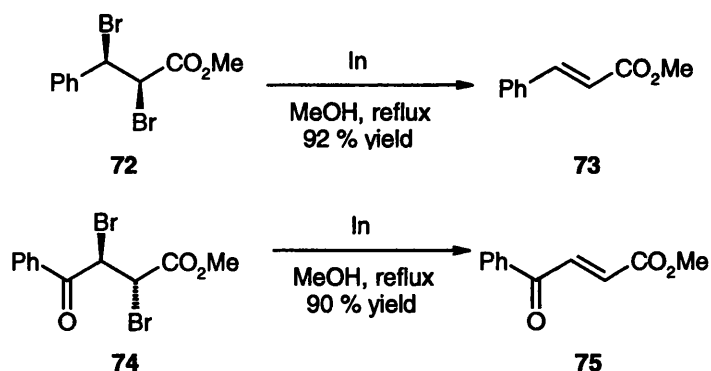
Scheme 25

Bose[41] and co-workers have demostrated the efficient use of indium in the preparation of highly substituted β-lactams. They carried out indium-mediated Barbier type additions of allyl bromides to azetidine 2,3-diones in aqueous media (Scheme 26). The addition provided two homoallylic alcohols, which on mesylation followed by elimination in the presence of DBU afforded a mixture of E and Z isomers of α-alkylidene-β-lactams in excellent yield.
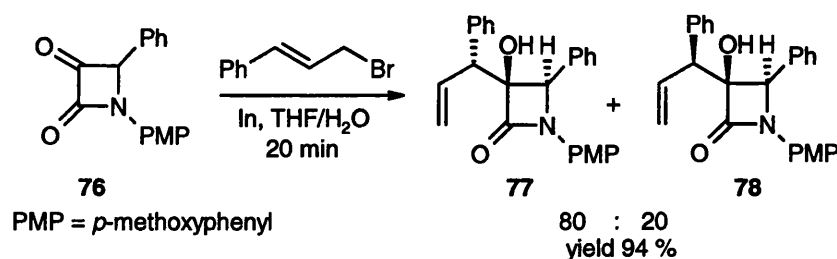
Scheme 26

α-Methylene-γ-butyrolactams have been found to exhibit less cytotoxic activity than α-methylene-γ-bityrolactones, making them suitable candidates for cancer treatment. A Spanish group[42] have recently reported the preparation of these α-methylene-γ-butyrolactams through the addition of 2-(bromomethyl) acrylic acid to aldimines, moderate yields were obtained from via this novel route which utilised easily available starting materials (Scheme 27).
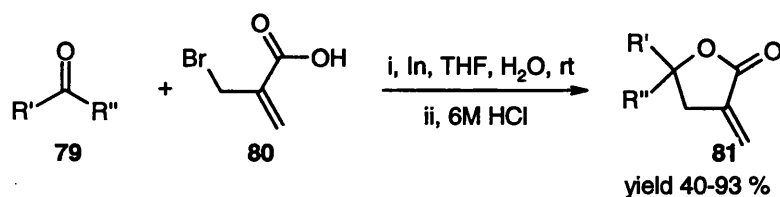
Scheme 27

There are few reported cases of indium being utilised in the total synthesis of natural products. However, Jun Li and co-workers[43] have reported indium mediated highly regio- and diastereoselective allenylation of carbonyl compounds in aqueous media

(Scheme 28), leading to the total synthesis of (+)-goniofufurone. (+)-Gonifufurone, an extract of the Asian tree of the *geus Goniothalamus*, has been found to exhibit moderate to significant cytotoxities against several human tumours.

85 (+) Goniofufurone
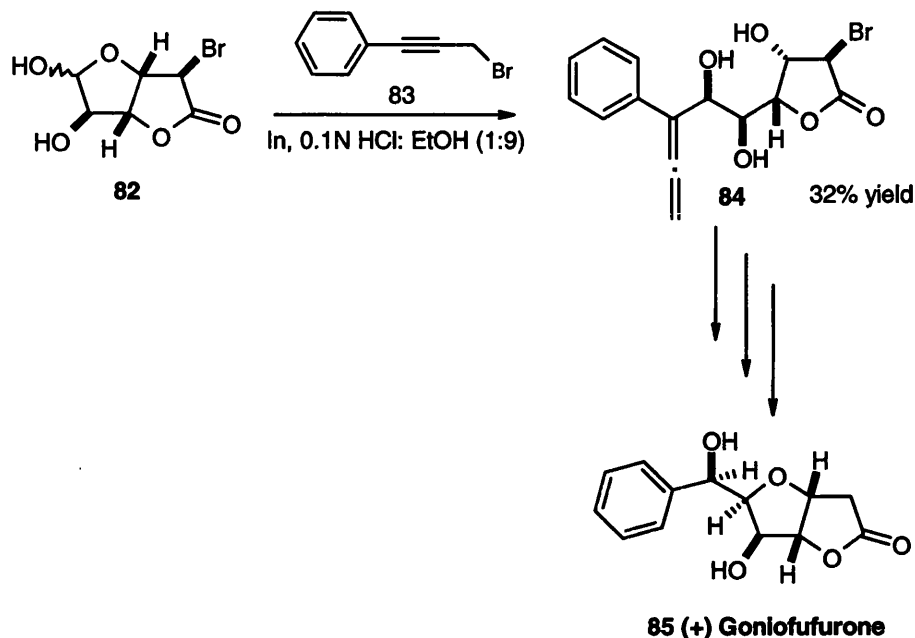
Scheme 28

The total synthesis of Antillatoxin[44-46] is another reported use of indium to mediate a reaction. Loh and co-workers utilised indium in the metal mediated allylation between an aldehyde and β-bromocrotylbromide in water to afford the desired homoallylic alcohol (Scheme 29).
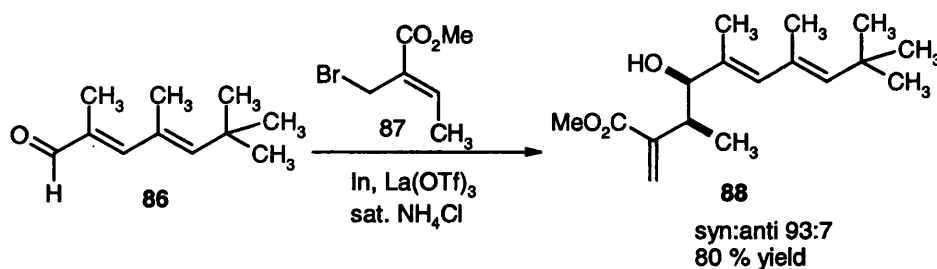
Scheme 29

Neuramic acid, a physiologically important carbohydrate and analogues have also been synthesised *via* an indium-mediated nucleophillic addition of ethyl 2-(bromomethyl)acrylate to N-derivatives of 2-amino-2-deoxymannose.[47]
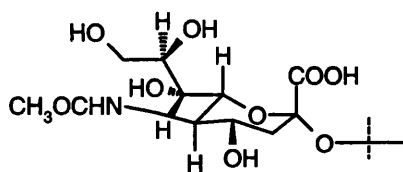
89 N-Acetylneuraminic Acid

1.4.3 Reactions using Indium tri-halide complexes

Indium like the other members of Group 13 (III) has three valence electrons in its electronic ground state with the configuration ns^2np^1. It is these three valence electrons that allow the formation of indium halide complexes. The powerful synthetic potential of indium complexes as Lewis acid catalysts is only now beginning to emerge.

By far the greatest number of indium mediated organometallic reactions involves the allylation of carbonyl compounds. Although rare, (compared with magnesium and zinc) the stoichiometric amount of indium used is often tolerated as the metal has demonstrated remarkable reactivity in aqueous media. Similar allylation reactions using a catalytic amount of indium (III) chloride in combination with zinc or aluminium have been reported but at the expense of reactivity.[48]

The Lewis acid-catalysed and metal mediated carbonyl addition reaction of allylic organometallic reagents is a versatile synthetic tool. Efficient methodology for the indium catalysed allylation of carbonyl compounds has recently been disclosed. The method is based on the transmetallation of indium (III) alkoxides by trimethylsilyl chloride and the *in situ* reduction of indium (III) species by manganese.[49] This system (Scheme 30) allows the efficient allylation of benzaldehyde **90** with allyl bromide in the presence of trimethylsilyl chloride, manganese and a catalytic amount of indium

powder. Formamide was shown to be the most efficient solvent for the reaction and the optimised conditions allow higher yields of product to be obtained when compared to reactions using a stoichiometric amount of indium.
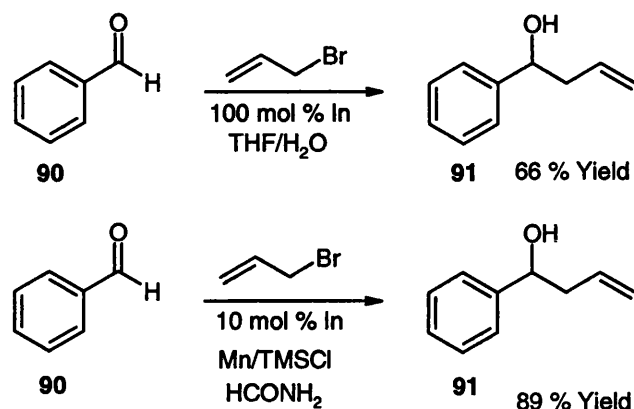
Scheme 30

The diastereoselectivity of the reaction is observed to be high. This is postulated to be a consequence of a chelation-controlled mechanism, which is illustrated by the allylation of benzoin methyl ether **92** which afforded the *syn* adduct **93** with >96 % selectivity (Scheme 31).
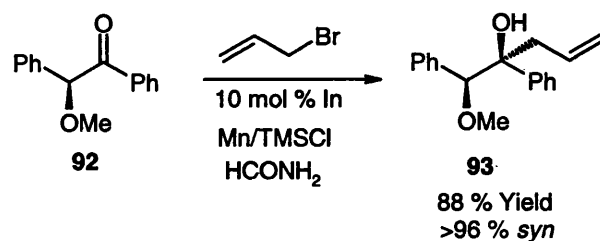
Scheme 31

Teck-Peng Loh[50] has established that the commercially available indium (III) fluoride is an effective catalyst for the addition of trimethylsilyl cyanide to aldehydes (Scheme 32). Thus 3-pyridinecarboxaldehyde **94** is converted to **95** in good overall yield. In the presence of a stoichiometric amount of indium (III) chloride a lower yield was

obtained. Under similar conditions ketones do not react, thus providing a chemoselective process.
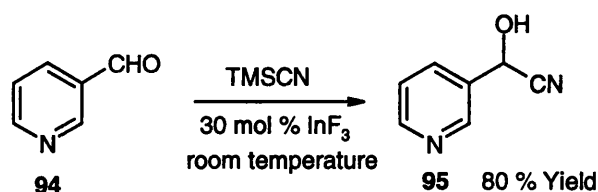
Scheme 32

Ranu[51] and co-workers have developed an $InCl_3$ catalysed one-pot synthesis of α-amino phosphonates utilising the reaction of a carbonyl compound, an amine and diethyl phosphite. The method is operationally simple and applicable to aldehydes and ketones. The reaction is tolerant of sensitive functional groups and chelating groups such as pyridine **96** which reacts with aniline **97** and diethyl phosphite under mild conditions to afford the highly functionalised product **98** in high yield (Sheme 33).

The reaction of a ketone, for example cyclohexanone **99** required the reaction to be heated to a higher temperature but efficient conversion to product is still observed, demonstrated by the preparation of **101** in respectable yield.
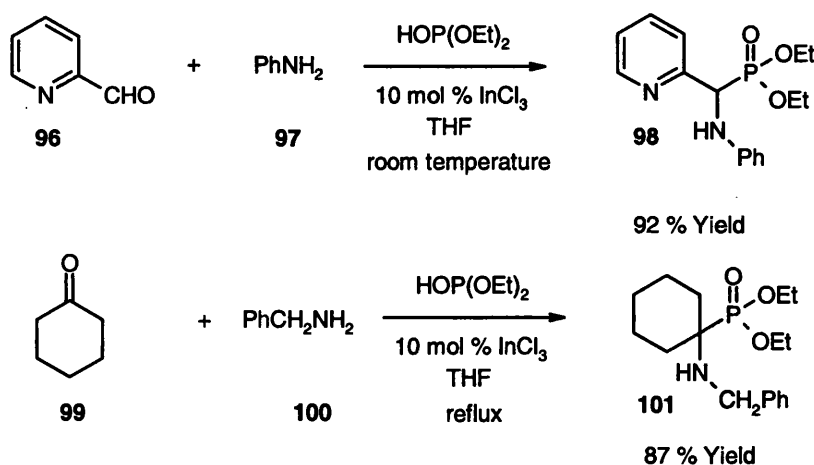
Scheme 33

The combination of chlorodimethylsilane and an indium catalyst is extremely effective for reductive deoxygenation processes. An illustration of the utility of this method is in the deoxygenation of tetralone **102**; the product **103** being obtained in quantitative yield.[52] Although the indium (III) chloride catalysed protocol is depicted in Scheme 34 several indium sources proved to be effective for the reduction of *sec*-benzylic alcohols as demonstrated by the transformation of **104** to the deoxygenated product **105**. It is of particular interest that the combination system is so selective towards carbonyls that the reduction conditions tolerate functionalities such as halogen, ester and ether groups.

Me₂SiClH

5 mol % InCl₃
CH₂Cl₂, 25 °C

102   **103**
                                               99 % Yield

Me₂SiClH

5 mol % InCl₃
CH₂Cl₂, 25 °C

OH
Ph   Ph
104

Ph   Ph
105
99 % Yield
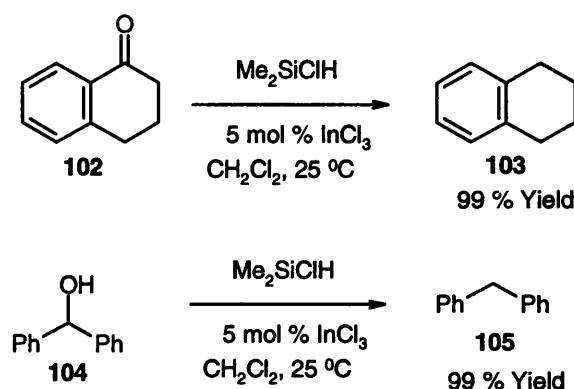
Scheme 34

The same catalytic combination proved equally effective in the reductive Friedel-Crafts alkylation of aromatics with ketones or aldehydes (Scheme 35).[53] The reaction of acetophenone **106** with toluene **107** in the presence of chlorodimethylsilane and indium (III) chloride furnished the reduced product **108** in quantitative yield as a mixture of regioisomeric products (predominantly *para* substituted).

O
Me
+
Me

Me₂SiClH

5 mol % InCl₃
60 °C

Me

Me

106   **107**   **108**
                                               99 % Yield
                                               o:m:p 15:4:81
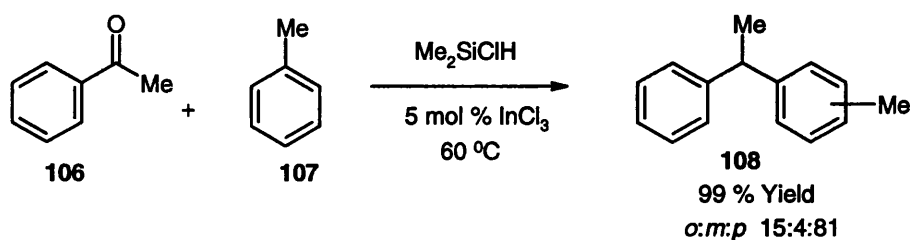
Scheme 35

The generation of dichloroindium hydride from tributyltin hydride and indium (III) chloride allows the reduction of carbonyl compounds and the dehalogenation of alkyl bromides.[34] The selective reduction of acyl halides to aldehydes is much harder to achieve mainly due to over-reduction of the produced aldehyde.

Baba and co-workers[53] have also reported a solution to this problem that allows the reduction of a range of acid chlorides 109 to the corresponding aldehydes 110. The over-reduction could be suppressed by the addition of 20 mol % of the triphenylphosphine leading to high yields of product (Scheme 36). Although neither electron-withdrawing nor electron-releasing substituents on the aromatic acyl chlorides affected the conversion, bulky aliphatic acid chlorides such as 111 afforded low yields of product 112 accompanied by formation of significant amounts of over-reduction product 113. Electron withdrawing groups were found to decrease the rate of reduction whereas electron donting groups were found to increase the yield of reduced product.

R=H   a) 97 % Yield
R=OMe   b) 99 % Yield
R=CN   c) 91 % Yield
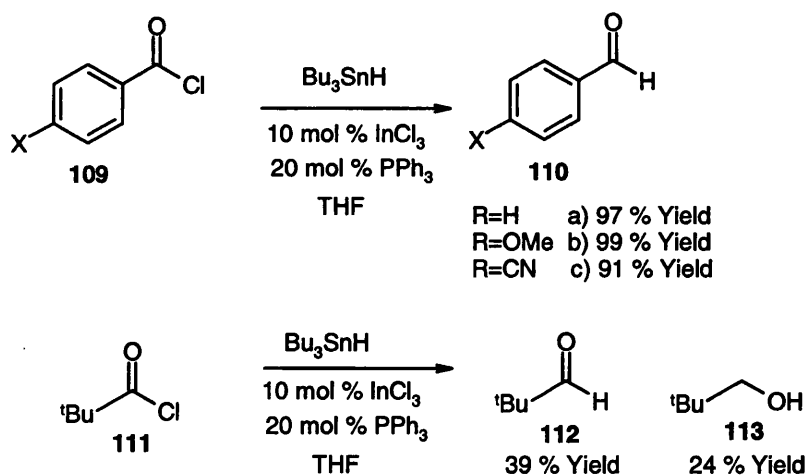
Scheme 36

Indium (III) chloride is reported to be an efficient catalyst for the synthesis of alkyl and aryl 2,3-unsaturated glycopyranosides 115 through the Ferrier rearrangement reaction.[54] Treatment of tri-O-acetyl-D-glucal 114 with various alcohols in the

presence of 20 mol% of indium (III) chloride at room temperature led to glucosidation

products **115 a-b** in excellent yields and good anomeric selectivity (Scheme 37).

a) R= Me 90 % Yield, alpha:beta, 9:1
b) R= Benzyl 86 % Yield, alpha:beta 6:1
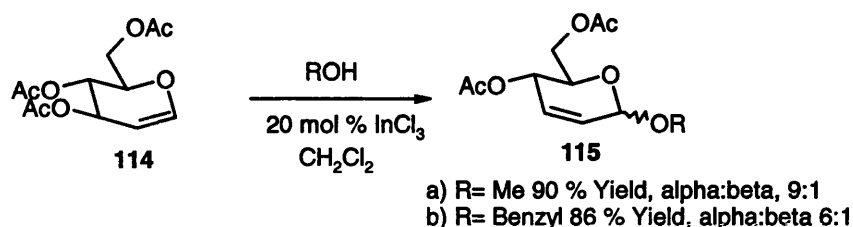
Scheme 37

The reaction was extended to methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside **115**,

which was coupled with **114** in 80 % yield with the α-anomer **116** as the major

product (Scheme 38).

80 % Yield alpha:beta, 9:1
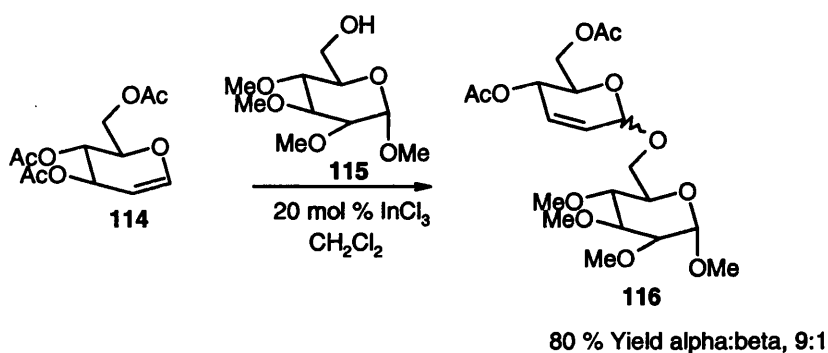
Scheme 38

The Ranu group[55] have reported a simple and efficient procedure for the

rearrangement of substituted epoxides catalysed by indium (III) chloride (Scheme

39). Aryl-substituted epoxides isomerise with complete regioselectivity to form a

single carbonyl compound. With close to thirty examples the methodology offers a

high yielding synthesis of benzylic aldehydes and ketones with complete

predictability.
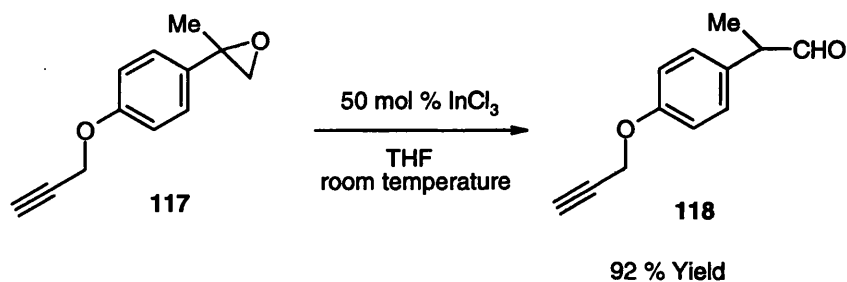
Scheme 39

The Frost group[56] has recently investigated the use of indium triflate in the sulfonylation of aromatics. The sulfonylation of aromatics traditionally relies on the use of stoichiometric promoters such as aluminium (III) chloride. For the sulfonylation of unactivated aromatics the most effective reported catalyst is bismuth (III) triflate but this is not commercially available and has to be prepared from triphenylbismuth and triflic acid. The Frost group has conducted the catalytic sulfonylation (Scheme 40) of activated and unactivated aromatics in very high yields (Table 5) with indium triflate.
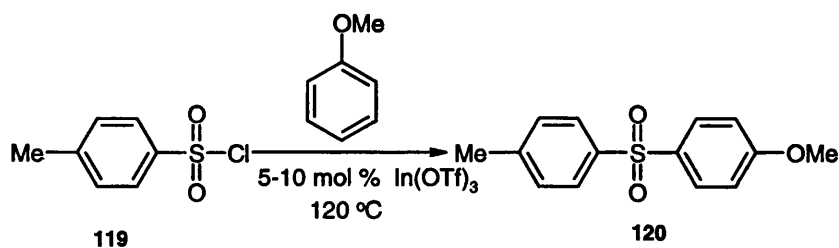
Scheme 40
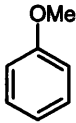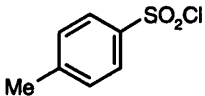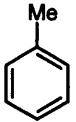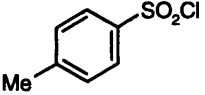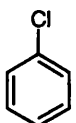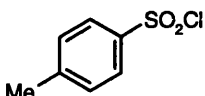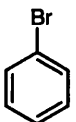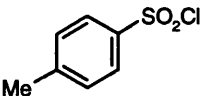
Entry	Aryl	Sulfonyl Chloride	Yield (%)	Isomers (o:m:p)
1	OMe (anisole)	4-Me-C₆H₄-SO₂Cl	88	38:0:62
2	Me (toluene)	4-Me-C₆H₄-SO₂Cl	80	38:0:62
3	Cl (chlorobenzene)	4-Me-C₆H₄-SO₂Cl	84	0:0:100
4	Br (bromobenzene)	4-Me-C₆H₄-SO₂Cl	71	0:0:100

Table 5

The Frost group has also very recently investigated the catalytic Friedel-Crafts acylation[57] reaction using indium triflate with lithium perchlorate. Anisole was acylated in the presence of indium triflate and lithium perchlorate as an additive in 96 % yield (Scheme 41).
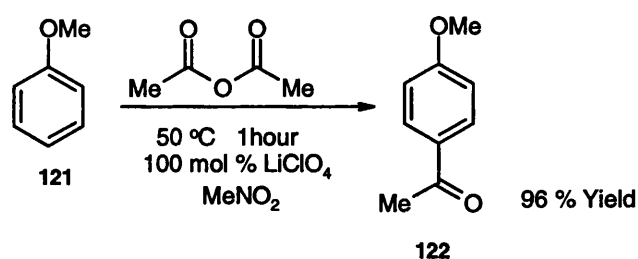
Scheme 41

Indium trifluoride has been investigated for its potential as a Lewis acid catalyst for the addition of TMSCN to aldehydes in water (Scheme 42)[58]. The products, cyanohydrins, would prove to be versatile synthetic intermediates bearing two functional groups that can be easily manipulated. α-Hydroxy aldehydes, α-hydroxy

ketones, β-hydroxy amines and α-amino acid derivatives are some of the useful products this simple reaction could produce. The research group found that InF_3 was a better lewis acid for this reaction than $InCl_3$ and the reaction proceeded smoothly at room temperature providing high yields.

$$PhCHO \quad + \quad TMSCN \quad \xrightarrow[\text{rt}]{InF_3 / H_2O} \quad Ph\overset{OH}{\underset{H}{-\!\!\!\!-}}CN$$

123

yield 95 %
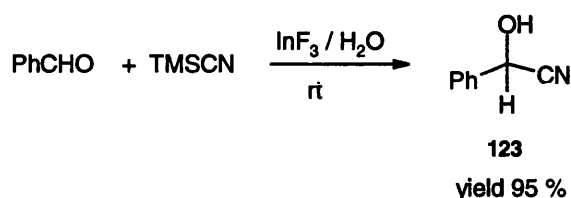
Scheme 42

Indium triiodide[59] has been utilised as an effective catalyst for the allylation of aldehydes. The advantage over indium trichloride was that only a catalytic quantity of indium triiodide was required in the transmetallation. InI_3 also effectively promoted the reaction in the absence of trimethyl silyl chloride, which is essential in the successful allylation using $InCl_3$. The stereoselectivity of the allylations utilising indium triiodide was also very promising, where predominant formation of *anti*-adducts from the *E*-form of allylic tins and a chelation-controlled allylation of α-alkoxyketones were observed (Scheme 44).

$$Ph\overset{O}{-\!\!\!\!-}H \quad \xrightarrow[\substack{InI_3 \text{ 10 mol } \% \\ MeCN, 25\ ^\circ C}]{Bu_3Sn\diagup\!\!\diagup} \quad Ph\overset{H}{\underset{OH}{-\!\!\!\!-}}\diagup\!\!\diagup$$

124

yield 98 %
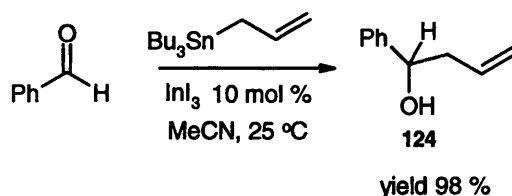
Scheme 44

Transesterifications of esters to the corresponding analogues with higher alcohol moieties is well documented, however the reverse transformations are not common in the literature. An Indian group in its attempts to resolve this difficulty, utilised

indium triiodide[31] with success. The reaction provides a simple and efficient method of transesterification (Scheme 46) and is superior to reported aluminium and titanium reagents.

Yield 90 %
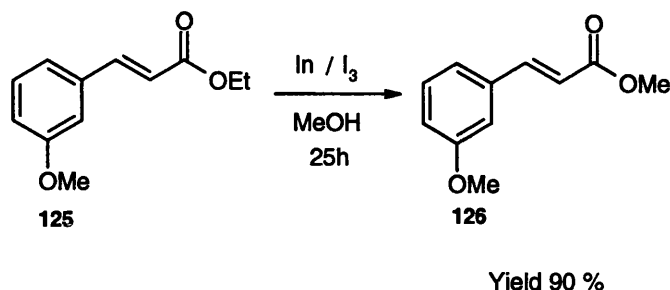
Scheme 46

Trost and co-workers[60] discovered an unexpected indium effect in palladium-catalysed trimethylenemethane cycloadditions, which are generally considered to be a conjugate addition followed by a cyclisation reaction. The presence of indium (III) acetylacetonate, as a cocatalyst redirected the reaction course from a 1,4-conjugate addition to a 1,2- addition (Scheme 47).

This indium effect has been interpreted on the basis of a stabilizing coordination by indium (III), thus favoring attack at the more electrophillic carbonyl group.
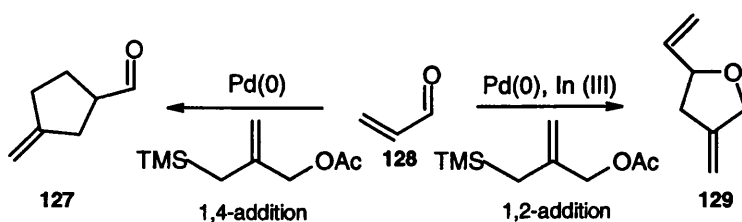
Scheme 47

This review has hopefully outlined a number of traditional uses of indium as an element and when alloyed with other metals, the emergence of indium as a metal in organic synthesis is also acknowledged. The remainder of this thesis will discuss the use of indium complexes and their use in everyday organic applications and the

emergence of indium triflate as a novel Lewis acid that can be used in a wide range

of organic transformations that are of importance to the synthetic chemist.

CHAPTER 2

ACYLATION

2. Acylation

2.1 Protecting Groups

Protecting groups impinge on virtually every aspect of organic synthesis and are fundamental for the successful realisation of the goals set. Blocking functions have been developed for nearly 100 years by numerous researchers from all disciplines of organic chemistry, and consequently solutions to existing problems for synthesis of molecules comprising a large array of sensitive functional groups have been devised.

It was Emil Fischer[61] who first realised that the application of protecting groups is often necessary for a successful synthesis. Fisher's notion was that an otherwise reactive functional group could be temporarily rendered inert by appending a suitable protecting group that could then be later removed.

In 1932 Bergmann and Zervas[62] were able to provide the breakthrough for the invention of easily and selectively removable protecting groups. They reported the use of the benzyloxycarbonyl group as a protecting group in peptide synthesis, and thereby opened up this new field of organic chemistry.

During the past century the highly selective construction of polyfunctional molecules, for example: peptides, oligosaccharides, nucleotides and complex natural products like prostaglandins, have seen dramatic improvements in the art of selective synthesis. The study concerned with the successful total synthesis of Maitotoxin[63], the most complex acyclic compound known to date, provides an impressive example of this.
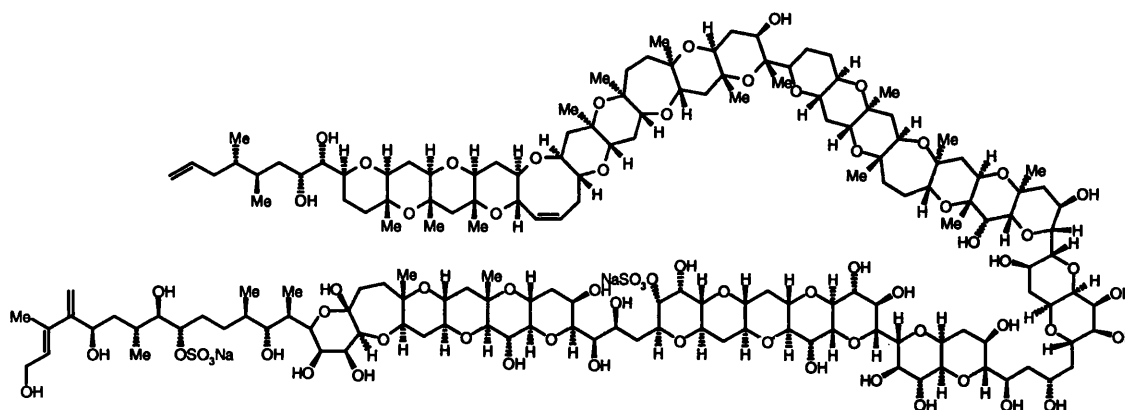
Maitotoxin

The considerations that define an effective protective group for its assigned role are that it should be cheap, easily introduced, easily characterised, stable for reaction, stable for work-up, removed selectively and the by-products of deprotection should be easily separated from the substrate[64].

The hydroxyl group is nucleophilic, moderately acidic (pK$_a$ 10-18), and is easily oxidised by a wide range of reagents to the corresponding aldehyde or ketone. The ability of the hydroxyl functionality to undergo numerous transformations under mild conditions creates a need, especially in multifunctional molecules, to be protected from unwanted reactions altogether or until it's intrinsic reactivity is required.

2.1.2 The Acetyl Protecting Group

Acetates are probably the commonest of all ester protecting groups. They are generally cleaved under mildly basic conditions, but can also be cleaved by acid-catalysed solvolysis (transesterification). However, in the absence of water or alcohol, esters are fairly resistant to attack by acid.

In 1954 R.B. Woodward used the acetyl-protecting group to great effect in the total synthesis of Strychnine[65] (Scheme 48). The protection of N^a with the acetyl function allowed the clean cleavage of the veratryl group. Subsequent deprotection enabled intramolecular attack by N^a upon the C-10 carbomethoxyl group to form the six membered lactam ring.
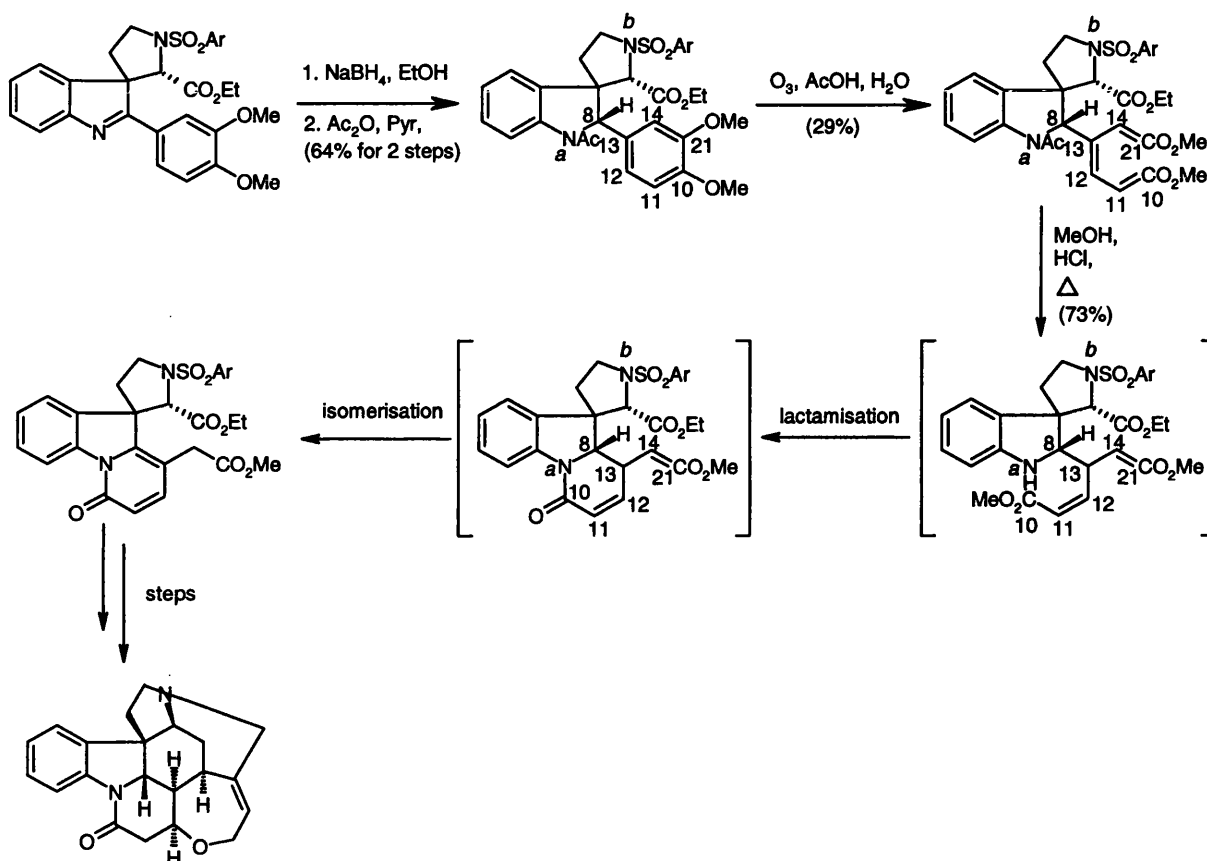
Scheme 48

Famvir™ **130**, a pharmaceutical drug produced by SmithKline Beecham[66], contains the active ingredient Famciclovir, an oral version of Penciclovir **131**, used for the treatment of the viral infection caused by Herpes simplex. To overcome the problems of absorption at the intestine-blood barrier, the acetate functionality was applied to mask the terminal hydroxyl groups of Penciclovir. Following oral administration Famciclovir is deacetylated and oxidised to form Penciclovir. This conversion is catalysed by aldehyde oxidase.

130 Famciclovir
2-[2-(amino-9H-purin-9yl)ethyl]-1,3- propanediol diacetate

131 Penciclovir
9-[4-hydroxy-3-(hydroxymethyl)butylguanine
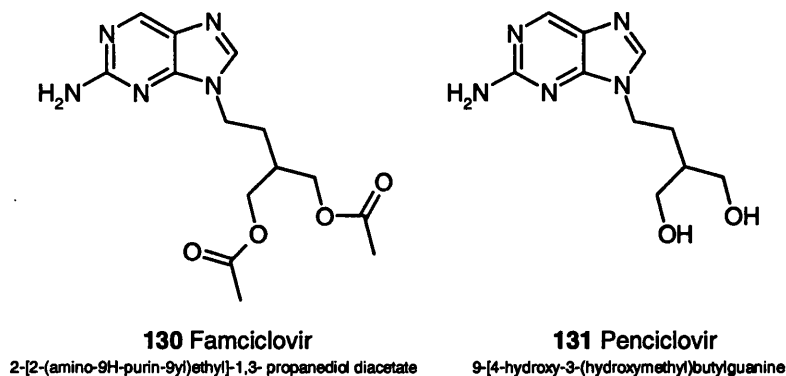
The traditional method employed for the acylation of alcohols and amines is to use acetic anhydride in the presence of pyridine[67]. However, this procedure often proves to be unsatisfactory for the acetylation of deactivated substrates.

It was not until the 1960's that certain 4-dialkylaminopyridines[68] were found to be far superior than pyridine as catalysts for difficult acylations. The rate enhancements observed when compared to uncatalysed reactions were several powers of ten greater, so that even hindered hydroxyl functions are smoothly acylated (Scheme 49).
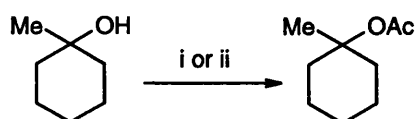
Reagents: i, Ac$_2$O, pyridine, 14h, r.t. (<5% yield)

ii, Ac$_2$O, DMAP (4 mol%), TEA, 14h, r.t. (86% yield)

Scheme 49

The catalyst that has proved most popular in the laboratory and in industry is 4-dimethylaminopyridine (DMAP) **132**. However, 4-pyrrolidinopyridine (4-PPY) **133** is a superior catalyst but a higher cost and lack of availability counterbalance this advantage[69].

132 DMAP   133 PPY
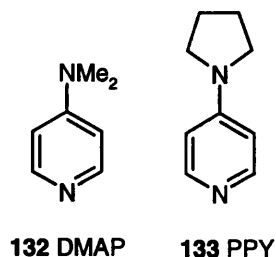
The hydrolysis of acetic anhydride (acetylation of water) in the presence of pyridine proceeds by nucleophilic catalysis (Scheme 50), and the unstable acetylpyridinium ion **134** is proposed as an intermediate. The mechanism presented was formulated on the basis of kinetic analysis[70].
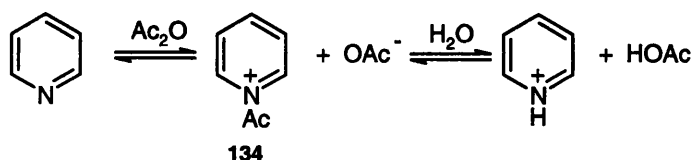
Scheme 50

The drastic rate enhancements caused by the utilisation of DMAP and PPY may be attributed to the formation of the acylpyridinium salt (Scheme 51), in which X⁻ serves as the base to deprotonate the alcohol during its nucleophilic attack on the carbonyl group.
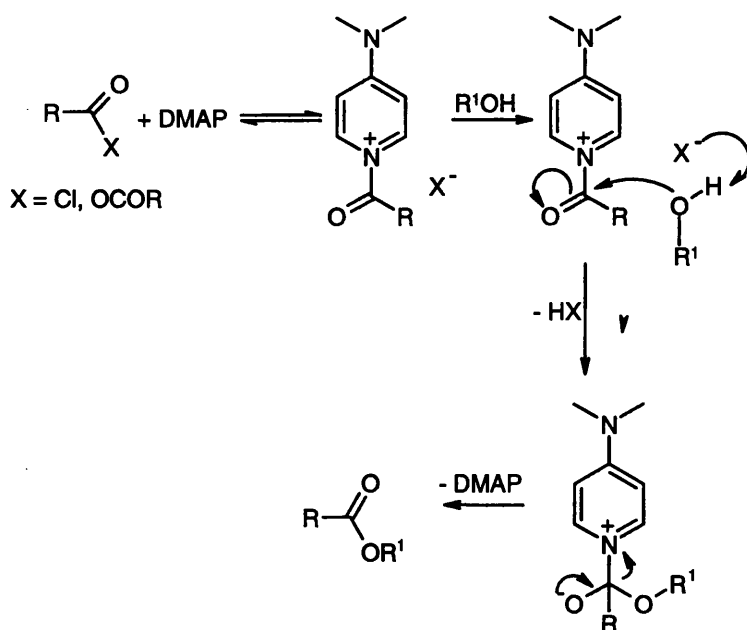
Scheme 51

The Lewis acid catalysed acylation of alcohols and amines with acid anhydrides is a mild, strategic alternative to basic and nucleophilic catalysts such as 4-(dimethylamino) pyridine (DMAP) or 4-pyrrolidinopyridine (PPY).

Although a number of catalysts have been reported to be useful, including tantalum chloride[71], trimethylsilyl triflate[72] and most recently copper triflate[73] (Table 6), most noteworthy is the reported high activity of scandium triflate[74,75] in both inter- and intra-molecular esterification reactions.
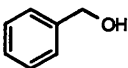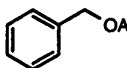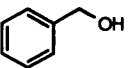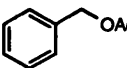
Entry	Substrate	Catalyst	Product	Yield (%)
1	(benzyl alcohol) OH	TaCl$_5$ 10 mol % TLC completion	(benzyl acetate) OAc	77
2	(benzyl alcohol) OH	Cu(OTf)$_2$ 2.5 mol % 0.5 hr	(benzyl acetate) OAc	97

Table 6

Yamamoto and co-workers[76] have demonstrated that commercially available scandium triflate is a highly active Lewis acid for the acylation of alcohols with acid anhydrides and shows higher catalytic activity than DMAP.

Ac$_2$O (1.5 equiv)
Sc(OTf)$_3$ (0.1 mol%)
MeCN (24 ml)
rt, 1 h,

134 → 135
Yield 98 %
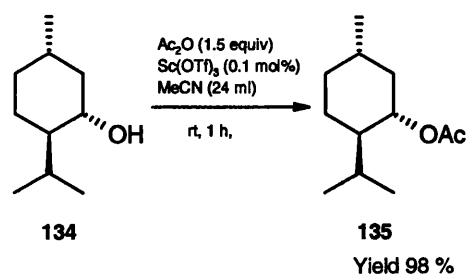
Scheme 52

Recently, the group has also shown complex **137** to be even more effective than scandium triflate in the acylation of alcohols.

134   **136**   **Complex 137**

Complex 137 : 69% yield
Sc(OTf)₃ : 3% yield
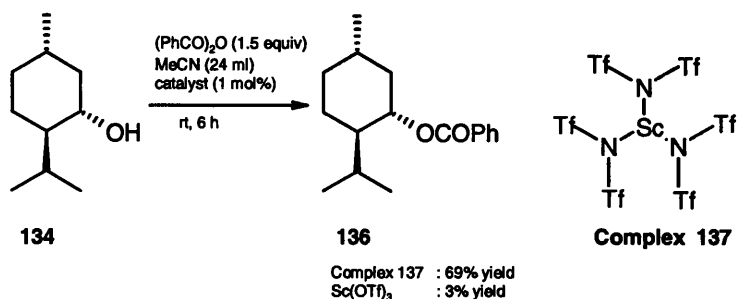
Scheme 53

Field and Kartha[77] have recently investigated the use of iodine in the acylation of unprotected sugars. However, they found that the acetylation of *O*-benzyl protected derivatives may also be accompanied with the concomitant cleavage of the benzyl-protecting group, allowing the acylation of the resulting deprotected alcohol. Thus treatment of the glucosamine derivative with iodine (50 mg per g of sugar) in acetic anhydride for 24 hours, resulted in the acetylation of the hydroxy group at C-4. The selective cleavage of the primary benzyl ether with subsequent acylation resulted in the formation of 4,6-di-*O*-acetyl derivative **139** in 95% yield (Scheme 54).

138   **139**
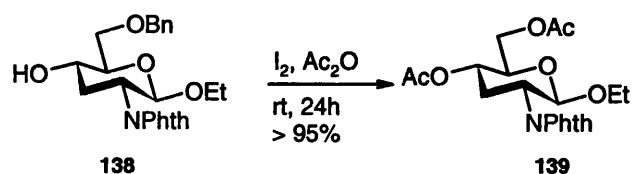
Scheme 54

The proposed mechanism of the reaction suggests that the coordination of iodine acts as a weak Lewis acid to the carbonyl thus promoting attack by the hydroxyl group (Scheme 55).
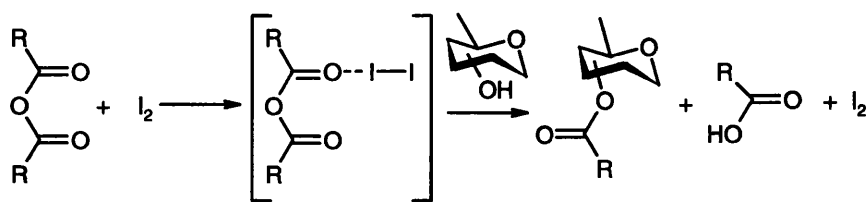
Scheme 55

Dicyclohexylcarbodiimide (DCC) **140** allows for more complex esterifications[1]; both acyl transfer to alcohols and hydroxyl group activation esterifications can be accomplished using this reagent. Acyl transfers to alcohol esterifications are accomplished by treatment of the carboxylic acid and alcohol with DCC in hexane or pyridine with a catalytic amount of p-TsOH. The O-acylisourea that is postulated as the intermediate reacts with the alcohol under elimination of the urea and formation of the desired ester (Scheme 56).
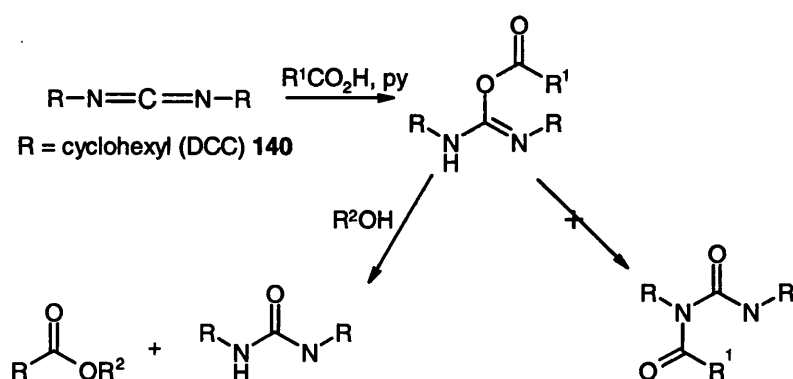
Scheme 56

Trimethylsilyltriflate[16] (TMSOTf) has been shown to carry out the clean acylation of highly functionalised primary, secondary, tertiary and allylic alcohols. Reaction of **141** with Ac_2O (6 equiv.) and TMSOTf (4 mol%) gave the corresponding diacetate product **142** in 99% yield after 30 minutes. This compares favourably with $Sc(OTf)_3$ (0.6 mol%), in which the mixture of products contained 44% diacetate and 56% monoacetate after 20 hours. Furthermore, it took a total of 39 hours to go to

completion with an extra 4 equivalents of Ac_2O and 0.6 mol% of $Sc(OTf)_3$ needing to be added after 20 hours.
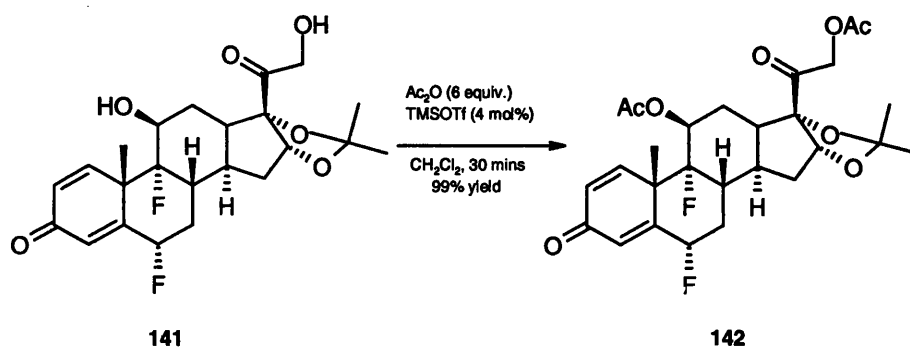
Scheme 57

The ability to acylate different types of alcohol selectively is of up most importance. Although not catalytic, the use of trimethylsilyl orthoacetate **144** and trimethylsilylchloride has been reported to selectively acylate aliphatic alcohols in the presence of phenolic hydroxyl groups (Scheme 58)[78].
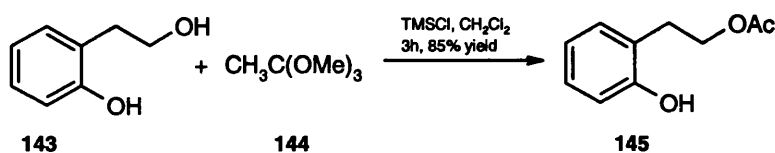
Scheme 58

The selective protection of primary alcohols over secondary alcohols can also play an important part in the synthesis of complex molecules. Ilankumaran and Verkade[79] have reported the selective acylation of primary alcohols over secondary alcohols using iminophosphoranes with enol esters (Scheme 59). The mild conditions utilised in the protocol enable the acylation to proceed in the presence of acid labile groups such as TBDMS, acetal and epoxide functionalities which undergo cleavage when exposed to the conditions of acetic anhydride in the presence of scandium triflate.
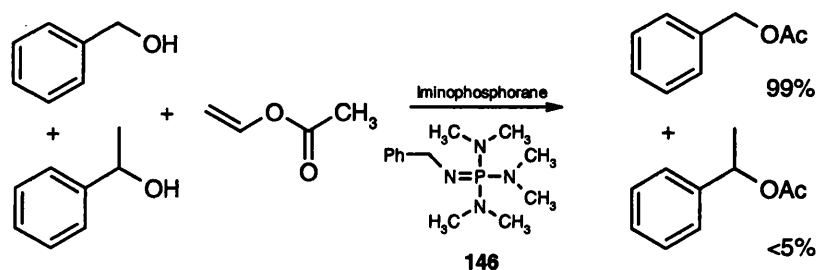
Scheme 59

Deprotection of protected groups in a selective manner is just as important in the synthesis of complex molecules. Orita[80, 81] and co-workers have recently reported a highly efficient and selective catalyst for deacetylations. The tin complex **147** was able to deacetylate primary acetates in 96% yield compared to 6% for the corresponding secondary alcohol (Scheme 60). However, the use of Lewis acid catalysts for the reverse deacetylation reaction has given disappointing results.
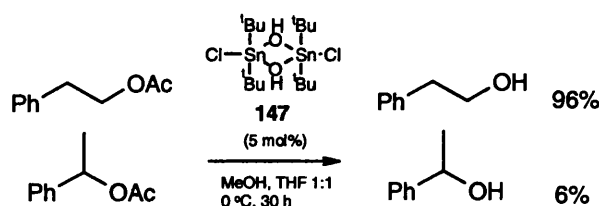
Scheme 60

The usual acyl sources for acetylations are acid anhydrides and acid halides in the presence of Lewis acids. Acylation by this method usually leads to the formation of an acid, carboxylic or halide, as a by-product of the reaction. Consequently, these methods are unfavorable for the acylation of acid- and base-sensitive substrates. This has lead to the development of efficient acylation methods under acid- or base-free conditions[82].

The alternative acyl sources have structures related to that of vinyl acetate, and isoprenyl acetate. Currently vinyl acetate is the acyl donor of choice, this is no doubt

due to the irreversible reaction that arises where the by-product generated is the neutral volatile acetaldehyde.

Ishii and co-workers have recently reported the use of cyclohexanone oxime **148** acetate as the acyl donor in the presence of a samarium complex[83] (Scheme 61). This methodology also allowed for the preparation of tertiary acetates.
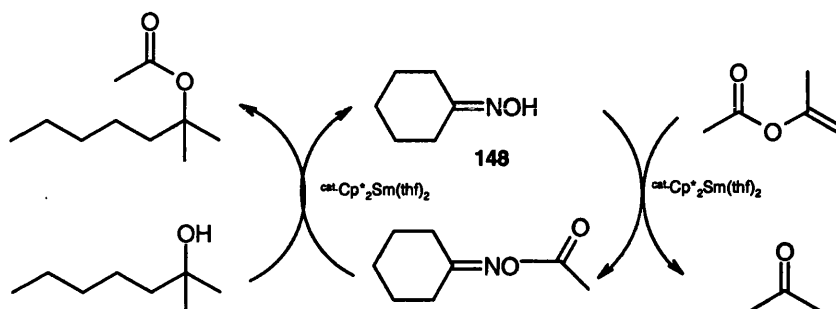
Scheme 61

Diethyl carbonate[82] **149** has also been investigated as an acylating agent for amines. In this case the formation of ethanol as a volatile co-product drives the reaction (Scheme 62).
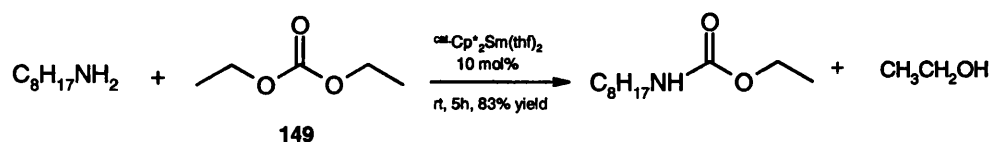
Scheme 62

2.2.2 Protection of Alcohols using Indium Triflate

The use of indium triflate as a Lewis acid was investigated in the acylation of various alcohols to establish whether it would prove to be a powerful lewis acid. If the reaction proved to be successful then this would provide a cheap, clean, efficient and environmentally friendly method of protecting alcohol moieties using a Lewis acid.

The initial substrate that was chosen for this reaction was benzyl alcohol **150**, this would allow for the acylation reaction to be carried out on a relatively planar and unhindered molecule. The reaction in the presence of just 0.1 mol% of indium triflate provided benzyl acetate **151** in 97% yield. This offered a very efficient method of acylating benzyl alcohol with the turnover being 647 acylations per minute (Scheme 63).
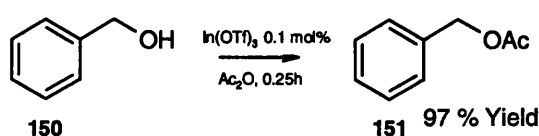
Scheme 63

Phenol, a more delocalised aromatic alcohol was also acylated in an efficient manner providing the product acetate in 97 % yield (Table 7).

Entry	Alcohol	Time (hours)	Product	Yield (%)
1	**152**	0.25	**153**	97
2	**154**	0.5	**155**	98

Table 7

The acylation of menthol **156** and 2-phenyl cyclohexanol **158** provided the corresponding acetate products **157, 159** in 97 and 95 % yield respectively (Table 8). Thus offering a procedure for the acylation of both aliphatic and aromatic compounds in very high yields.
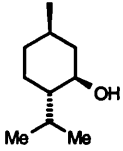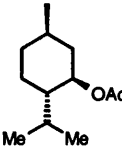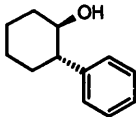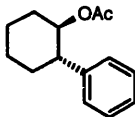
Entry	Alcohol	Time (hours)	Product	Yield (%)
1	**156**	0.5	**157**	95
2	**158**	0.25	**159**	97

Table 8

The optimized acylation reactions were performed by adding acetic anhydride (1.5 equiv. per OH) to the substrate alcohol in acetonitrile at room temperature in the presence of just 0.1 mol % of indium triflate. The reactions were monitored by TLC until the starting material had been consumed and in each case the ^{1}H NMR of the crude reaction mixture revealed complete conversion to product. After a normal aqueous work-up the mixture was purified by flash chromatography to afford the product in high isolated yield.

This process therefore offers a very clean and efficient process for acetylating alcohols and compares favorably with tantalum, scandium and copper catalysts. The catalyst is also cheaper than most conventional and lanthanide catalysts such as scandium triflate.

A proposed mechanism for the acylation of alcohols using indium triflate is outlined below (Scheme 64). The lone pair of electrons from the acetic anhydride is thought to coordinate to the indium Lewis acid providing the driving force for the lone pair from the alcohol to attack the electrophillic carbon-centre of acetic anhydride. This is followed by the expulsion of an acetate anion and the protonated acetate product.

Scheme 64

2.2.3 The Protection of Polyols using Indium Triflate

The ease with which the various alcohols were acylated prompted the investigation for indium triflates efficacy in the acylation of polyols under similar conditions. The initial substrate to be acylated was D-mannitol **160**, given the low catalyst loading; the exhaustive acetylation of D-mannitol to provide hexa-O-acetyl-D-mannitol **161** at room temperature impressively demonstrates the practical utility of this method (Scheme 65). It is also significant to note that D-mannitiol is insoluble in acetonitrile, but as the acetylation proceeds the product becomes soluble.

160   **161**   94 % Yield
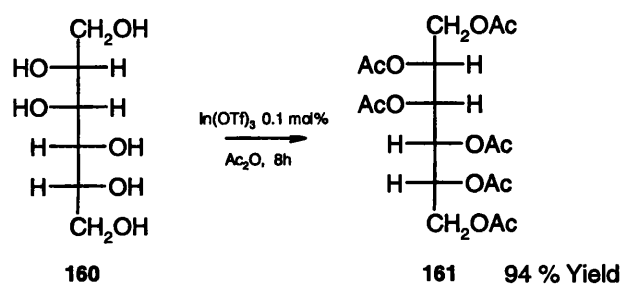
Scheme 65

Binol **162**, a delocalised diol, was also protected using indium triflate to give the product acetate **163** in high yield (Scheme 66).
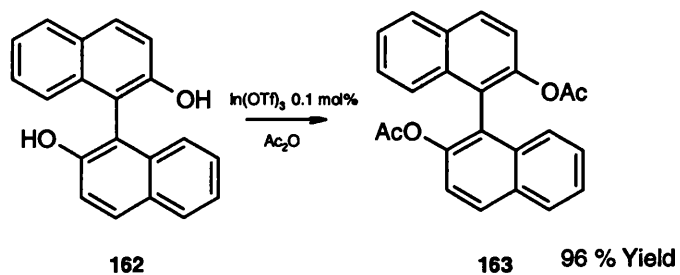
Scheme 66

Similarly, 1,2-dihydroxy-1-phenylethane **164**, bis-2-hydroxyethylether **166** and triol **168** were also acylated to provide the corresponding acylated products in high yields (Table 9).

Entry	Polyol	Product	Yield (%)
1	164	165	93
2	166	167	92
3	168	169	96

Table 9

2.2.4 The Protection of Amines using Indium Triflate

The methodology was extended to the protection of various amines under the same conditions, however the reactions generally took longer to reach completion. Aniline 170 was acylated under the general conditions applied to the acylation of alcohols to afford N-phenyacetamide 171 in 99 % yield (Scheme 67).
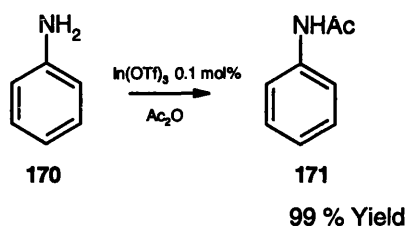
Scheme 67

Aromatic and aliphatic amines were successfully acylated in the presence of 0.1 mol% of indium triflate (Table 10).

Entry	Amine	Product	Time (h)	Yield (%)
1	172	173	3	94
2	174	175	2.5	92
3	176	177	2.5	98
4	178	179	8	91

Table 10

2.3 Acyl Donors

Ethyl acetate, acetic acid and 1-cyclohexenyl acetate were investigated as acyl donors in the acetylation of benzyl alcohol **150**. However, the only effective alternative proved to be 1-cyclohexenyl acetate **180** which prompted an extremely rapid acetylation reaction (Scheme 68). This is no doubt due to the unstable enol liberated during the reaction tautomerising instantaneously to the keto form when the reaction becomes irreversible.
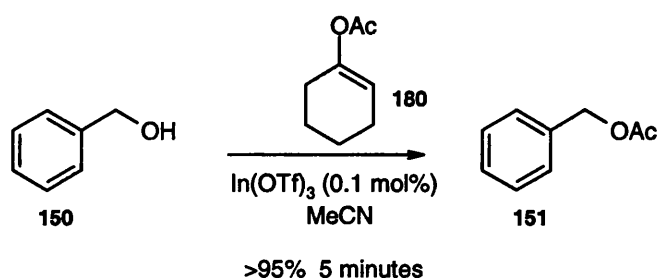
Scheme 68

2.4 The Protection of Aldehydes

The protection of the aldehyde functionality is also an important factor in synthesis of novel compounds[84]. Again, a popular method of protecting aldehydes is by reacting them with acid anhydrides to form acetals[85] (these products are often referred to as acylals or diacetates).

The development of an efficient procedure is of particular importance in the formation of enol acetates, especially for unsaturated aldehydes where the enol acetate is an acetoxybutadiene, which can be utilised in Diels-Alder reactions[86]. Lewis acids such as FeCl$_3$[84] (Scheme 69), PCl$_3$[87] and ZnCl$_2$[88] have been investigated for the protection of aldehydes. However, these methods are often accompanied by long reaction times or low yields[89].

$$\text{PhCHO} \quad \xrightarrow[\text{FeCl}_3]{\text{Ac}_2\text{O}} \quad \text{PhCH(OAc)}_2$$

yield 79%
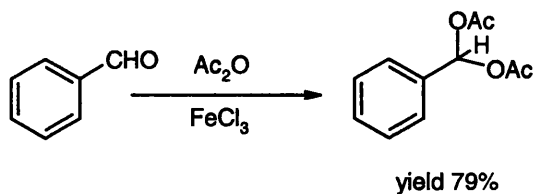
Scheme 69

Nafion-H™ (Dupont), a perfluorinated resin sulfonic acid, has been recently utilised for the diacetate formation of various aldehydes (Table 11) by Olah and Mehrotra[90] (Scheme 70). The advantages of its use are: sub-stoichiometric amounts of catalyst in the presence of no solvent, and an easy non-aqueous work-up after short reaction times.

$$\text{RCHO} \quad + \quad \text{Ac}_2\text{O} \quad \xrightarrow{\text{Nafion-H}} \quad R\text{CH(OAc)}_2$$
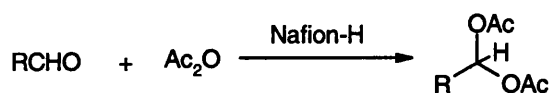
Scheme 70

Entry	Aldehyde	Time (h)	Yield (%)
1	PhCHO	1	99
2	2-Cl-C₆H₄CHO	5	50

Table 11

Sydnes and Sandberg[91] have carried out effective transformations of acylals into nitriles with trimethyl azide in the presence of titanium tetrachloride (Scheme 71). The products were obtained in good to high yields (Table 12).

$$\text{ArCH(OAc)}_2 \quad \xrightarrow[\text{CH}_2\text{Cl}_2, \ -78\ ^\circ\text{C} \to \text{rt}]{\text{TMSA, TiCl}_4} \quad \left[\text{Ar—CH(OOCMe)(N}_3) \right] \quad \longrightarrow \quad \text{Ar—CN}$$
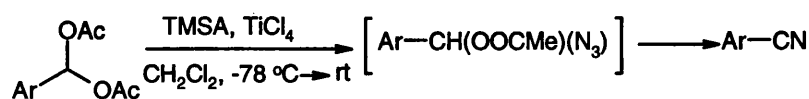
Scheme 71

Entry	Ar	Yield (%)
1	C_6H_5	73
2	4-Me-C_6H_5	95
3	4-MeO-C_6H_5	82
4	4-Cl-C_6H_5	97

Table 12

Aggarwal and co-workers[89] have been able to carry out the efficient chemoselective protection of aldehydes in the presence of ketones using scandium triflate as a Lewis acid (Scheme 72). The group was also able to effectively deprotect acylals in the presence of scandium triflate and water.
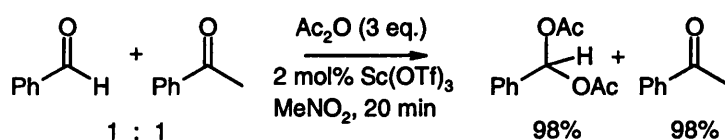
Scheme 72

2.4.1 The Protection of Aldehydes using Indium Triflate

The scope of indium triflate at an acylating agent was also investigated in the preparation of diacetates (Scheme 73). Various aldehydes were reacted with acetic anhydride in the presence of low loadings of indium triflate provided acylals in good to high yield (Table 13).
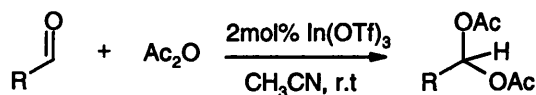
Scheme 73

Entry	Aldehyde	Diacetate	Yield (%)
1	CHO **181**	$CH(OAc)_2$ **182**	99
2	CHO F **183**	$CH(OAc)_2$ F **184**	95
3	Ph CHO **185**	Ph $CH(OAc)_2$ **186**	61

Table 13

The ^{1}H NMRs showed in the cases of benzaldehyde **181**, 2-fluorobenzaldehyde **183**, and trans-cinnamaldehyde **185** the characteristic proton of the aldehyde (~ 10 ppm) being replaced by a sharp methyl singlet at 2.1 ppm of the corresponding acylal. Electronic variations in the substrate aldehyde were also investigated and *para*-bromo-, methoxy-, and nitrobenzaldehyde were also acylated (Table 14). However, there was no real significant difference in the yields to suggest that certain aldehydes were more prone to acylation using indium triflate as the catalyst. All that could be deduced was that indium triflate was able to catalyse the acylation in a smooth and efficient manner.

Entry	Aldehyde	Diacetate	Yield (%)
1	O_2N CHO **187**	O_2N $CH(OAc)_2$ **188**	86
2	Br CHO **189**	Br $CH(OAc)_2$ **190**	90
3	MeO CHO **191**	MeO $CH(OAc)_2$ **192**	93

Table 14

2.5 The Acylal-Ene Reaction

Initially the carbonyl ene reaction was investigated with indium triflate to predict whether it would be a suitable catalyst for the more demanding imino-ene reaction. However at the same time Aggarwal and co-workers[92] published results on the carbonyl ene reactions using unactivated aldehydes.

Scheme 74

Aggarwal found that when various aldehydes were reacted with methylene cyclohexane the reaction only produced pyran products. The reasoning being, two aldehyde groups had become incorporated into the final molecule.
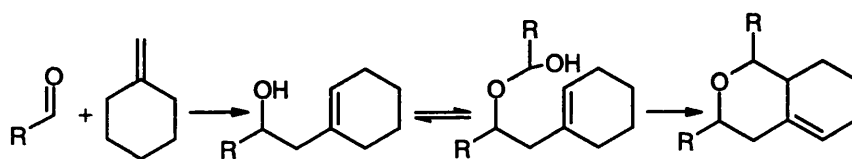
Scheme 75

In order to inhibit the incorporation of a second aldehyde unit the homoallylic alcohol product was acetylated *in situ* using the acetylation methodology that had been developed earlier by their group.

The mechanism that Aggarwal had postulated was that the reaction proceeded by either acylation of the product homoallylic alcohol followed by acetylation or by the formation an oxonium ion before reaction with the alkene.
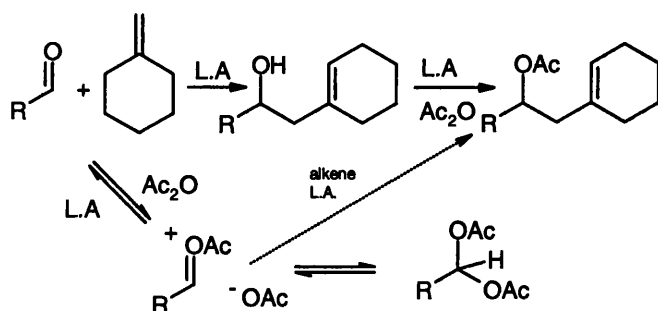
Scheme 76

Benzaldehyde diacetate was reacted with methylene cyclohexane **193** in the presence of 5mol % indium triflate to give the product homoallylic alcohol in 45 % yield. It was also found that the presence of Lewis acid was essential for the reaction to proceed
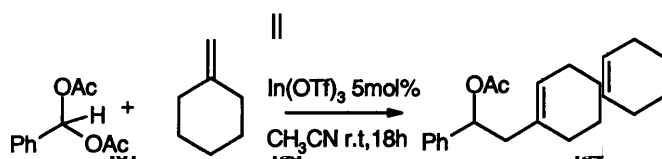
Scheme 77

LEWIS ACID	TIME(h)	YIELD (%)
In(OTf)₃	18	45
-	18	0

Table 15

A higher yield was attained when the aldehyde is reacted with acetic anhydride and methylene cyclohexane in one pot rather than isolating the acylal. This would suggest that when benzaldehyde diacetate is reacted without excess acetic anhydride it tends to undergo hydrolysis in the presence of indium triflate due to there being no acetic anhydride to re-acetylate any aldehyde that may have been inadvertently produced.
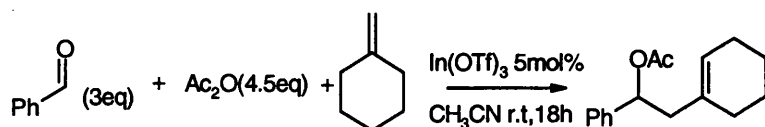
Scheme 78

LEWIS ACID	TIME (h)	YIELD (%)
In(OTf)₃	18	66
Sc(OTf)₃	18	73 (lit.)
-	18	0

Table 16

Efforts to carry out the same reaction with the substituted diacetates resulted in degredation of the acylal back to the corresponding aldehyde. This would suggest that the diacetate prepared from benzaldehyde is a stable acylal in this reaction and that the acylals with electron-withdrawing or donating groups do not undergo the reaction. The mechanism postulated by Aggarwal, in that, the formation of the oxonium ion may be required for the reaction to proceed may also support this finding. Thus by changing the electronic character of the acylal the oxonium ion is not produced and therefore cannot react with methylene cyclohexane.

Benzaldehyde diacetate was also reacted with trimethylsiloxy-1-methoxy propene, the reaction proceeded to provide **(196)** in 45 % yield thus allowing for the preparation of protected aldol products.
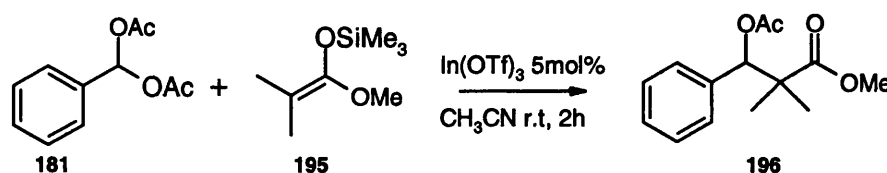
Scheme 79

This chapter demonstrates the use of indium triflate in the protection of functionalities that may be susceptible to undergo undesired transformations unless they are protected. The use of indium triflate has been shown to be highly catalytic at very low catalyst loadings (0.1 mol %) and at highly desirable conditions to both the laboratory and industrial chemist.

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CHAPTER 3

IMINE ALDOL AND IMINO-ENE

3. The Imine Aldol and Imino Ene Reactions

Although various Lewis acid-catalysed reactions of aldehydes including chiral versions have been developed, less progress has been made in the reactions of imines using Lewis acids, this is probably because Lewis acids are often deactivated or decomposed by the relatively basic nature of imines. Thus, the reactions of imines using Lewis acids are sometimes unsuccessful, or if the reactions do proceed, more than stoichiometric amounts of Lewis acids are needed.

3.1 The Imine Aldol Reaction

The imine aldol reaction allows for the convenient formation of a carbon-carbon bond in one step from the reaction between an imine and an unsaturated silyl ether.

In 1991 it was first reported that both indium metal and indium (I) iodide promoted the aldol condensation between α-halo ketones and aldehydes.[93] Kobayashi and co-workers subsequently disclosed that indium (III) chloride in combination with chlorotrimethylsilane catalyses the aldol reaction between aldehydes (and the corresponding dimethyl acetals) with trimethylsilyl enol ethers.[94] This catalyst system had previously been found to be effective in the reaction of O-trimethylsilyl monothioacetals with triethylsilane to afford good yields of the corresponding sulfides.[95]

Further work by Kobayashi demonstrated that the aldol reaction was strongly influenced by the substituents on the silicon of the silyl enol ether such that one could achieve the preferential activation of aldehydes in the presence of the

corresponding acetals. To illustrate this the mixed acetal/ aldehyde substrate **197** smoothly reacts with *t*-butyldimethylsilyl enol ether **198** to afford the corresponding aldol adduct **199** whilst the acetal part of **197** remains untouched (Scheme 80).
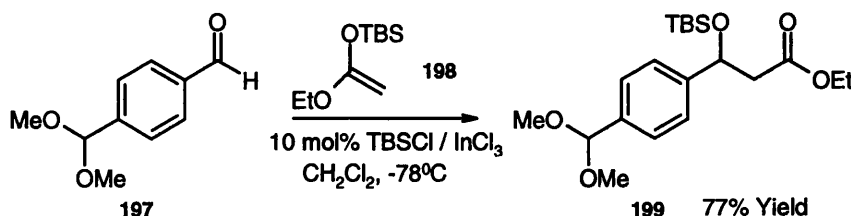
Scheme 80

In 1996 Teck-Peng Loh and co-workers in Singapore reported the indium (III) chloride catalysed Mukaiyama aldol reaction affording good yields of products at room temperature using water as a solvent.[96] This report was not consistent with results obtained by Kobayashi who concluded that the hydrolysis of silyl enol ethers is superior to the desired condensation in the same indium (III) chloride catalysed Mukaiyama aldol reaction.[97]

A subsequent reinvestigation of the reaction revealed that reasonable yields of the product could be obtained under neat (solvent-free) conditions albeit with severe substrate limitation. This is shown by reaction of benzaldehyde **181** with silyl enol ether **200** to give aldol product **201** (Scheme 81). Futhermore, it was found that the reaction proceeded smoothly in water in the presence of a small amount of surfactant (Table 17).
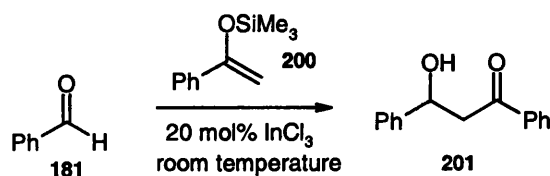
Scheme 81

Solvent	Yield %
none	61
water	20
water/SDS	75

Table 17

The many benefits of using water as a solvent for catalytic carbon-carbon bond formation continues to drive research in this area. The group of Teck-Peng Loh have reported an efficient aldol reaction between commercially available aqueous formaldehyde and silyl enol ether **202** furnishing **203** which is promoted by indium (III) chloride (Scheme 82).[98]
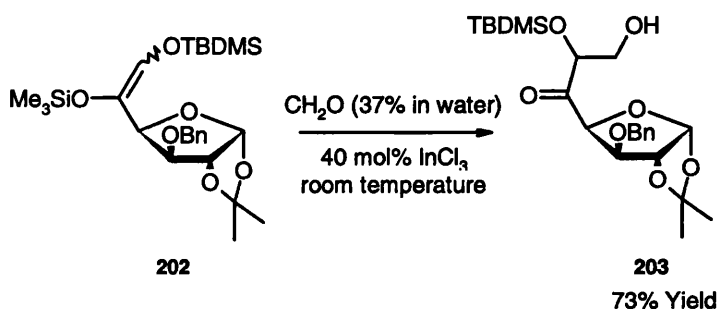
Scheme 82

The Mannich-type reaction is one of the most fundamental and useful methods for the synthesis of β-amino ketones and esters. The reaction is a variant of the Mukaiyama aldol reaction in that the substrates are imines rather than aldehydes.

To circumvent the problems associated with the synthesis and purification of imines an elegant one-pot Mannich-type reaction has been developed employing indium (III) chloride as catalyst.[99] The reaction between aldehyde **204**, amine **205** and silyl enol ether **195** is catalysed by 20 mol% of indium (III) chloride in water and affords

the product β-amino ester **206** in high yield (Scheme 83). The approach is also useful for the synthesis of β-amino ketones.
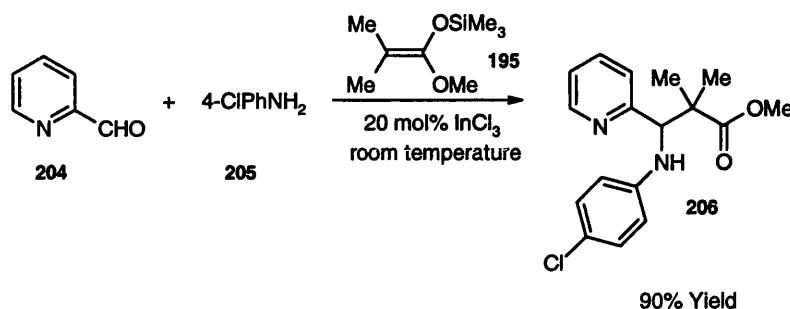
Scheme 83

3.1.1 Indium Triflate Catalysed Imine Aldol Reactions

With a view to finding a suitable Lewis acid for the imino-ene reaction the Mannich-type reaction was screened with a variety of Lewis acids to determine the catalytic efficacy displayed by indium triflate. Initially, the imine **207** prepared from aniline and benzaldehyde was reacted with the silyl enol ether **195** to give the product **208** in good yield (Scheme 84).
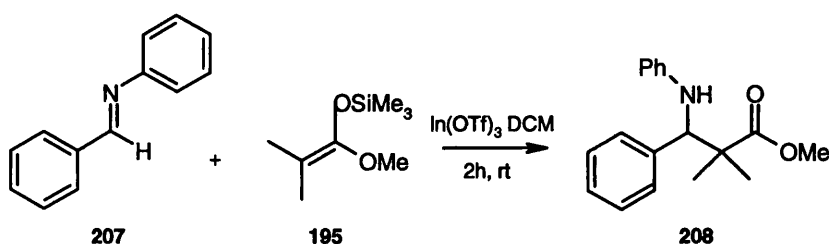
Scheme 84

Investigations of this reaction shows that indium triflate does indeed catalyse the Michael type reaction quite efficiently and although not as efficient as the lanthanide triflates, compares well against Lewis acids such as copper triflate and zinc triflate.

Entry	Lewis Acid	Yield %
1	In(OTf)$_3$	72
2	Sc(OTf)$_3$	84
3	Yb(OTf)$_3$	88
4	Cu(OTf)$_3$	73
5	Zn(OTf)$_3$	70
6	InCl$_3$	52

Table 18

Furthermore the imine aldol reaction was investigated using various imines to provide a general protocol using indium triflate in this important reaction. Various imines were also reacted initially with the silyl enol ether trimethylsiloxy-1-methoxy propene. The reactions were found to proceed to provide the desired products in good yield. The imine prepared from cinnamaldehyde and aniline also underwent the imine aldol reaction to provide an unsaturated β-amino ester (Scheme 85).
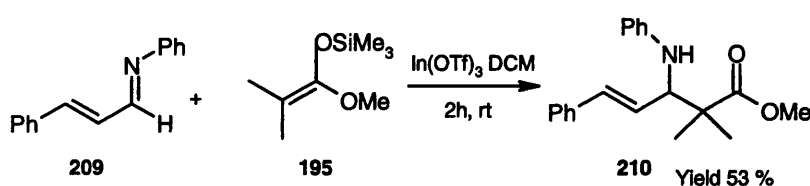
Scheme 85
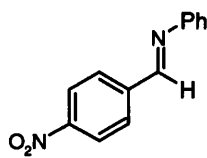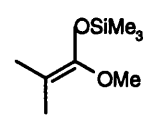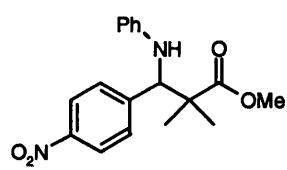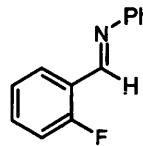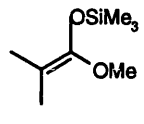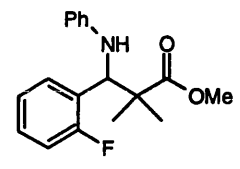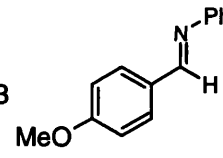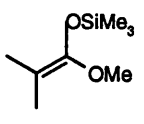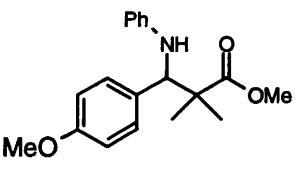
Entry	Imine	Silyl enol ether	Product	Yield %
1	211	195	212	63
2	213	195	214	65
3	215	195	216	57

Table 19

Another enol silane substrate, 1-cyclohexenyloxy-trimethyl silane **217** was also investigated the imine aldol reaction (Scheme 86). The substrate was again reacted with various imines in the presence of indium triflate to provide the desired products in moderate yields.
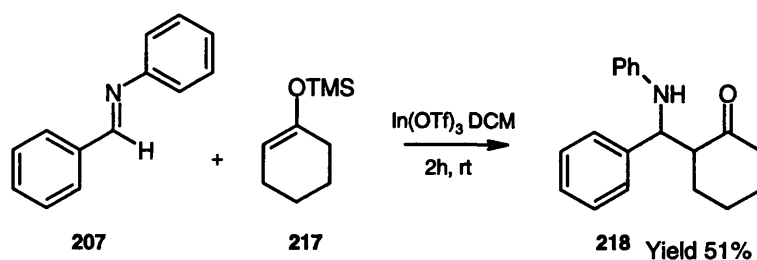
Scheme 86
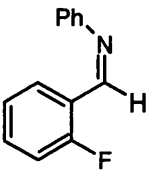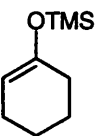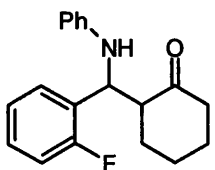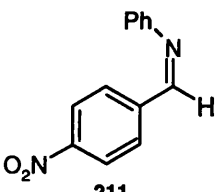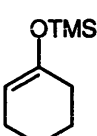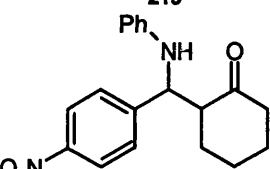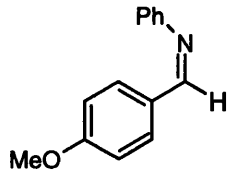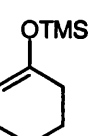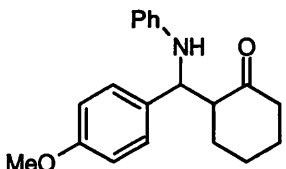
Entry	Imine	Silyl Enol Ether	Product	Yield %
1	213	217	219	45
2	211	217	220	42
3	215	217	221	49

Table 20

Surprisingly the reaction between the various imines and a third substrate, 1-phenyl-1-(trimethylsiloxy) ethylene resulted in none of the expected results (Scheme 87).
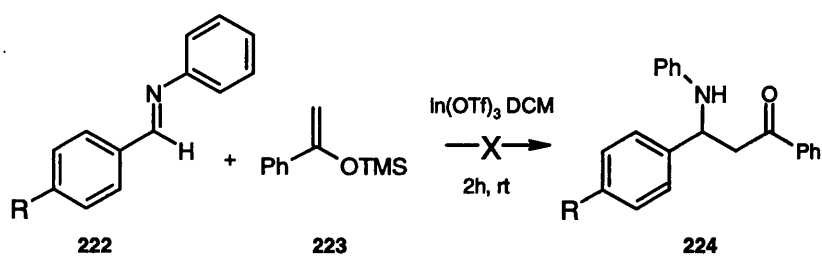
Scheme 87

3.1.2 Asymmetric Imine Aldol Reactions using Indium Triflate

The asymmetric version of this reaction was also investigated using various chiral ligands (Scheme 88) in order to determine whether indium would be able to facilitate the enantioselective imine-aldol reaction.

(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl
(R)-(+)-BINAP

(R)-(+)-1,2-Bis(diphenylphosphino)propane
(R)-(+)- PROPHOS

(R)-(+)-1,1'-Bi(2-napthol)
(R)-(+)- BINOL

(-)-2,3-O-Isoprpylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino) butane
(S)-(-)-DIOP

(2R,3R)-(+)-Bis(diphenylphosphino)butane
(R)-(+)-CHIRAPHOS

(1R,2R)-(-)-1,2-Diaminocyclohexane
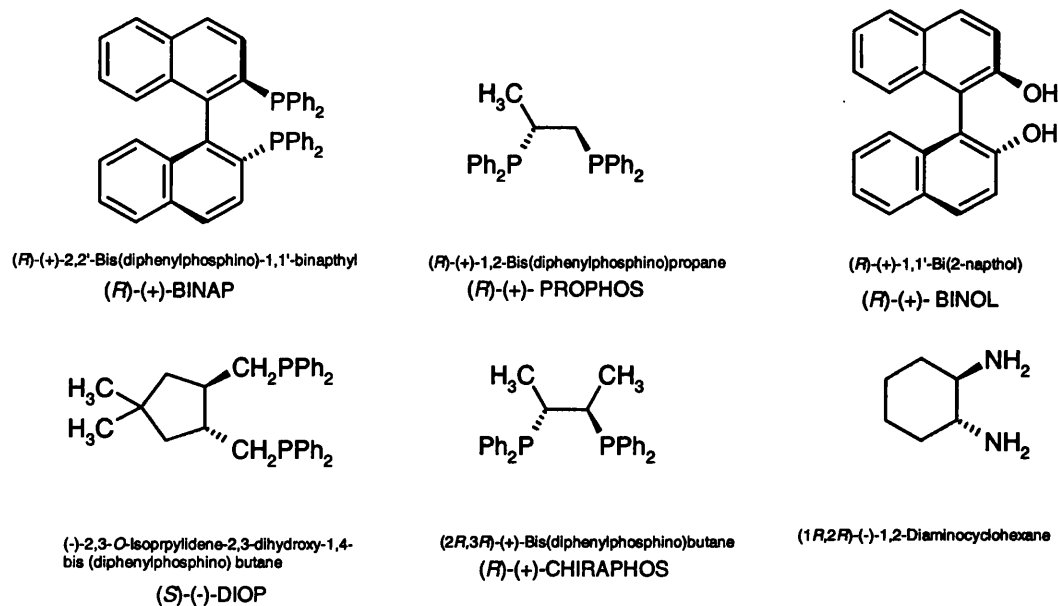
Scheme 88

Aniline benzilidene was added to a stirred solution of various ligands and indium triflate in dichloromethane followed by the addition of trimethylsiloxy-1-methoxypropene.

Entry	Ligand	Yield (%)	e.e (%)
1	(R)-(+)-BINAP	70	0
2	(R)-(+)-PROPHOS	68	0
3	(-)-DIOP	67	0
4	(R)-(+)-CHIRAPHOS	69	0
5	(R)-(+)-BINOL	71	0
6	(1R,2R)-(-)-1,2-Diaminocyclohexane	66	0

Table 21

Although the reactions proceeded in good yield, no enantiomerically enriched β-aminoesters were obtained. The reasons for this could be the fact that the indium was not complexed to the ligand and therefore no enantioselective reaction could take place or the imine used in this reaction has no chelating moiety for the indium complex to bind to in order to create some diversity in a rather planar imine.

After careful examination of the literature it was found that Kobayashi and co-workers[100] had reported an enantioselective version of this reaction using a chiral zirconium complex **227** with the imine prepared from benazladehyde and 2-aminophenol **225** (Scheme 89)
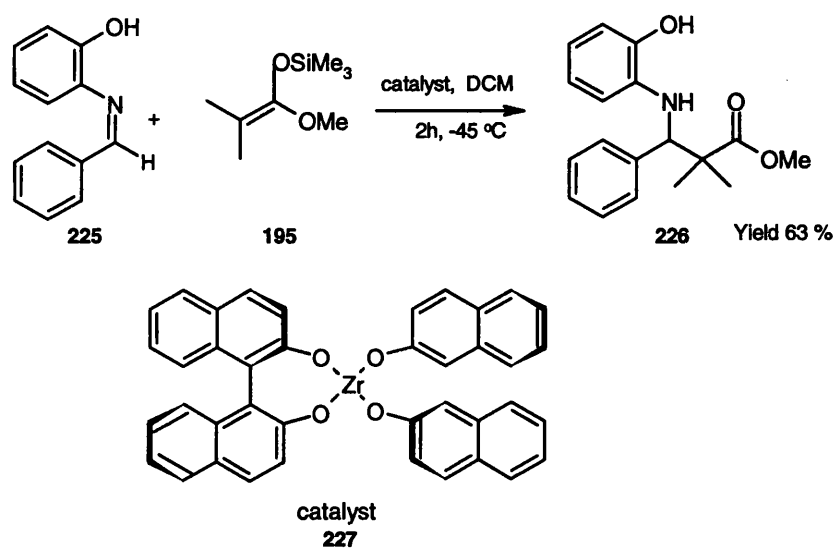
Scheme 89

This prompted the investigation of using the imine from 2-amino phenol and benzaldehyde with indium triflate and various chiral ligands to ascertain whether it was a lack of chelation in the imine substrate that was inhibiting the reaction from furnishing enantiomerically enriched products.
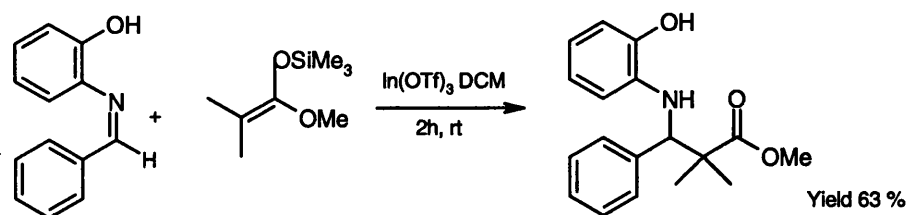
Scheme 90

Unfortunately, these efforts were to no avail as no enantiomeric excess was observed by chiral HPLC (Table 22).

Entry	Ligand	Yield (%)	e.e (%)
1	(R)-(+)-BINAP	59	0
2	(R)-(+)-PROPHOS	56	0
3	(-)-DIOP	58	0

Table 22

The reaction was further investigated by lowering the temperature. The reaction was conducted at -78 ° C and although the reaction again proceeded in a smooth manner to give the product in 61 % yield no enantiomeric excess was observed.

Although this was a rather negative result in one sense it proved that the lack of enantioselectivity was due to the formation of the chiral complex and this would therefore require further investigation. Nevertheless, the use of indium triflate has been shown to facilitate the imine aldol reaction in a catalytic fashion at desirable conditions.

3.2 The Imino-ene reaction

The imino-ene reaction is conceptually very similar to the cabonyl-ene reaction, however the latter has received much more attention over the years. The ene reaction was first described by Alder and co-workers[101] in 1943. The ene reaction (Scheme 91) involves the addition of an olefin which possesses an allylic hydrogen (the ene component) to a compound containing a multiple bond (the enophile).

ene: alkene, alkyne, allene, arene,
carbon-heteroatom bond
X = Y : C = C, C = O, C = N, C = S,
O = O, N = N, C = C
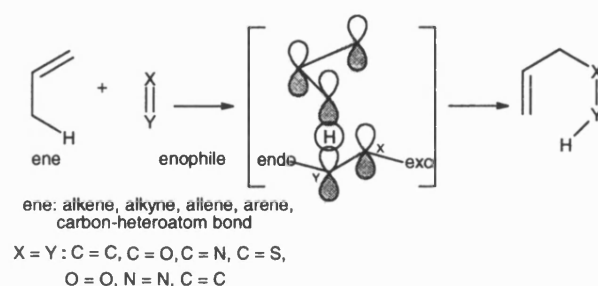
Scheme 91

For the imino-ene reaction, the enophile is a carbon-nitrogen double bond containing compound, and the ene component is an olefin possessing an allylic hydrogen. The intramolecular and intermolecular version of this reaction is thought to proceed via a concerted, pericyclic six-electron pathway[102] (Scheme 92).

Direct ene reactions involving unactivated imines are rare. However, if the imine is activated using suitable electron-withdrawing groups the intermolecular process can proceed quite efficiently.

Intramolecular imino-ene

Intermolecular imino-ene
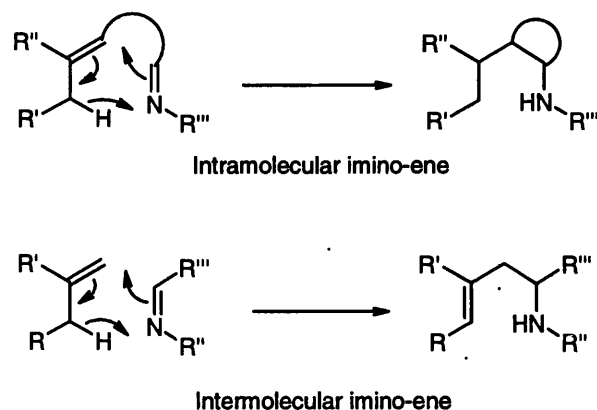
Scheme 92

To a greater extent, the research on the imino-ene reaction has been directed towards activated imines, predominately using N-acyl and N-sulfonyl imine derivatives. This activation lowers the $LUMO_{imine}$, reducing the magnitude of the $HOMO_{ene}$ - $LUMO_{imine}$ energy separation in the transition state and thus increasing the rate of the normal electron demand ($HOMO_{ene}$) imino ene reaction.[103]

Achmatowicz and co-workers[104] were the first to report an example (Scheme 93) of an ene reaction involving the active imine group. n-Butyl N-(toluene-*p*-sulphonyl)iminoacetate **227** was reacted with various alkenes to form adducts which could then be easily converted into α-amino or γδ-unsaturated α-amino acids.

227

ene   activated imine   amino acid derivative
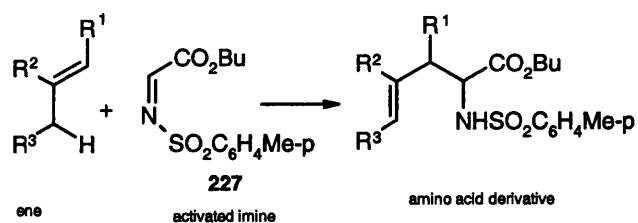
Scheme 93

Recently, an N-sulfonyl imine **228** derived from (-)-8-phenylmenthol glyoxalate, has been found to exhibit high diastereofacial selectivity (98 % d.e.) in the imino ene reaction with methylenecyclohexane **88** (Scheme 94).[105]
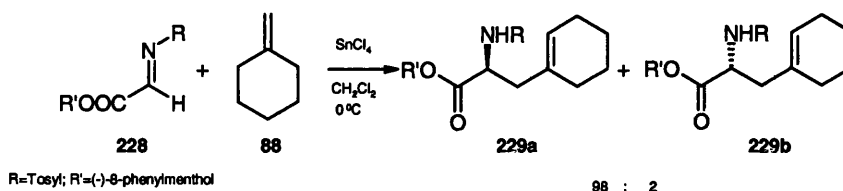
Scheme 94

The rapid construction of versatile, unnatural α-amino acids demonstrates the practical utility of this strategy. The imino ene reaction has also been of great importance to the pharmaceutical industry and in the total synthesis of natural products.

Research has been carried out into the thermal behaviour of cocaine as a consequence of the new practice of cocaine abuse.[106] Labelled starting material (-)-cocaine-[N-CD₃] was used to show the thermal reaction pathway leading to methyl pyridylbutanoate. The reaction proceeded *via* an intramolecular imino-ene cyclisation, in which the olefin acted as a hydrogen acceptor (Scheme 95).

Scheme 95

70
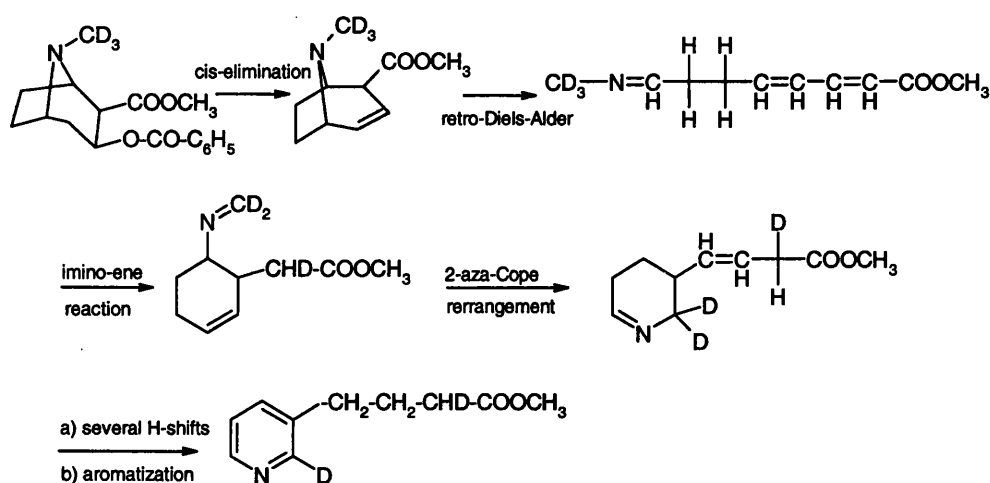
Another report provides a convergent enantioselective total synthesis of (-)-Perhydrohistrionicotoxin[107], in which an intra-molecular imino-ene type reaction is the key step. This is regarded to be a non-natural derivative of the spirocyclic alkaloid (-)-histrionicotoxin which exhibits important neurotoxic properties (Scheme 96).

231 Perhydrohistrionicotoxin (post imino-ene)   (pre imino-ene)

230 (-)-histrionicotoxin
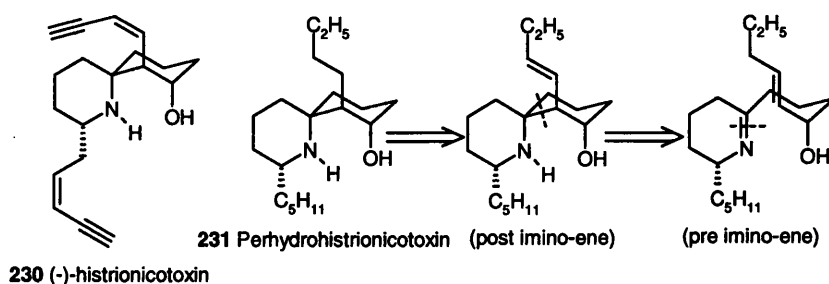
Scheme 96

Substance P[108] belongs to the tachykinin family of neurotransmitters, which is involved in the transmission of pain signals and the initiation of inflammatory responses.

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH$_2$

Substance P

232 CP-99,994

Substance P antagonist

X=NCH$_2$Ar
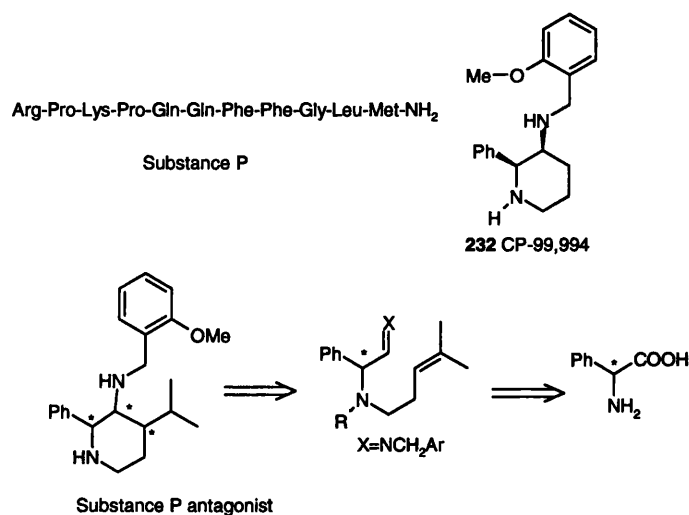
Scheme 97

Substance P has several other biological effects; for example smooth muscle contraction, secretion from exocrine and endocrine glands, vasodilation, increased vascular permeability (neurogenic inflammation) and regulation of immune responses.

Therefore, substance P antagonists may be useful as novel analgesics and as anti-inflammatory agents in the treatment of migraine and rheumatoid arthritis.

For this reason a limited number of substance P antagonists have been reported where their syntheses also occur *via* an imino-ene process. CP-99,994 has been found to act as a potent substance P antagonist and the analogue shown above (Scheme 97) has been based on its structure.

Papuamine **234** is an alkaloid (marine) found to possess antifungal acitivity. Bozirelli and Weinreb[109] were able to report an enantioselective total synthesis of papuamine utilizing a novel imino ene reaction as a key step.

234 Papuamine
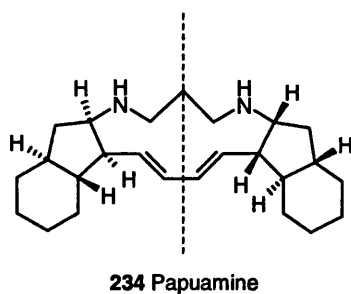
3.2.1 The Intramolecular Imino Ene Reaction

The intramolecular imino-ene reaction was investigated initially due to the favourable entropic considerations with respect to the intermolecular reaction. The use of simple unactivated imines in imino-ene reactions are rare, however these transformations can occur if Lewis acid catalysts are used. 3-Methyl citronellal **235**, prepared from a commercially available substrate citral, was investigated in the intramolecular imino-ene reaction. The advantage of using an imine prepared from 3-methyl citronellal would be the effect of the two di- geminal methyls which provide a Thorpe-Ingold[109] effect, inducing the cyclisation (Scheme 98) more efficiently.

Me、_Me   Me、_Me

           PhCH₂NH₂
           Toluene
         O   ⟶
         MgSO₄   N-CH₂Ph
         4h, r.t

Me   Me   Me   Me
235 3 Methyl citronellal   236 imine
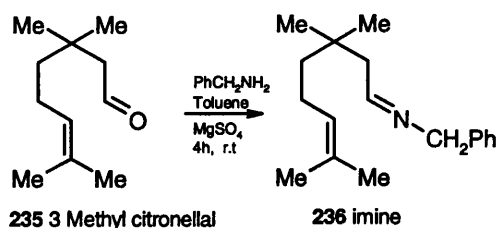
Scheme 98

The crude ^{1}H NMRs of the intramolecular imino-ene reaction of imine also showed degradation of the imine resulting in the aldehyde peak of 3- methyl citronellal reappearing in cases where tin and titanium lewis acids were employed. However, some of the cyclised product (Scheme 99) was isolated in a rather low yield (Table 25)

Me、_Me   Me、_Me

      Lewis Acid   H
    N-CH₂Ph ⟶   N-CH₂Ph
      24 h, rt

Me   Me   Me
236   237

Scheme 99

73
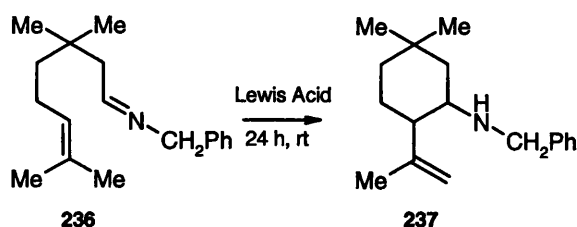
IMINE	LEWIS ACID (eq)	CYCLISATION (%)
3-Methyl Citronellal/Benzylamine	SnCl₄ (4)	19%
3-Methyl Citronellal/Benzylamine	ZrCl₄ (4)	<10%
3-Methyl Citronellal/Benzylamine	ZnBr (0.3, 1, 4)	-

Table 25

The reaction of the imines with the lanthanide triflates also did not yield any results (Table 26), however there was no breakdown of the imines into the corresponding aldehyde and amine.

IMINE	LEWIS ACID (eq)	CYCLISATION
3-Methyl Citronellal/Benzylamine	Sc(OTf)₃ (0.3)	-
3-Methyl Citronellal/Benzylamine	Yb(OTf)₃ (0.3)	-
3-Methyl Citronellal/Benzylamine	In(OTf)₃ (0.3)	-

Table 26

3.2.2 The Intermolecular Imino-ene Reaction

As previously mentioned a more activated imine is required for the intermolecular imino-ene reaction. Initially the Kresze[111] method was investigated (Scheme 100). This reaction requires vigorous heating for 8 days using thionyl chloride. The procedure also requires the removal of excess thionyl chloride and hydrogen chloride at the end of the reaction. This initial step prepares the N-sulfonyl-p-toluenesulfonamide which is then distilled and reacted with an aldehyde or glyoxalate to furnish the required activated tosylimine, liberating SO₂ as the byproduct. This method of preparing the N-tosyl imine proved difficult and hazardous.

$$R-SO_2-NH_2 \;+\; SOCl_2 \xrightarrow[\text{8 days}]{\text{reflux}} R-SO_2-NSO \;+\; 2\,HCl$$

$$R-SO_2-NSO \;+\,R'-\underset{H}{C}=O \xrightarrow{AlCl_3} R-SO_2-N\!=\!CHR' \;+\; SO_2$$
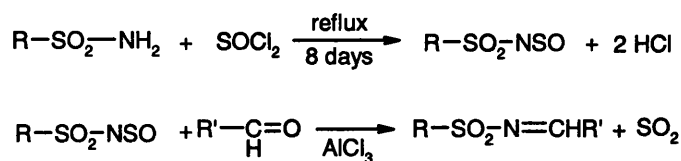
Scheme 100

Therefore, other methods were sought in order to circumvent the long reaction times and hazardous conditions required in the Kresze procedure. Initially, the method reported by Georg and co-workers[112] *via* a halogen mediated conversion of *N*-(trimethylsilyl) imines in the presence of *p*-toluene sulfonyl chloride and thionyl chloride was investigated (Scheme 101). The reaction was reported to proceed quantitatively using neat reactants at reflux.
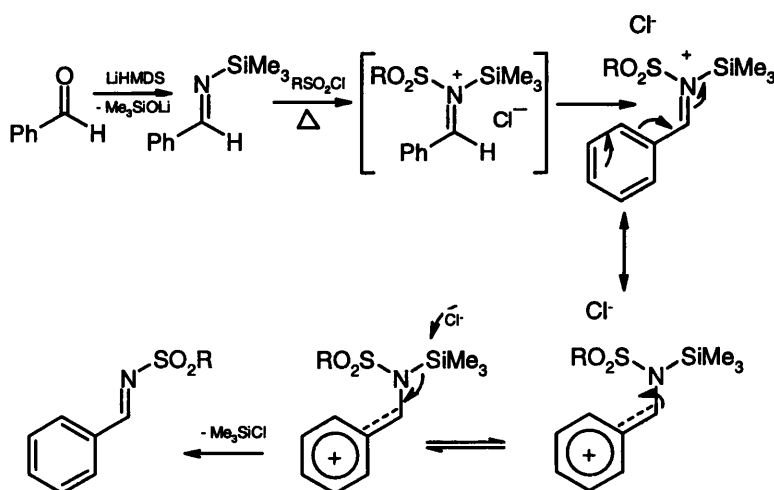
Scheme 101

Investigations of this method using benzaldehyde and furaldehyde as the substrates led to the preparation of the corresponding silyl-imines in quantitative yields. However, the reported method suggested a facile one-flask conversion of the silyl-imines to *N*-sulfonyl imines without purification, numerous attempts to synthesise the *N*-sulfonated imines followed by purification by recrystallisation resulted in the hydrolysis of the imines (Scheme 102). The explanation for this could

be the fact that the by-product of the final transformation would be trimethylsilylchloride and this could cause degradation of the imines.
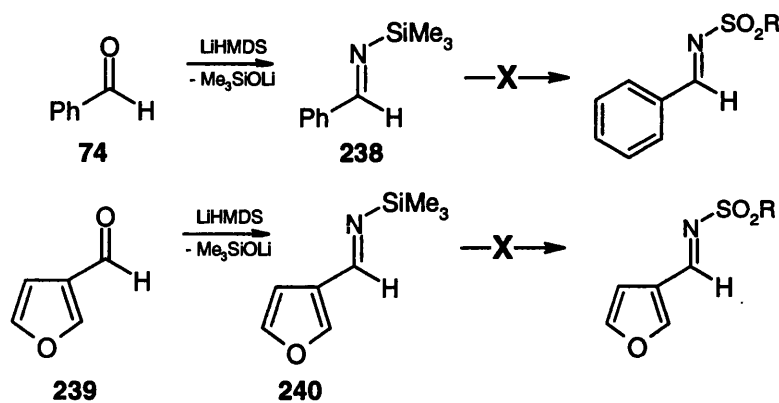
Scheme 102

Other methods for preparing *N*-sulfonylimines have been reported in the literature. Boger and Corbett[113] developed a procedure to synthesize tosylimines from oximes; Love and co-workers[114] have used tetraethyl orthosilicate to prepare the imines under neutral conditions and Trost and Marrs[115] developed a method using *N,N'*-ditosyltelluordiimide.

However a derivative of the method reported by Holmes and co-workers[116] was found to be the most suitable procedure for preparing tosylimines (Scheme 103). The group found that on reacting *p*-toluenesulfonyl isocyanate with freshly distilled methyl glyoxalate they were able to prepare the corresponding tosylimine by a [2+2] cycloaddition which liberates CO_2 as the only byproduct. This would provide an efficient and less hazardous alternative method to prepare the tosylimines relative to the Kresze method. The group used the method to prepare the tosylimine from methyl glyoxalate to carry the hetero Diels Alder reaction *in situ* with a number of dienes
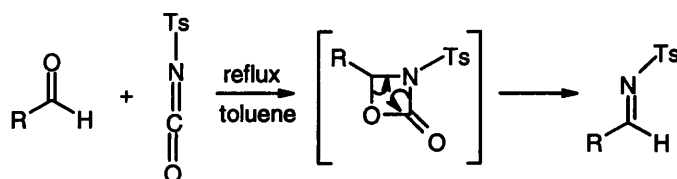
Scheme 103

The synthesis of the tosylimine from ethylglyoxalate was initially investigated due to the electron withdrawing ability of the glyoxalate functionality. The isolation of this imine proved difficult due to the relative unstability of ethylglyoxalate.

Ethylglyoxalate can be prepared in a number of ways[117], however after attempting the various methods cracking of the commercially available ethylglyoxalate/toluene (50:50) solution (Fluka) was utilised. This solution is a polymeric mixture in toluene and requires cracking to obtain the monomeric ethylglyoxalate (Scheme 104).
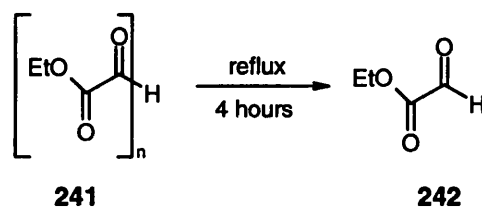
241   **242**
Scheme 104

It was found that the use of short path distillation apparatus allows for the cracking of the ethylglyoxalate/ toluene solution however some of the undesired polymeric glyoxalate distilled over or perhaps reform whilst the distillation was in progress.

The optimal conditions for the use of ethylglyoxalate was to crack a ethylglyoxalate solution at 110 °C for 4 hours. When the solution is subjected to prolonged heating the ethylglyoxalate was found to decompose. The cracked ethylglyoxalate also needs to be used immediately as repolymerisation and degradation occurs if left

over a period of time. Attempts to isolate the glyoxalate by distilling off the toluene solvent is also not possible as this also leads to degradation of the glyoxalate monomer.

The preparation of *N*-Sulfonylimines has proved quite difficult, the literature also suggests that other groups[118] have also had difficulty in preparing activated imines. Whiting and co-workers[119] have recently reported the preparation of brominated *N*-arylsulfonylglycine esters in order to generate the required *N*-sulfonyl imino esters *in situ* due to the difficulty in isolating *N* – sulfonyl imines after attempting the method reported by Kresze and co-workers.

With respect to the above methods the procedure utilised for the investigations with indium triflate were carried out in the following facile manner. An equivalent amount of *p*-toluene sulfonyl isocyanate was added to the cracked ethylglyoxalate solution (equivalent in moles to the ethylglyoxalate) and heated for a further 4 hours at reflux (Scheme 105). The resulting tosyl imine is also unstable and must be used immediately. Attempts to distill the excess toluene off produce a thick sludge, which is difficult to use and results in degradation of the imine when attempts were made to transfer from a round bottom flask. Therefore the crude reaction mixture must be used when it has cooled to room temperature.
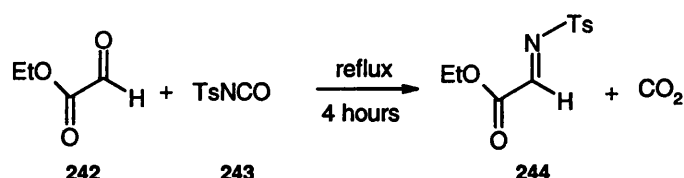
Scheme 105

This method of preparing activated imines was investigated further by refluxing various relatively stable aldehydes with *p*-toluenesulfonylisocyanate in toluene

(Scheme 106). The reactions were generally complete in 24 hours. The product tosylimines from various aldehydes were recrystallised from ethyl acetate to give the pure tosylated imines in one easy step (Table 27) and were relatively more stable compared to the ethylglyoxalate tosylimine.

Scheme 106

The formation of the tosylimines was also investigated in trifluorotoluene to elucidate whether a more polar solvent would induce the cycloaddition. It was found that trifluorotoluene did enhance the formation of the tosylimines for benzaldehyde and dichlorobenzaldehyde, however in the case of 2-napthaldehyde and trans-cinnamaldehyde trifluorotoluene did not facilitate the cyclisation relative to performing the cyclisation in toluene.
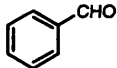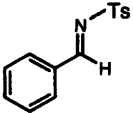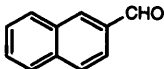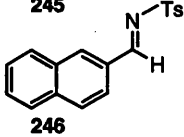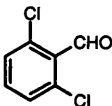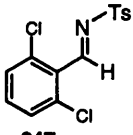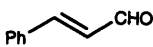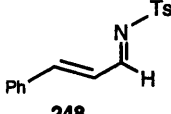
Entry	Aldehyde	Solvent	Imine	Yield (%)
1		Toluene BTF	245	64 79
2		Toluene BTF	246	85 73
3		Toluene BTF	247	56 80
4		Toluene BTF	248	90 84

Table 27

The formation of the tosylimine from tosyl isocyanate and 2-napthaldehyde was also investigated over time and was found to reach a maxima at ~28 h (Graph 1).

Formation of Napthaldehyde Tosylimine

Graph 1
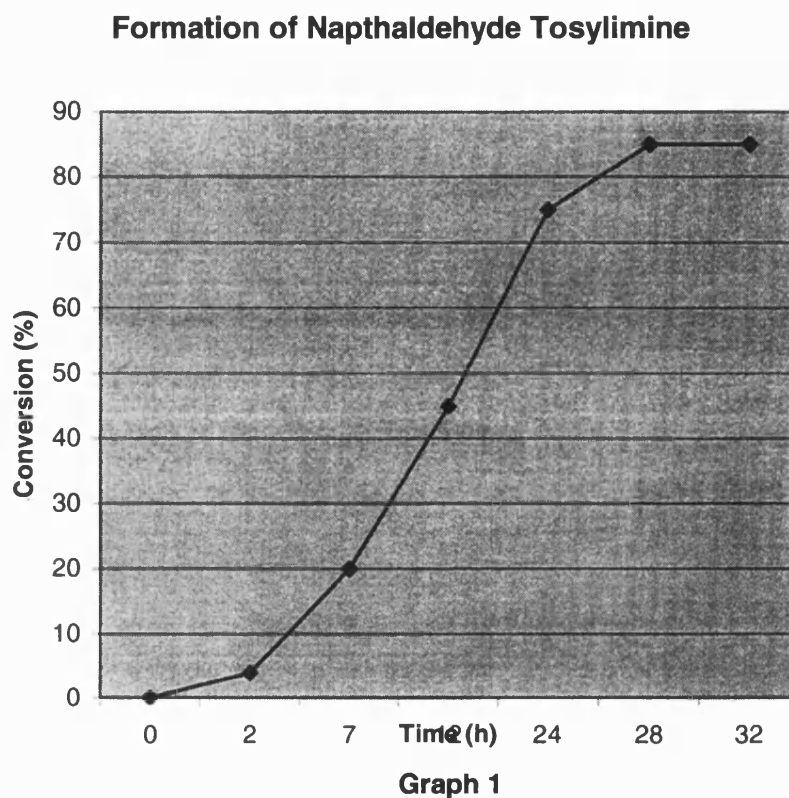
The ethylglyoxalate tosylimine prepared in method described above was added to the corresponding ene substrate in a 1: 1 ratio in the presence of indium triflate in toluene. Initially, it was thought that no product had been formed and that the tosylimine had decomposed resulting in broad peaks in NMR spectra, however on closer inspection, followed by careful separation of the mixture, the allylic amine product was indeed isolated. This reaction was later reinvestigated using the tosylimine in excess and the yield of the reaction increased from less than 5% when an equimolar amount of imine to ene was used to 88% when the imine was used in excess, thus demonstrating the instability of the activated imine.
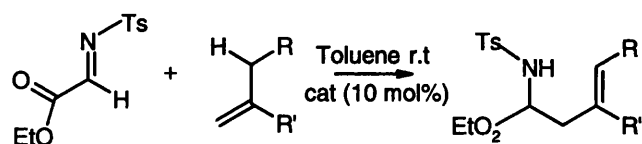
Scheme 107

ENTRY	ENE	CATALYST	YIELD
1	Methylene Cyclohexane	In(OTf)$_3$	<5%[a]
2	Methylene Cyclohexane	AgClO$_4$/TolBinap	<10%[a] 55% e.e
3	Methylene Cyclohexane	AgClO$_4$	<10%[a]
4	Methylene Cyclohexane	In(OTf)$_3$	88%[b]
5	Methylene Cyclohexane	AgClO$_4$	85%[b]
6	α-Methyl Styrene	In(OTf)$_3$	55%[b]

Table 28

[a] The molar ratio of the imine to the ene substrate in these reactions was 1:1

[b] The activated imine was added in excess and the yield was determined from the conversion of the ene substrate.

The tosylimines prepared from 2, 5 dichlorobenzaldehyde, benzaldehyde and 2-napthaldehyde were also reacted with methylene cyclohexane. Unfortunately it would seem that the nature of these activated imines were not strong enough to undergo the imino ene reaction.

In order to elucidate why these tosyl imines were not successful in the imino – ene reaction, the charge separation between the carbon–nitrogen bond was investigated to provide some rationalisation.

The SPARTAN[120] molecular orbital program was employed with the Austin Method 1 for geometry optimisation in solution using a polarised continuum model. The semi-emperical quantum mechanical method seeks an approximate solution to the many electron Schrodinger equations, but which involve emperical parameters.

The solution Mulliken population analysis, which is a charge partitioning scheme in which electrons are shared equally between different basis functions, was calculated from the optimised structures in solution to provide the results shown in Table 29.
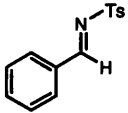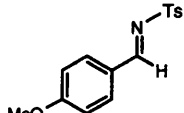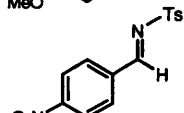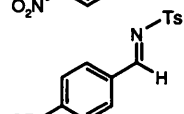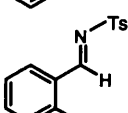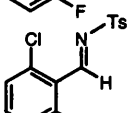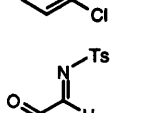
Entry	Tosylimine	Electronic Charge	Δ N - C
1		N -1.00 C + 0.35	-1.35
2		N -1.01 C + 0.36	-1.37
3		N -0.97 C + 0.33	-1.30
4		N -0.96 C + 0.34	-1.30
5		N -0.99 C + 0.35	-1.34
6		N -0.99 C + 0.34	-1.31
7		N -0.89 C + 0.28	-1.17

Table 29

Table 29 shows that the charge on the nitrogen and the carbon atom of the ethylglyoxalate tosylimine is the lowest of all the activated tosylimines investigated. The difference between the electronic charges of the two atoms is also the lowest of

all tosylimines. The results suggest that the electron withdrawing capability of the ethylglyoxalate moiety is adequate enough for the imino-ene reaction to proceed via a concerted reaction pathway.

However this does not provide an explanation for the imino-ene reaction to proceed in the case for the imine prepared from benzaldehyde and tosylisocyanate described below. One explanation for this could be that the reaction proceeds in a Mannich stepwise reaction as documented by Weinreb and Borzirelli[103]. Thus, a formal an iminium ion reacts with the ene substrate via a carbonium ion intermediate to afford the desired homoallylic amine.
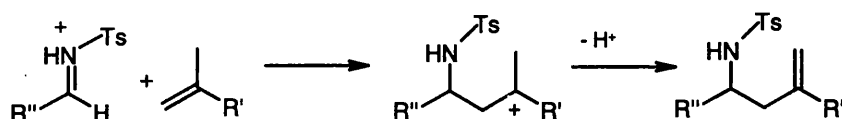
Scheme 108

This theory could be justified by the work of Nakagawa and co-workers[121] who utilised a simple unactivated imine in the presence of ytterbium triflate (Scheme 109). Initially the group conducted the imino-ene in the presence of ytterbium triflate without any additives. Thus, reacting N-toluenesulfonyl benzaldimine with α-methlstyrene in CH_2Cl_2-THF (4:1) at room temperature for 48 h, the imino-ene product was obtained in 58% yield.
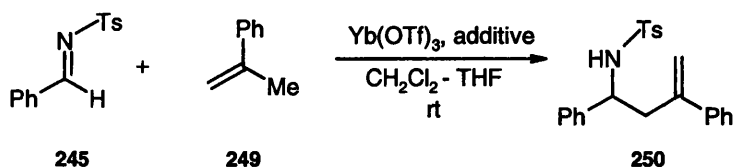
Scheme 109

The group further investigated reaction by adding trimethylsilylchloride as an additive agent as described by Riera and co-workers for diethyl zinc additions. The

additives were found to enhance the reaction dramatically, and the reaction was complete within 15 minutes to give the product in 90% yield (Table 30).

Entry	Yb(OTf)$_3$ (mol%)	Additive (mol%)	Time (hr)	Yield (%)
1	25	none	48	58
2	25	TMSCl (120)	0.25	90
3	none	TMSCl (120)	48	0

Table 30

Experiments were also conducted to show that the imino-ene reaction did not proceed due to any *in-situ* production of TMS-OTf. Additionally, the results also indicate that the *N*-substituent must possess an electron-withdrawing character for the imino-ene reaction to occur.

This experiment was also investigated using the various activated tosyl imines that had been prepared using indium triflate as the catalyst. However, only the imine derived from benaldehyde and tosylisocyanate underwent the imino-ene reaction (Scheme 110). Thus indicating some inherent electronic property of this activated imine to undergo the imino-ene reaction.
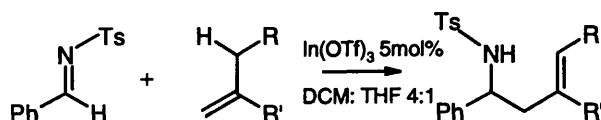
Scheme 110.

ENTRY	ENE	TIME (h)	ADDITIVE	YIELD (%)
1	α-Methyl Styrene	2	MgSO₄ (1eq)	51
2	α-Methyl Styrene	0.25	TMSCl (2eq)	69
4	α-Methyl Styrene	2	-	59
5	Methoxy propene	2	-	0
6	Methylene cyclohexane	2	-	0

Table 31

Therefore the choice of ene substrate is also an important aspect to induce a succesful imino-ene reaction. Initial attempts to perform the imino-ene reaction were attempted using cyclohexene and 1-octene, however both of these ene substrates resulted in no product being formed with the activated ethylglyoxalate tosylimine in the presence of indium triflate.
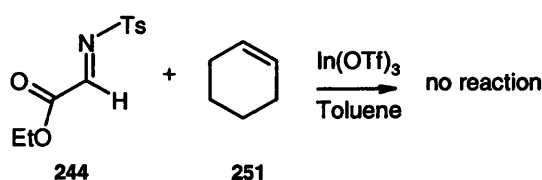
Scheme 111

Kumadaki and co-workers[122] also found this to be the case in their investigations when reacting N-(p-toluenesulfonyl)trifluoroacetaldehyde imine with cyclohexene and 1-octene. It would seem that more activated ene substrates are required.

1,1-Disubstituted alkenes are known to be more reactive and β-Tetralin[123], prepared using the Wittig reaction from the commercially available β-tetralone (Scheme 112), was investigated in the imino-ene reaction (Scheme 113).
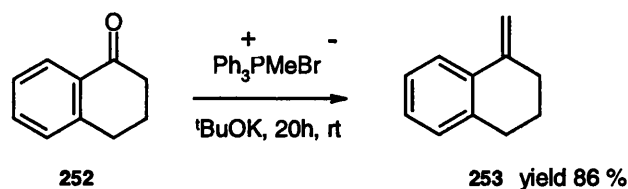
Scheme 112

The reaction was found to proceed in the presence of indium triflate to afford the desired product in moderate yield.
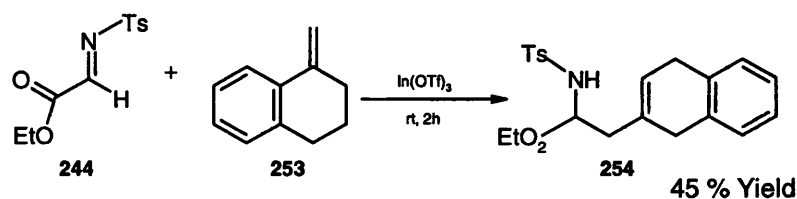
Scheme 113

Efforts to perform an asymmetric imino-ene reaction were also attempted using various ligands with methylene cyclohexane as the ene substrate (Scheme 114). Although the reaction was catalysed by indium triflate to afford the desired product, again no enantioselectivity was observed (Table 32). This would imply that the chiral complex was not formed under the reaction conditions of stirring in DCM/THF for 30 minutes.
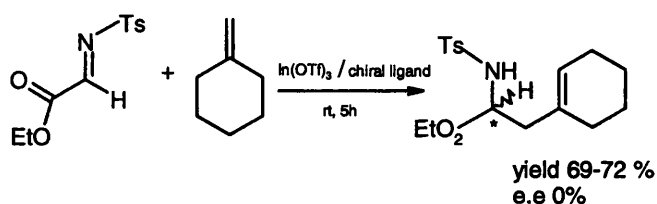
Scheme 114

Entry	Ligand	Yield (%)	e.e (%)
1	(R)-(+)-Tol-BINAP	72	0
2	(R)-(+)-PROPHOS	67	0
3	(-)-DIOP	68	0
4	(R)-(+)-CHIROPHOS	64	0

Table 32

During investigations into the imino-ene reaction Lectka and co-workers[124] reported a copper binap complex catalysed imino ene reaction resulting in high yield and enantiomeric excess (Scheme 115).
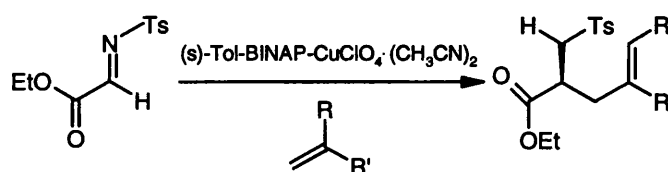
Scheme 115

The reactions took place over 18 hours at a catalyst loading of 0.025 mmol. The yields varied from 85-94% and the enantioselectivity 85-99% e.e. However an interesting result was the use of the solvent benzotrifluoride (BTF) which dramatically enhanced the yields (c.f. THF 35%yield).

After further examination of the literature on indium complexes the absence of enantioselectivity could be explained by the work of Scmidbaur and co-workers.[125] Their investigations on the coordination and structural chemistry of indium (III) halides found that when $InCl_3$ is heated with 1,2-bis(diphenylphosphanyl) benzene for 2 hours in toluene at 80 °C an ionic complex is produced (Scheme 116).

255   **256**
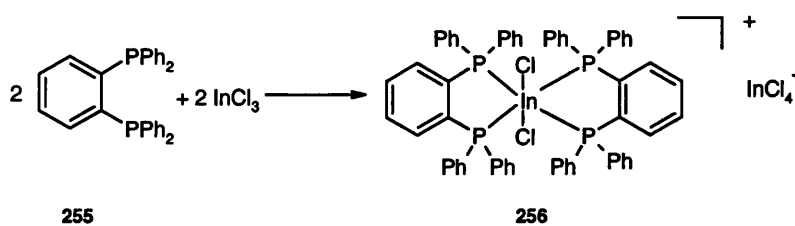
Scheme 116

However, when 1,2-bis(diphenylphosphanyl) benzene is reacted with indium bromide under the same conditions, a neutral complex is formed (Scheme 117).

255   **257**   Yield 89 %
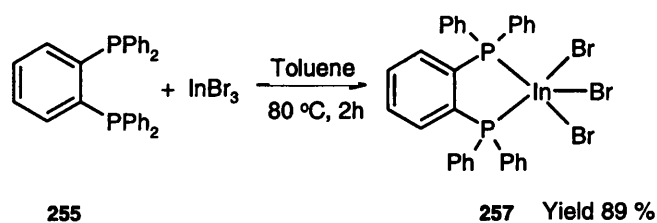
Scheme 117

This prompted an investigation into whether an indium bromide / chiral ligand complex could be prepared and furthermore induce an enantioselective reaction. Initially the reaction between the ethylglyoxalate tosyl imine and methylene cyclohexane was conducted in the presence of indium tribromide. The reaction was found to proceed to give the desired product however in much lower yield than when the reaction was catalysed by indium triflate (Scheme 118).

yield 14 %
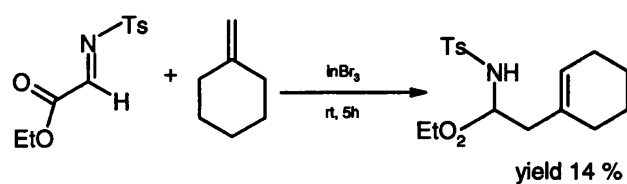
Scheme 118

As a result of this the formation of complexes between indium bromide and Tol-BINAP, DIOP, CHIROPHOS, and PROPHOS were also investigated. Scmidbaur's conditions were applied in attempting to prepare the desired chiral indium Lewis acid complexes, however, the resulting brown oily products did not correspond to the desired theoretical products by Mass Spectrometric analysis.

This may be rationalised by the fact that the ligand used by Schmidbaur to chelate to indium bromide produced a 5 membered ring around indium The preparation of complexes using Tol-BINAP and DIOP with indium tribromide could be entropically disfavoured as they would form 7-membered rings around indium. However, this would not be the case for CHIROPHOS and PROPHOS, the reason for the lack of enantioselectivity with respect to these two ligands could be due to the fact that they do not have a rigid backbone as in the aromatic diphosphine example reported Schmidbauer and co-workers.

This chapter demonstrates the use of indium triflate in two relatively more demanding organic transformations, providing the desired products in moderate to high yields especially in the reaction between imines and the silyl enol ethers. Unfortunately, the reaction could not be developed to provide enantiomerically enriched products. However, a better understanding of why the reaction did not proceed enantioselectively has been achieved.

CHAPTER 4

HETERO DIELS-ALDER

4. The Hetero Diels-Alder Reaction

The hetero Diels-Alder reaction is one of the most powerful methods of C-C bond construction in synthetic organic chemistry. It enables, in a one-step inter- or intramolecular reaction, the rapid preparation of a six-membered heterocyclic ring. Although Lewis acids promote the reactions, quite often the acids are required in stoichiometric quantities due to the strong coordination of the acids to the nitrogen atom. Therefore, the key to realising the true potential of this reaction has been the substantial progress in activating the imine system toward cycloaddition.

The Diels-Alder reaction has several attractive features that have resulted in its use in innumerable syntheses of natural products. The high regio- and stereoselectivity typically displayed by this reaction, the ease of its execution, and the ability, during the course of a [4+2] cycloaddition, to create up to four new stereocentres. Furthermore, the Diels-Alder reaction is regarded[126] as one of the most efficient reaction in terms of atom economy and broad versatility.

Although Lewis acids promote the reactions, quite often the acids are required in stoichiometric quantities due to the strong coordination of the acids to the nitrogen atom.

Loh and co-workers first investigated indium trichloride as a Lewis acid catalyst for the Diels Alder reaction[127]. They investigated the ability of indium trichloride to catalyse the Diels Alder reaction in water. The results obtained, showed that the reactions proceeded smoothly, the desired Diels-Alder adducts were obtained in good to excellent yields. The reaction was found to proceed with either cyclic or non-cyclic dienes and $InCl_3$ could be recovered for reuse after the reaction.

The synthetically important Diels-Alder reaction is known to show increased reactivity rates in water. This is enhanced in the presence of a water-stable Lewis acid. The reliable indium (III) chloride has been found to catalyse the Diels-Alder reaction between various dienes and dienophiles in water[128] (Scheme 119). Acrylaldehyde **258** reacts with cyclohexadiene **259** to afford the cycloadduct **260** in high isolated yield as a single regioisomer.
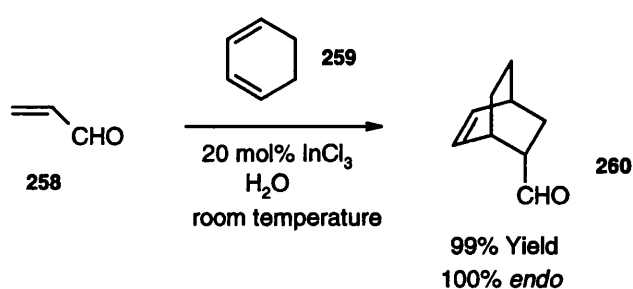
Scheme 119

Imines derived from aromatic amines have been found to act as heterodienes. The group of Perumal have been foremost in utilising indium (III) chloride to catalyse this process. The reaction of Schiff's bases with cyclopentadiene, cyclohexen-2-one and cyclohepten-2-one results in the rapid synthesis of cyclopentaquinolines, azabicyclooctanones and azabicyclononanones respectively[129]. As illustrated in Scheme 120, this protocol allows for the facile synthesis of functionalised phenanthridene derivative 35 from 33 and 3,4-dihydro-2H-pyran 34[120].

Scheme 120

92
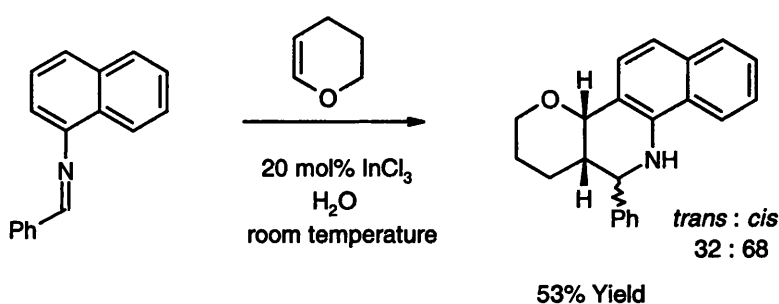
The Diels-Alder reaction has found important use in transannular processes to provide tricyclic compounds possessing up to four new stereogenic centres. An example of the use of the hetero Diels-Alder to synthesise the natural substrate (±)-eburnamonine **261**.

261 (±)-eburnamonine
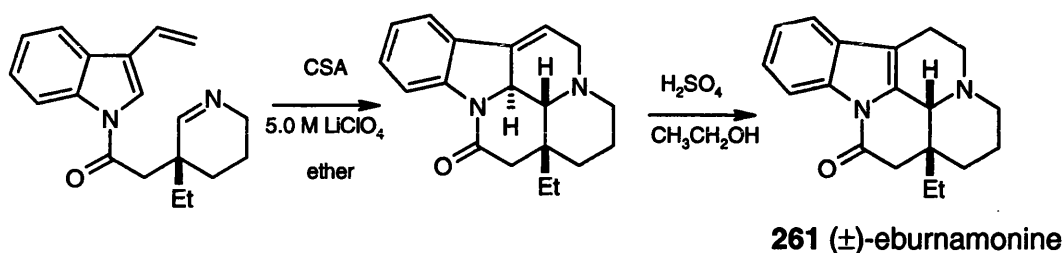
Wang and co-workers[131] have also conducted the hetero Diels-Alder reaction using solid support to afford cycoladduct products (Scheme 121). The resulting cycloadduct products were found to incorporate the aromatic group from the polymer.
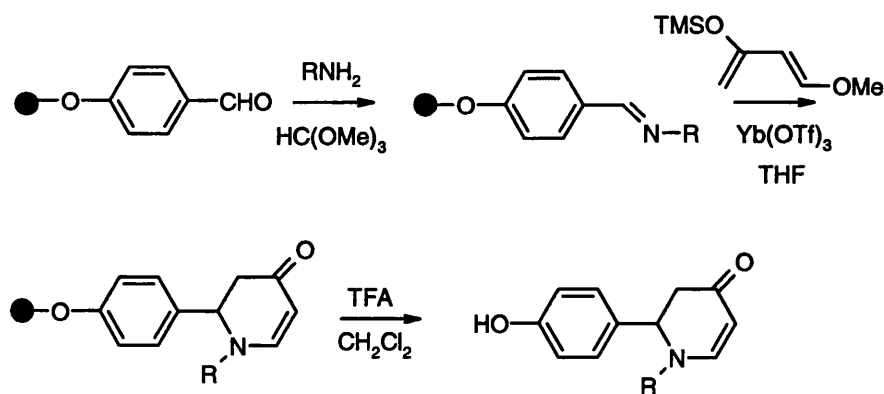
Scheme 121

Chiral Lewis acids have also been employed to catalyse the hetero Diels-Alder reaction in a highly enantioselective manner[132]. The chiral Lewis acid prepared from binapthyl phosphine ligands X and copper perchlorate afforded the cycloadduct in high enantioselectivity when the tosylimine from methyl glyoxalate was reacted with Danishefsky's diene (Scheme 122)
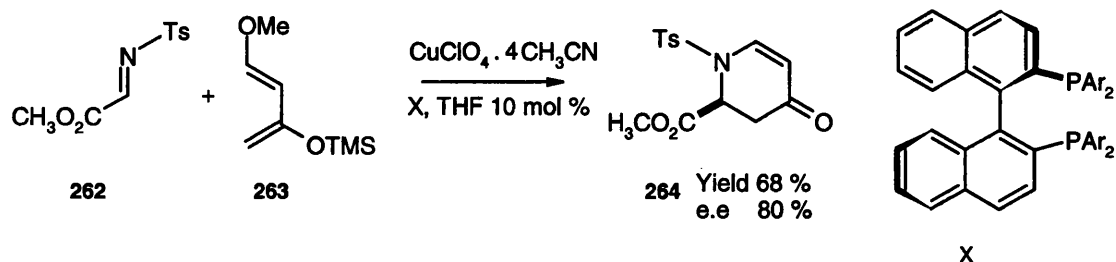
Scheme 122

Another example where a chiral Lewis acid has been employed to good effect in catalysing the hetero Diels-Alder reaction to afford highly enantioselective products is that reported by Kobayashi and co-workers[133, 134] (Scheme 123). In this protocol the chiral Lewis acid was derived from zirconium and modified with binapthol derivatives. 2-Aminophenol was used as the nitrogen source in the imine and N-methylimidazole (NMI) proved to be the most suitable ligand.

Np = alpha napthyl
Yield 96 %
e.e   88 %
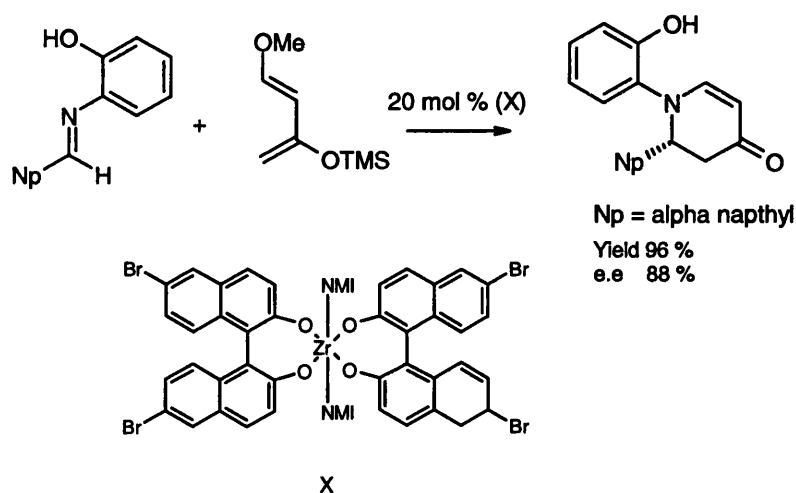
Scheme 123

Although a few examples of recent investigations into the very useful hetero Diels Alder reactions have been outlined above the scope of the reaction is such that the reader is directed towards the excellent reviews that have been published in this area.[135, 136, 137, 138]

4.1 The Hetero Diels Alder Reaction using Indium Triflate

Initial work utilising indium triflate examined the reaction between benzaldehyde and 1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefskys' diene (Scheme 124). In the presence of 10 mol% of indium (III) triflate the two components react to afford the product in just thirty minutes at -20°C.
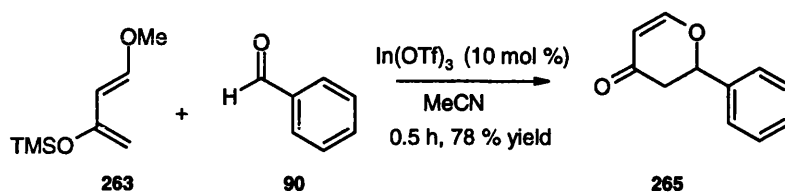
Scheme 124

The efficiency of this process prompted the investigation of the closely related imino Diels-Alder reaction between imine and Danishefsky's diene. The catalyst loading was lowered to 0.5 mol% and the reaction is still effectively complete within thirty minutes at room temperature furnishing the product in 93 % yield (Scheme 125). This compares favourably to scandium triflate (83 % yield) for which the reported reaction time is twenty hours and at a loading of 10 mol % (Table 33)
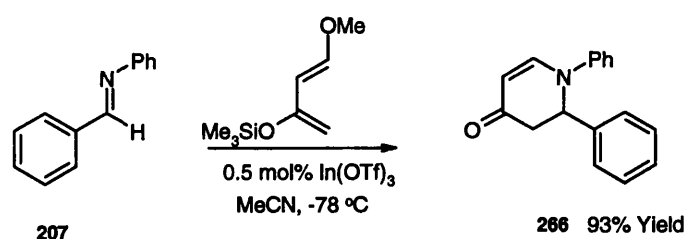
Scheme 125

Entry	Catalyst	Time (hours)	Yield (%)
1	None	24	< 5
2	Sc(OTf)$_3$ (10mol %)	20	83
3	In(OTf)$_3$ (10mol %)	0.5	89
4	In(OTf)$_3$ (0.5 mol %)	0.5	93

Table 33

In the absence of any catalyst there was only a trace (< 5 %) of product after 24 hours at room temperature. The reaction between imine and Danishefsky's diene was carried out in the presence of triflic acid to determine whether or not the reaction was being catalysed by any adventitious triflic acid rather than indium triflate. However, no product was observed, the only by-product from this reaction was the hydrolysis of Danishefsky's diene to the enone.

A competition reaction was also investigated between Danishefsky's diene (Scheme 126), the imine and benzaldehyde. When Danishefsky's diene was added to a 1 : 1 mixture of benzaldehyde and N-benzilideneaniline in the presence of 0.5 mol % of indium (III) triflate, the product arising from reaction with the imine was isolated in 83 % yield. However, the product arising from the reaction with benzaldehyde was less than 5 %. The chemoselectivity of this process along with the precedent that imine formation can be promoted by the same catalyst prompted the investigation of a three component coupling reaction.
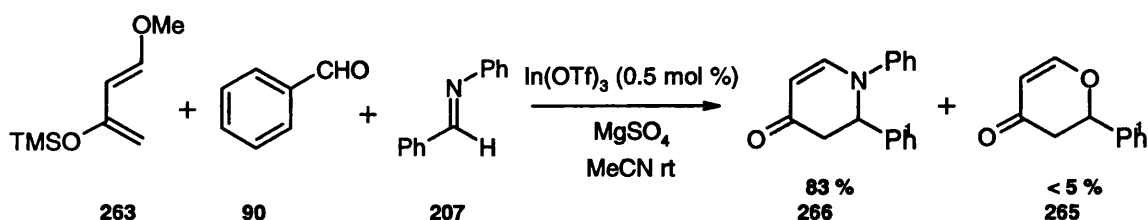
Scheme 126

The coupling reaction of Danishefsky's diene with imines derived *in situ* from aromatic aldehydes (Scheme 127) and the primary amines aniline and benzylamine were examined (Scheme 128).

Scheme 127

$$\text{TMSO} \underset{\text{TMSO}}{\overset{\text{OMe}}{\bigwedge}} + R^1CHO + R^2NH_2 \xrightarrow[\substack{\text{MgSO}_4 \\ \text{MeCN rt}}]{\text{In(OTf)}_3 \text{ (0.5 mol \%)}} \underset{O}{\bigwedge} \overset{R^2}{\underset{R^1}{N}}$$
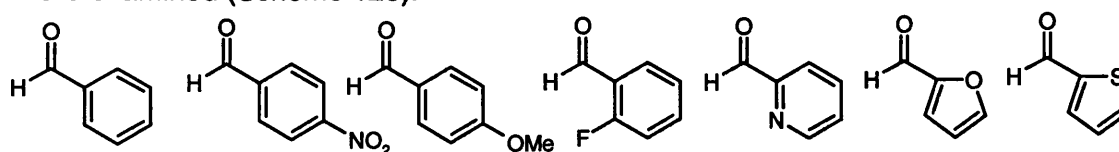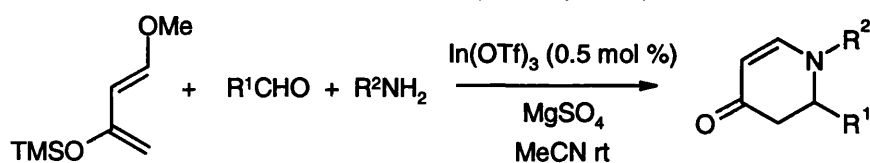
Scheme 128

The reaction proceeded smoothly to afford reasonable yields of aryl and heteroaryl substituted tetrahydropyridine products in the presence of 0.5 mol % of indium triflate, with the exception of 2-thiophene carboxaldehyde (Table 34).

Entry	Aldehyde	Amine	Product	Yield (%)
1		$PhNH_2$	**266**	51
2		$PhNH_2$	**267**	84
3		$PhCH_2NH_2$	**268**	50
4		$PhNH_2$	**269**	95

Table 34

The reaction was further investigated using electron donating and electron withdrawing moieties on the aldehyde substrates. Table 35 shows that the product from p-methoxybenzaldehyde was generated in slightly higher yield when compared to the products from the imines generated *in situ* using p-nitro benzaldehyde and furaldehyde. This could be due to the fact that the formation of the imines from these

two substrates is relatively slower in comparison to that of the *p*-methoxy

benzaldehyde.
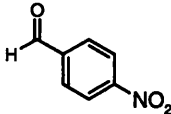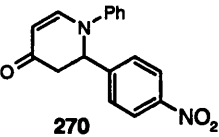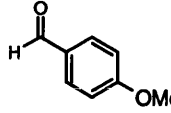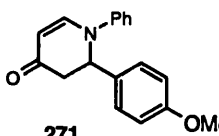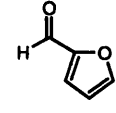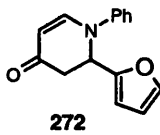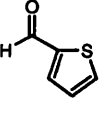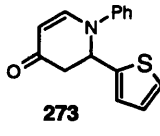
Entry	Aldehyde	Amine	Product	Yield (%)
1		PhNH$_2$	**270**	64
2		PhNH$_2$	**271**	71
3		PhNH$_2$	**272**	61
4		PhNH$_2$	**273**	no reaction

Table 35

The general formation of these aryl and heteroaryl substituted tetrahydropyridine

products has been shown to proceed in relatively high yields at low catalyst loadings

of indium triflate. Thus demonstrating that indium triflate is a superior Lewis acid for

the hetero Diels-Alder reaction of Danishefsky's diene and imines.

CHAPTER 5

CONCLUSION

5. Conclusion

This thesis has shown the development of indium triflate as an efficient, cheap and environmentally friendly Lewis acid for a multitude of reactions that are of importance in organic synthesis. Chapter 1 discusses the traditional uses of indium in the field of semiconductors and other physical applications and this is where the use has remained for most of the last century.

Although the use of indium metal has been well documented in the allylation reaction its use in other organic methodology has remained sparse. Traditional Lewis acids such as titanium tetrachloride and tin tetrachloride have been the Lewis acids of choice even though they prove difficult to handle and are relatively hazardous and required in some cases to be used in stoichiometric quantities.

Chapter 2 outlines the importance of protecting groups using various Lewis acids and more traditional methods such as DMAP and pyridine. Indium triflate has been found to perform the acylations of alcohols, polyols, amines and aldehydes using very low catalyst loading in a short period of time, thus demonstrating its practical use in this simple yet sometimes trivialised reaction.

The third chapter demonstrates the catalytic use of indium triflate in more demanding reactions and thus provides some evidence for itself as a useful Lewis acid. The imine aldol reaction proceeded in a smooth and facile manner to provide some useful products.

Indium triflate has also been found to catalyse the much more demanding imino ene reaction, which has until recently, only been performed using stoichiometric

amounts of Lewis acid or at very high temperatures.   There is still further scope within this reaction as the reaction itself is rather substrate limited and therefore it would be interesting to see if a more general protocol can be developed thus expanding the possibilities of this rather important organic transformation.

Finally Chapter 4 provides an explicit example of the catalytic efficacy of indium triflate in the important hetero-diels alder reaction. At very low catalyst loading with respect to other reported methods indium triflate is able to catalyse the reaction to provide structurally diverse products in an efficient manner.

Although unsuccessful attempts were made at synthesising chiral complexes using indium triflate it would seem that there is scope for producing these complexes to furnish organic transformations in an enantioselective fashion. Varying the conditions in which the chiral complexes are prepared and the careful selection of chiral ligand used will hopefully achieve the use of indium triflate in an enantioselctive manner in the not too distant future.

It will also be interesting to see if indium triflate is capable of carrying out these various transformations in the presence of other sensitive groups. For example an intramolecular hetero-diels alder transformation of a molecule with a large number of sensitive functionalities.

CHAPTER 6

EXPERIMENTAL

CHAPTER 6. EXPERIMENTAL

6.1 General Experimental

Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Apparatus, needles and syringes were oven-dried and cooled. General solvents were distilled before use. Diethyl ether, ethyl acetate, hexane, petroleum ether (boiling point between 40 $^{\circ}$C and 60 $^{\circ}$C), THF, and toluene were distilled from sodium wire. DCM and MeCN were distilled from CaH_2. All solvents used were stored in the presence of 4 Å molecular sieves.

TLC using commercially available glass-backed plates coated with Merck Kieselgel 60 GF_{254} silica monitored all reactions. Visualisation of these plates was by 254-nm light or with $KMnO_4$ / Vanillin dips followed by heating. Organic layers were dried with anhydrous Na_2SO_4 / $MgSO_4$ and evaporated with a Büchi evaporator. Further evaporation was carried out on a high-vacuum line where necessary. Flash column chromatography was carried out on Kieselgel 60 H silica.

IR spectra were recorded as thin films (DCM) using a Perkin-Elmer 1600 Series FT–IR spectrophotometer in the range 4000-600 cm^{-1}, with internal background scan, absorption maxima (v) are recorded in wavenumbers (cm^{-1}).

Proton (δ ^{1}H) NMR spectra were run in $CDCl_3$ using either a Bruker AC-250 (250 MHz), Bruker WH-400 (400 MHz), Jeol (270 MHz), or Jeol (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm) as internal standard. Coupling constants (J) are given as Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (b). Carbon-13 (δ ^{13}C) NMR spectra

were run in $CDCl_3$ at 100 MHz unless otherwise stated. Spectra were recorded using a Bruker AC-250 (250 MHz), Bruker WH-300 (300 MHz), Bruker WH-400 (400 MHz), Jeol (270 MHz), or Jeol (400 MHz) instrument.

HPLC was performed using SP ThermoSeparation SpectraSERIES and Spectra-Phyisics spectrometer, SP4290 Integrator, SP8700 Solvent Delivery System and Spectra 100 Variable Wavelength Detector. All separations were performed using a Chiracel AD, OJ or OD column obtained from Fisher Scientific.

Mass-spectra, including high resolution spectra, were recorded on a Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+) ionisation and/ or Fast Atom Bombardment (FAB+) ionisation.

Visualisation dips: Preparation of Potassium Permanganate: 0.5g $KMnO_4$ per 100 cm^3 water. Preparation of Vanillin dip: 3g Vanillin / 100 cm^3 ethanol + 3 cm^3 conc. sulpuric acid / 100 cm^3 ethanol

6.2 Acylation of Alcohols

General procedure for the acylation of alcohols

To a stirred solution of indium triflate (0.006 mmol) in dry acetonitrile (24 ml) under nitrogen at room temperature was added the corresponding alcohol (6 mmol). After 10 min at room temperature acetic anhydride (9 mmol) was added dropwise and the reaction stirred until complete by TLC. The solution was quenched with sodium hydrogen carbonate solution (3 x 5ml), and the product was extracted with diethyl ether. The organic layers were dried over magnesium sulphate, filtrated and concentrated *in vacuo* to afford the crude product. Further purification by column

chromatography (petrolum ether 40-60: ethyl acetate, 20:1) gave the corresponding acylated alcohol.

Acetoxybenzene 153[139]

153
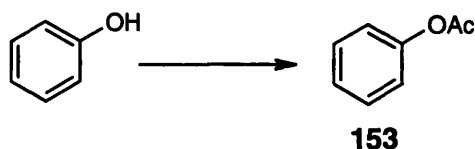
Phenol (6 mmol) was acylated using the general procedure to provide acetoxybenzene as a white crystalline solid (isolated yield 97 %, 0.79 g). The data for acetoxybenzene was consistent with that found in the literature. v_{max} (thin film)/cm^{-1}: 3031.6, 1741.8, 1377.9, 1362.3, 1229.2, 1024.7, 749.9. δ_H (270 MHz, CDCl$_3$): 2.23 (s, 3H), 7.04-7.36 (m, 5H). δ_C (400 MHz, CDCl$_3$): 21.50 (CH$_3$), 121.87 (CH), 126.06 (CH), 129.68 (CH), 150.94 (q), 169.57 (q).

Acetoxymethylbenzene 151[139]

151
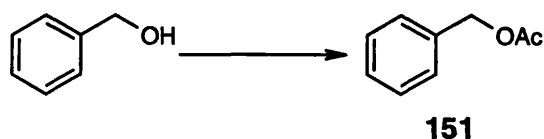
Benzyl alcohol (6 mmol) was acylated using the general procedure to provide acetoxymethylbenzene as a white crystalline solid (isolated yield 97 %, 0.88 g). The data for acetoxymethlybenzene was consistent with that found in the literature. v_{max} (thin film)/cm^{-1}: 3034.4, 1743.5, 1381.0, 1363.0, 1230.1, 1027.3, 750.2. δ_H (270 MHz, CDCl$_3$): 2.07 (s, 3H), 5.09 (s, 2H), 7.32-7.35 (m, 5H). δ_C (400 MHz, CDCl$_3$): 21.40 (CH$_3$), 66.58 (CH$_2$), 128.77 (CH), 128.45 (CH), 136.18 (q), 170.93 (q).

1-Acetoxy-1-phenylethane 155[139]

155

sec-Phenethyl alcohol (6 mmol) was acylated using the general procedure to provide

1-acetoxy-1-phenylethane as a white crystalline solid (isolated yield 97 %, 0.79 g).

The data for acetoxybenzene was consistent with that found in the literature. V_{max}

(Nujol)/cm^{-1}: 1727, 1265. δ_H (270 MHz, CDCl$_3$): 1.53 (d, 3H, J= 6.6 Hz), 2.06 (s, 3H),

5.85 (q, 1H, J= 6.6 Hz), 7.24-7.35 (m, 5H,). δ_C (270 MHz, CDCl$_3$): 21.23 (CH$_3$), 22.10

(CH$_3$), 72.18 (CH), 125.98 (CH), 127.75 (CH), 128.38 (CH) 141.60 (q), 170.19 (q).

(1R)-(-)-Menthylacetate 157[139]

157
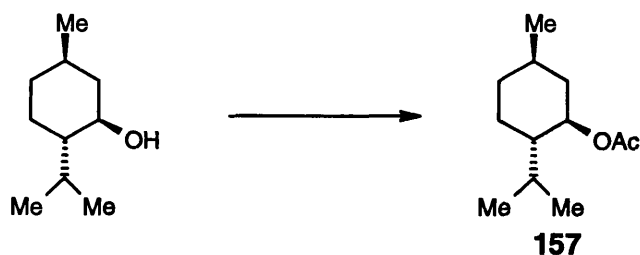
Menthol (6 mmol) was acylated using the general procedure to provide menthyl

acetate as a white crystalline solid (isolated yield 98 %, 1.16 g). The data for menthyl

acetate was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 2956.4,

2871.0, 1736.1, 1456.4, 1370.4, 1246.6, 1025.1. δ_H (270 MHz, CDCl$_3$): 0.76 (d, 3H,

J= 7.0 Hz), 0.89 (d, 3H, J= 7.0 Hz), 0.90 (d, 3H, J= 6.6 Hz), 0.84-1.14 (m, 3H), 1.30-

1.60 (m, 2H), 1.79-1.93 (m, 2H), 1.93-2.04 (m, 2H), 2.03 (s, 3H), 4.67 (dt, 1H, J= 4.4,

10.8 Hz). δ_C (400 MHz, CDCl$_3$): 16.37 (2CH$_3$), 21.41 (CH$_3$), 22.58 (CH$_3$), 23.42 (CH$_2$),

26.04 (CH) 32.02 (CH) 34.88 CH$_2$, 45.25 (CH$_2$), 47.29 (q), 50.30 (CH), 71.68 (CH),

74.51 (q).

Trans-(±)-1-acetoxy-2-phenylcyclohexane 97[140]

159

Trans-(±)-2-phenyl-1-cyclohexanol (6 mmol) was acylated using the general

procedure to provide trans-(±)-1-acetoxy-2-phenylcyclohexane as a white crystalline

solid (isolated yield 97 %, 1.26 g). The data for trans-(±)-1-acetoxy-2-

phenylcyclohexane was consistent with that found in the literature. v$_{max}$ (Nujol)/cm^{-1}:

3029.7, 2936.5, 1736.0, 1494.8, 1372.8, 1243.5, 1125.4, 1036.9. δ$_H$ (270 MHz,

CDCl$_3$): 1.20-1.60 (m, 4H), 1.70-1.90 (m, 4H), 1.96 (s, 3H), 2.6 (dt, 1H, J= 3.8, 10.8

Hz), 4.90 (m, 1H), 7.17-7.40 (m, 5H). δ$_C$ (400 MHz, CDCl$_3$): 21.34 (CH$_3$), 25.16 (CH$_2$),

26.21 (CH$_2$), 32.7 (CH$_2$), 34.17 (CH$_2$), 50.06 (CH), 76.11 (CH), 126.59 (CH), 127.69

(CH), 128.42 (CH), 143.27 (q), 170.42 (q).

General Procedure for the Acylation of Polyols

To a stirred solution of indium triflate (0.006 mmol) in dry acetonitrile (24 ml) under

nitrogen at room temperature was added the corresponding alcohol (6 mmol). After

10 min at room temperature acetic anhydride (9 mmol per hydroxy unit) was added

drop wise and the reaction stirred until complete by TLC. The solution was quenched

with sodium hydrogen carbonate solution (3 x 5ml), and the product was extracted

with diethyl ether. The organic layers dried over magnesium sulphate, filtrated and

concentrated in vacuo to afford the crude product. Further purification by column

chromatography (petrolum ether 40-60 : ethyl acetate, 20:1) gave the corresponding

acylated polyol.

1,2-Diacetoxy-1-phenylethane 165[141]

165
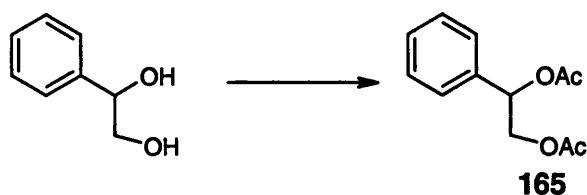
1,2-dihydroxy-1-phenylethane (6 mmol) was acylated using the general procedure to

provide 1,2-diacetoxy-1-phenylethane as a white crystalline solid (isolated yield 93

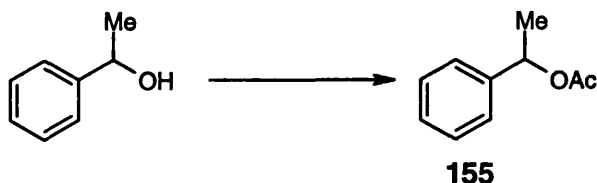%, 1.27 g). The data for 1,2-diacetoxy-1-phenylethane was consistent with that found

in the literature. V_{max} (thin film)/cm^{-1}: 3065.7, 3035.1, 2954.6, 1744.3, 1372.1, 1225.5,

1047.5, 951.1, 915.1. δ_H (270 MHz, CDCl$_3$): 2.04 (s, 3H), 2.11 (s, 3H), 4.24-4.35 (m,

2H), 6.00 (q, 1H, J= 4.2 Hz), 7.26-7.37 (m, 5H). δ_C (400 MHz, CDCl$_3$): 21.18 (CH$_3$),

21.49 (CH$_3$), 66.41 (CH$_2$), 73.62 (CH), 126.89 (CH), 128.82 (CH), 128.85 (CH),

136.68 (q), 170.19 (q), 170.77 (q),.

Bis-2-acetoxyethylether 167[142]

167
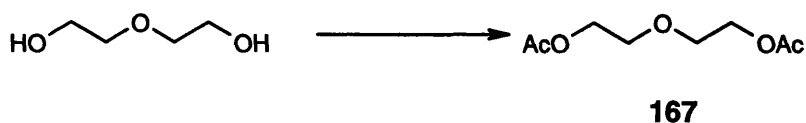
Bis-2-hydroxyethylether (ethylene glycol) (6 mmol) was acylated using the general

procedure to provide bis-2-acetoxyethylether as a colourless oil (isolated yield 92 %,

1.05 g). The data for 1,2-bis-2-acetoxylethylether was consistent with that found in

the literature. V_{max} (Nujol)/cm^{-1}: 3460.1, 2956.5, 2880.7, 1740.1, 1440.6,

1373.5,1239.0, 1137.6, 1054.7. δ_H (270 MHz, CDCl$_3$): 2.09 (d, 6H, J= 1.1 Hz), 3.69-

3.73 (m, 4H), 4.22-4.25 (m, 4H). δ_C (300 MHz, CDCl$_3$): 21.24 (CH$_3$), 63.76 (CH$_2$),

69.37 (CH$_2$), 171.32 (q).

(±)-2,2'-diacetoxy-1,1'-binapthyl 163[143]

163
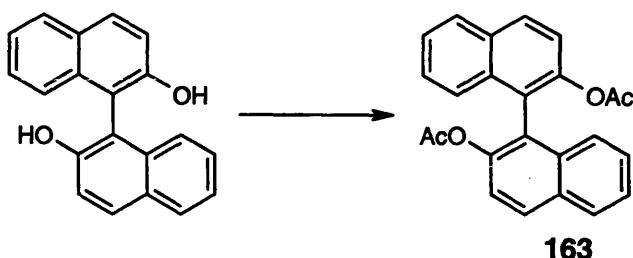
Binol (6 mmol) was acylated using the general procedure to provide (±)-2,2'-

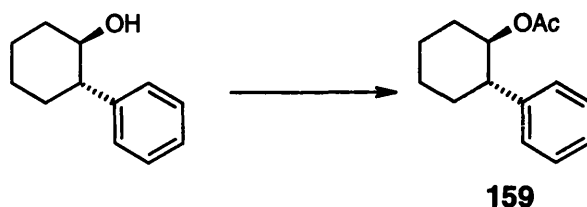diacetoxy-1,1'-binapthyl as a white crystalline solid (isolated yield 92 %, 1.05 g). The

data for (±)-2,2'-diacetoxy-1,1'-binapthyl was consistent with that found in the

literature , V$_{max}$ (Nujol)/cm^{-1}: 3059.9, 2928.9, 1762.9, 1509.1, 1367.6, 1202.0, 1073.6,

1013.0. δ_H (270 MHz, CDCl$_3$): 1.86 (s, 6H), 7.16-7.49 (m, 8H), 7.92-8.01 (m, 4H). δ_C

(300 MHz, CDCl$_3$): 20.80 (CH$_3$), 20.99 (CH$_3$), 122.17 (CH), 124.94 (q), 126.57 (CH),

127.13 (CH), 127.86 (CH), 131.91 (q), 133.73 (q), 147.14 (q), 169.81 (q). m/z (EI)

(Found: M+ 371.2, 328.1, 286.1, Expected M, 371). CHN (Found: C, 78.5; H, 5.1.

C$_{24}$H$_{18}$O$_4$ requires C, 78.1; 4.9 H %).

1, 1, 1-tris-(acetoxymethyl) ethane 169

169
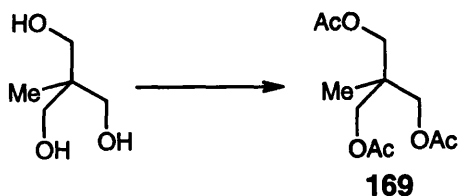
Triol (6 mmol) was acylated using the general procedure to provide 1, 1, 1-tris-

(acetoxymethyl) ethane as a colourless oil (isolated yield 96 %, 1.14 g). V$_{max}$ (thin

film)/cm^{-1}: 2975.5, 2899.6, 1744.1, 1473.9, 1384.1, 1366.1, 1235.2, 1044.1, 988.9,

904.6. δ_H (270 MHz, CDCl$_3$): 1.02 (s, 3H), 2.07 (s, 9H), 4.00 (s, 6H). δ_C (300 MHz,

CDCl$_3$): 17.24 (CH$_3$), 20.77 (CH$_3$), 20.94 (CH$_3$), 38.44 (q), 66.31 (3CH$_2$), 170.93 (q).

m/z (EI) (Found: M+ 247.2, Expected M, 247.2). CHN (Found: C, 52.9; H, 7.3.

C$_{11}$H$_{18}$O$_6$ requires C, 53.7; H 7.3%).

Hexa-O-acetyl-D-mannitol 161[144]

161
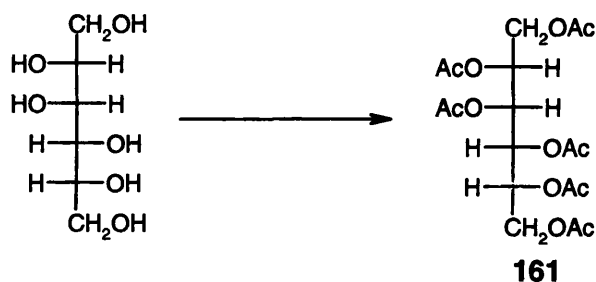
D-Mannitol (6 mmol) was acylated using the general procedure to provide hexa-O-
acetyl-D-mannitol as a white crystalline solid (isolated yield 94 %, 2.45 g). The data

for hexa-O-acetyl-D-mannitol was consistent with that found in the literature , V_{max}

(Nujol)/cm^{-1}: 3057.0, 2987.6, 1749.1, 1424.8, 1371.7, 1266.0, 1222.2, 1072.1,

1034.9. δ_H (270 MHz, CDCl$_3$): 2.06 (s, 6H), 2.08 (s, 6H), 2.10 (s, 6H), 4.10 (m, 4H),

5.05 (m, 2H), 5.44 (m, 2H). δ_C (270 MHz, CDCl$_3$): 20.53 (CH$_3$), 20.61 (CH$_3$), 20.79

(CH$_3$), 61.80 (CH$_2$), 67.40 (CH), 68.84 (CH), 169.64 (q), 169.85 (q), 170.51 (q).

General Procedure for the Acylation of Amines

To a stirred solution of indium triflate (0.006 mmol) in dry acetonitrile (24 ml) under

nitrogen at room temperature was added the corresponding amine (6 mmol). After 10

min at room temperature acetic anhydride (9 mmol) was added drop wise and the

reaction stirred until complete by TLC. The solution was quenched with sodium

hydrogen carbonate solution (3 x 5ml), and the product was extracted with diethyl

ether. The organic layers dried over magnesium sulphate, filtrated and concentrated

in vacuo to afford the crude product. Further purification by column chromatography (petrolum ether 40-60: ethyl acetate, 20:1) gave the corresponding acylated amine.

N-Phenylacetamide 171[145]

171

Aniline (6 mmol) was acylated using the general procedure to provide *N*-phenylacetamide as a white crystalline solid (isolated yield 99 %, 0.80 g). The data for *N*-phenylacetamide was consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3302.5, 3055.1, 2360.6, 1669.9, 1599.9, 1440.3, 1265.8. δ_H (270 MHz, CDCl$_3$): 2.16 (s, 3H), 7.07-7.48 (m, 5H), 7.65 (brs, 1H). δ_C (300 MHz, CDCl$_3$): 24.77 (CH$_3$), 120.62 (CH), 124.67 (CH), 129.28 (CH), 138.49 (q), 169.53 (q).

N-(2,6-dimethylphenyl)acetamide 173[146]

173
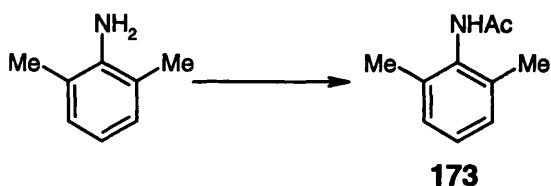
N-(2,6-dimethyl)aniline (6 mmol) was acylated using the general procedure to provide *N*-(2,6-dimethylphenyl)acetamide as a white crystalline solid (isolated yield 94 %, 0.93 g). The data for *N*-(2,6-dimethylphenyl)acetamide was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3503.4, 3059.9, 2928.9, 1762.9, 1509.1, 1367.6, 1202.0, 1073.6, 1013.0. δ_H (270 MHz, CDCl$_3$): 1.73 (s, 1H), 2.15 (s, 3H), 2.19 (s, 6H), 7.03-7.17 (m, 3H). δ_C (300 MHz, CDCl$_3$): 23.49 (CH$_3$), 23.55 (CH$_3$), 27.95 (CH$_3$), 132.10 (CH), 133.08 (CH), 133.21 (CH), 139.71 (q), 140.68 (q), 174.37 (q).

N-(2-biphenyl)acetamide 175[147]

175
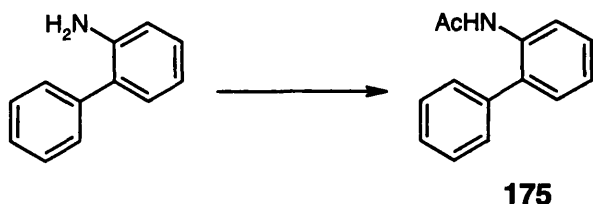
N-(2-phenyl)aniline (6 mmol) was acylated using the general procedure to provide *N*-(2-biphenyl)acetamide as a purple crystalline solid (isolated yield 92 %, 1.17 g). The data for *N*-(2-biphenyl)acetamide was consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3235.5, 3055.8, 1674.3, 1584.3, 1304.1, 1073.9, 1009.7. δ_H (270 MHz, CDCl$_3$): 2.02 (s, 3H), 7.15-7.51 (m, 9H). δ_C (300 MHz, CDCl$_3$): 24.97 (CH$_3$), 122.13 (CH), 124.77 (CH), 128.36 (CH), 128.80 (CH), 129.47 (CH), 129.62 (CH), 130.46 (CH), 132.65 (CH), 134.69 (CH), 135.09 (q), 168.23 (q).

N-Benzylacetamide 176[148]

176
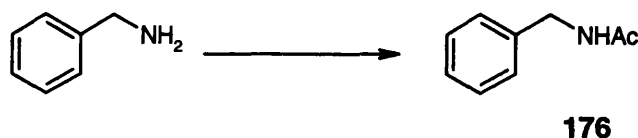
Benzylamine (6 mmol) was acylated using the general procedure to provide *N*-benzylacetamide as a white crystalline solid (isolated yield 98 %, 0.88 g). The data for *N*-benzylacetamide was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3293.4, 3054.5, 1651.9, 1556.0, 1454.2, 1266.9, 1078.1, 1029.4, 733.9. δ_H (270 MHz, CDCl$_3$): 2.03 (s, 3H), 4.43 (d, 2H, J= 5.7 Hz), 6.17 (br s, 1H), 7.27-7.34 (m, 5H). δ_C (300 MHz, CDCl$_3$): 23.58 (CH$_3$), 44.08 (CH$_2$), 127.87 (CH), 128.21 (CH), 129.06 (CH), 138.67 (q), 170.38 (q).

Trans-diacetamido-(1R, 2R)-(-)-1,2-cyclohexane 179[149]

179
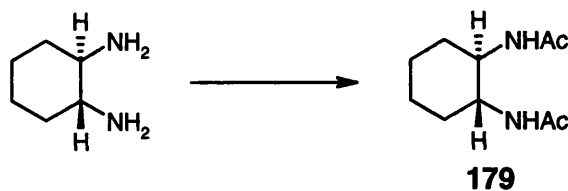
(1R, 2R)-(-)-1,2-Diaminocyclohexane (6 mmol) was acylated using the general procedure to provide *trans*-diacetamido-(1R, 2R)-(-)-1,2-cyclohexane as a white crystalline solid (isolated yield 91 %, 1.08 g). The data for *trans*-diacetamido-(1R, 2R)-(-)-1,2-cyclohexane was consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3282.3, 3054.8, 2931.2, 2360.4, 1633.0, 1550.4, 1422.0, 1372.9, 1266.1, 737.9. δ_H (270 MHz, CDCl$_3$): 1.27 (m, 4H), 1.75 (m, 2H), 1.94 (s, 6H), 2.03 (m, 2H), 3.65 (m, 2H), 6.15 (br s, 2H).

6.3 Acylalation of aldehydes

To a stirred solution of indium triflate (0.006 mmol) in dry acetonitrile (24 ml) under nitrogen at room temperature was added the corresponding aldehyde (6 mmol). After 10 min at room temperature acetic anhydride (9 mmol) was added drop wise and the reaction stirred until complete by TLC. The solution was quenched with sodium hydrogen carbonate solution (3 x 5ml), and the product was extracted with diethyl ether. The organic layers dried over magnesium sulphate, filtrated and concentrated *in vacuo* to afford the crude product. Further purification by column chromatography (petrolum ether 40-60 : ethyl acetate , 20:1) gave the corresponding acylal.

Benzaldehyde diacetate 182[150]

182

Benzaldehyde (6 mmol) was acylated using the general procedure to provide benzaldehyde diacetate as a white crystalline solid (isolated yield 99 %, 1.24 g). The data for benzaldehyde diacetate consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3068.8, 3039.9, 1759.2, 1497.7, 1456.4, 1432.4, 1372.2, 1240.8, 1202.9, 1088.5, 1061.1, 763.7. δ_H (270 MHz, CDCl$_3$): 2.13 (s, 6H), 7.39-7.42 (m, 3H), 7.50-7.54 (m, 2H), 7.68 (s, 1H). δ_C (400 MHz, CDCl$_3$): 20.98 (2CH$_3$), 89.69 (CH), 126.55 (CH), 128.47 (CH), 128.76 (CH), 129.62 (CH), 135.35 (q), 168.56 (q)

4-Bromobenzaldehyde diacetate 190[151]

190
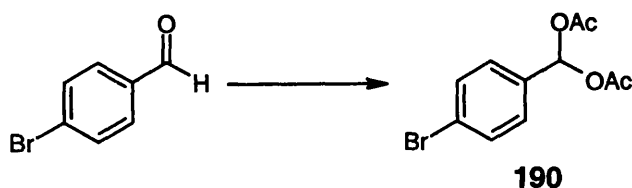
p-Bromobenzaldehyde (6 mmol) was acylated using the general procedure to provide p-bromobenzaldehyde diacetate as a straw-yellow crystalline solid (isolated yield 90 %, 1.55 g). The data for p-bromobenzaldehyde diacetate was consistent with that found in the literature, V_{max} (thin film)/cm^{-1}: 3057.6, 2986.7, 1763.5, 1491.9, 1373.3, 1266.2, 1241.7, 1203.2, 1070.6, 1012.9. δ_H (400 MHz, CDCl$_3$): 2.13 (s, 6H), 7.39 – 7.41 (m, 2H), 7.53 –7.55 (m, 2H), 7.62 (s, 1H). δ_C (400 MHz, CDCl$_3$): 20.88 (CH$_3$), 89.02 (CH), 123.79 (q), 128.25 (CH), 131.62 (CH), 134.31 (q), 168.41 (q)

4-Methoxybenzaldehyde diacetate 192[152]

192
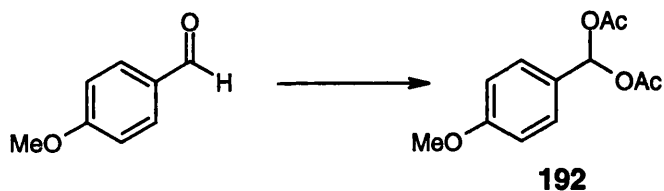
4-Methoxybenzaldehyde (6 mmol) was acylated using the general procedure to provide 4-methoxybenzaldehyde diacetate as a white crystalline solid (isolated yield 93 %, 1.33 g). The data for 4-methoxybenzaldehyde diacetate *was* consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3005.4, 2840.3, 1759.7, 1614.5, 1518.8, 1465.1, 1372.9, 1243.0, 1205.6, 1009.4, 831.9. δ_H (400 MHz, CDCl$_3$): 2.11 (s, 6H), 3.82 (3H), 6.91-6.93 (m, 2H), 7.45-7.47 (m, 2H), 7.62 (s, 1H). δ_C (400 MHz, CDCl$_3$): 20.98 (CH$_3$), 55.33 (CH$_3$), 89.70 (CH), 113.82 (CH), 127.61 (q), 128.00 (CH), 160.40 (q), 168.57 (q).

4-Nitrobenzaldehyde diacetate 188[152]

188
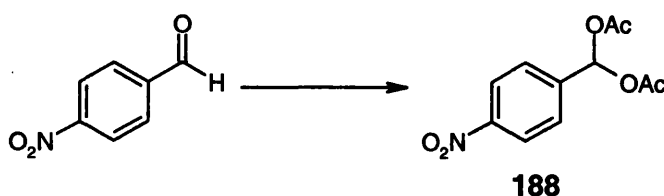
4-Nitrobenzaldehyde (6 mmol) was acylated using the general procedure to provide 4-nitrobenzaldehyde diacetate as a straw-yellow crystalline solid (isolated yield 86 %, 1.31 g). The data for 4-nitrobenzaldehyde diacetate *was* consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3056.2, 2987.5, 1763.9, 1609.9, 1527.5, 1422.8, 1373.6, 1350.9, 1265.5, 1199.7, 1073.4, 1011.1, 853.1, 742.9. δ_H (400 MHz, CDCl$_3$): 2.16 (s, 6H), 7.70-7.72 (m, 2H), 7.73 (s, 1H), 8.26-8.28 (m, 2H). δ_C (400 MHz, CDCl$_3$): 20.83 (CH$_3$), 88.32 (CH), 123.72 (CH), 127.73 (CH), 141.76 (q), 148.50 (q), 168.71 (q)

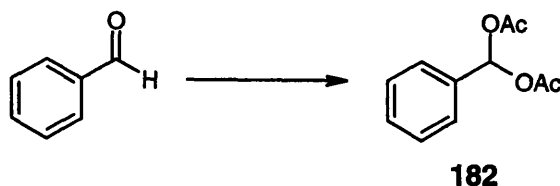## 2-Fluorobenzaldehyde diacetate 184[153]

184
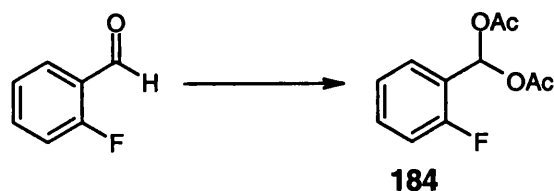
2-Fluorobenzaldehyde (6 mmol) was acylated using the general procedure to provide 2-fluorobenzaldehyde diacetate as a white crystalline solid (isolated yield 95 %, 1.36 g). The data for 2-fluorobenzaldehyde diacetate *was* consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3088.4, 1711.3, 1613.6, 1586.1, 1484.2, 1462.0, 1406.2, 1276.4, 1228.0, 1190.3, 912.4, 843.4. δ_H (270 MHz, CDCl$_3$): 2.13 (s, 6H), 7.07-7.56 (m, 4H), 7.91 (s, 1H). δ_C (400 MHz, CDCl$_3$): 20.87 (CH$_3$), 87.79 (CH), 123.59 (CH), 126.73 (CH), 128.21 (CH),145.89 (q), 147.92 (q), 169.35 (q)

Trans-cinnamaldehyde diacetate 186[150]

186
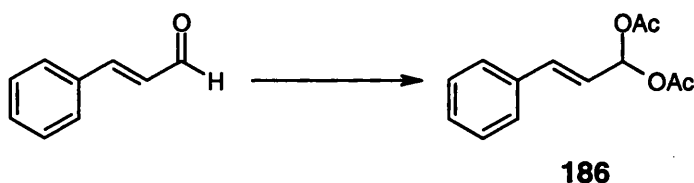
Trans-cinnamaldehyde (6 mmol) was acylated using the general procedure to provide *trans*-cinnamaldehyde diacetate as a white crystalline solid (isolated yield 61 %, 0.86 g). The data for *trans*-cinnamaldehyde diacetate *was* consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3062.4, 3030.6, 1760.7, 1677.4, 1627.0, 1450.9, 1372.4, 1240.2, 1125.8, 962.0, 750.4. δ_H (400 MHz, CDCl$_3$): 2.12 (s, 6H), 6.18-6.24 (dd, 1H, J= 6.6, 8.6, Hz), 6.85-6.89 (d, 1H, J = 6 Hz), 7.30-7.45 (m, 7H). δ_C (400 MHz, CDCl$_3$): 21.00 (CH$_3$), 89.70 (CH), 121.61 (CH), 126.89 (CH), 128.18 (CH),

128.55 (CH), 128.82 (CH), 128.98 (CH), 131.13 (q), 135.01 (CH), 135.47 (q), 168.47

(q)

General Procedure for the Acylal Ene Reaction

To a stirred solution of indium triflate (0.05 mmol) in dry acetonitrile (10 ml) under

nitrogen at room temperature was added the corresponding acylal (1 mmol). After 10

min at room temperature the ene substrate (1.2 mmol) was added drop wise and the

reaction stirred until complete by TLC. The solution was quenched with sodium

hydrogen carbonate solution (3 x 5ml), and the product was extracted with diethyl

ether. The organic layers dried over magnesium sulphate, filtrated and concentrated

in vacuo to afford the crude product. Further purification by column chromatography

(petrolum ether 40-60 : ethyl acetate , 90:10) gave the corresponding product.

6.4 Acylal Ene[92]

Acetic acid 2-cyclohex-1-enyl-2-methyl-1-phenylpropylester 196

196
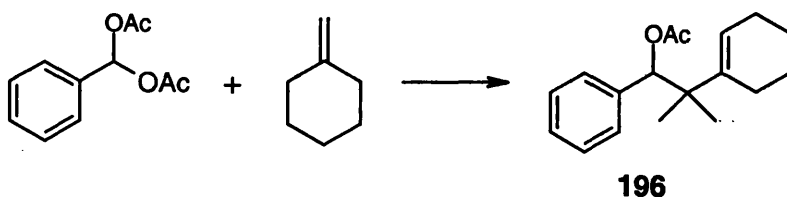
Benzaldehyde diacetate (1 mmol) was reacted with methylene cyclohexane (1.2

mmol) using the general procedure to provide acetic acid 2-cyclohex-1-enyl-2-

methyl-1-phenylpropylester as a white crystalline solid (isolated yield 45 %, 0.11 g).

The data for acetic acid 2-cyclohex-1-enyl-2-methyl-1-phenylpropylester was

consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3331.5, 2932.9, 1738.5,

1659.8, 1539.8, 1538.1, 1435.2, 1265.8, 1244.4, 1206.3, 1030.7, 737.6. δ_H (270 MHz,

CDCl$_3$): 1.50-1.59 (m, 4H), 1.93 (bs, 4H), 2.05 (s, 3H), 2.29-2.35 (m, 1H), 2.48-2.56

(m, 1H), 5.40 (bs, 1H), 5.85-5.90 (q, 1H, J = 5.5, 7.2, 5.4 Hz), 7.28-7.34 (m, 5H). δ_C

(400 MHz, CDCl$_3$): 21.68 (CH$_3$), 22.65 (CH$_2$), 23.32 (CH$_2$), 25.76 (CH$_2$), 28.99 (CH$_2$),

45.69 (CH$_2$), 74.65 (CH), 125.14 (CH), 126.68 (CH), 127.96 (CH), 128.50 (CH),

133.43 (q), 140.93 (q), 170.32 (q)

3-Acetoxy-2,2-dimethyl-3-phenylpropionic acid methylester
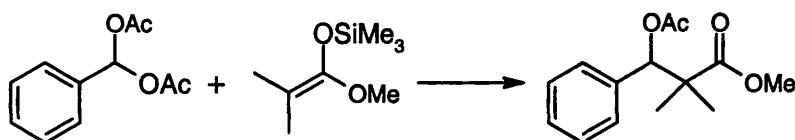
Benzaldehyde diacetate (1 mmol) was reacted with trimethylsiloxy-1-methoxy

propene (1.2 mmol) using the general procedure to provide 3-acetoxy-2,2-dimethyl-3-

phenylpropionic acid methylester as a white crystalline solid (isolated yield 45 %,

0.11 g). The data for 3-acetoxy-2,2-dimethyl-3-phenylpropionic acid methylester was

consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: δ_H (270 MHz, CDCl$_3$):

1.10 (s, 3H), 1.21 (s, 3H), 2.07 (s, 3H), 3.68 (s, 3H), 6.06 (s, 1H), 7.28-7.42 (m, 5H).

δ_C (270 MHz, CDCl$_3$): 19.87 (CH$_3$), 20.76 (CH$_3$), 21.88 (CH$_3$), 47.01 (q), 51.90 (CH$_3$),

79.01 (CH), 127.49 (CH), 127.83 (CH), 127.99 (CH), 128.51 (CH), 129.66 (CH),

169.42 (q), 175.86 (q).

6.5 Imines

General Procedure for Preparing Unactivated Imines

The mechanism for general imine formation is shown below (Scheme 14). The key

step is the removal of water in order to quantitatively produce pure imines. The use of

molecular sieves, azeotropic removal of water using Dean-Stark apparatus, reflux in

methanol, are all common methods, however the use of magnesium sulphate in toluene seemed to provide a facile route to the production of the required imines.

To a stirring solution of magnesium sulphate (1 g) in DCM was added the corresponding aldehyde (1 mmol) followed by the corresponding amine (1 mmol). The reactions were allowed to stir overnight at room temperature, dried, concentrated and recrystalised from ethyl acetate.
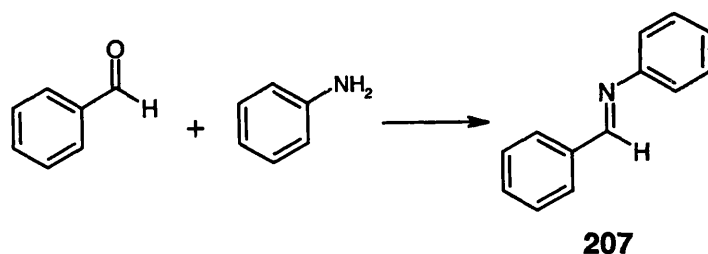
Proton transfer

CARBINOLAMINE   IMINIUM ION   IMINE

N-Benzilideneaniline 207[154]

207

Benzaldehyde (5 mmol) was reacted with aniline using the general procedure to provide N-benzilideneaniline as a straw-yellow crystalline solid (isolated yield 98 %, 0.89 g). The data for N-benzilideneaniline was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 3061.8, 2881.6, 1627.9, 1591.5, 1578.8, 1485.3, 1451.5, 1265.6, 1191.0, 1169.5, 1073.9, 767.8. δ_H (270 MHz, CDCl$_3$): 7.20-7.23 (m, 3H), 7.25-7.50 (m, 5H), 7.89-7.92 (m, 2H), 8.46 (s, 1H). δ_C (400 MHz, CDCl$_3$): 120.84 (CH), 125.92 (CH), 128.77 (CH), 128.98 (CH), 129.12 (CH), 129.25 (CH), 131.35 (CH), 136.16 (q), 152.05 (q), 160.41 (CH).

N-Pyridinecarboxylideneaniline[155]
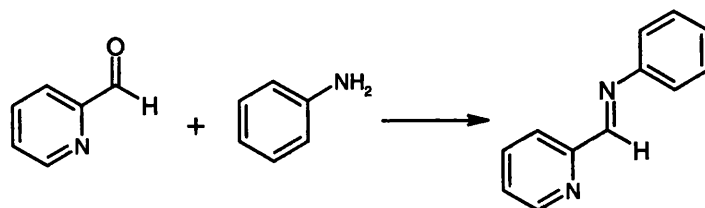
Pyridinecarboxaldehyde (5 mmol) was reacted with aniline using the general procedure to provide N-pyridinecarboxylideneaniline as a straw-yellow crystalline solid (isolated yield 94 %, 0.86 g). The data for N-pyridinecarboxylideneaniline was consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3055.0, 3008.4, 1628.3, 1592.2, 1567.1, 1486.7, 1435.9, 1200.4, 992.7. δ_H (400 MHz, CDCl$_3$): 7.30-7.45 (m, 6H), 7.78-7.84 (t, 1H, J = 7.8 Hz), 8.18-8.22 (d, 1H, J = 7.8 Hz), 8.61 (s, 1H), 8.71-8.72 (d, 1H, J = 5.2 Hz). δ_C (400 MHz, CDCl$_3$): 120.94 (CH), 121.73 (CH), 124.96 (CH), 126.55 (CH), 129.05 (CH), 136.47 (CH), 149.49 (q), 150.76 (CH), 154.35 (q), 160.38 (CH).

N-4-Nitrobenzilideneaniline 211[156]

211
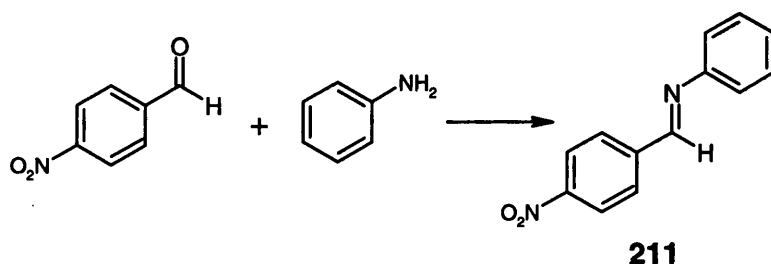
N-4-Nitrobenzaldehyde (5 mmol) was reacted with aniline using the general procedure to provide N-4-nitrobenzilideneaniline as a straw-yellow crystalline solid (isolated yield 96 %, 1.08 g). The data for N-4-nitrobenzilideneaniline was consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3056.2, 2986.3, 1629.9, 1600.2,

1524.3, 1486.1, 1345.5, 1265.8, 1189.9, 1109.7, 852.8. δ_H (400 MHz, CDCl₃): 7.24-

7.32 (m, 3H), 7.40-7.46 (m, 2H), 8.05-8.11 (m, 2H), 8.31-8.36 (m, 2H), 8.56 (s, 1H).

δ_C (400 MHz, CDCl₃): 120.84 (CH), 123.89 (CH), 126.94 (CH), 129.20 (CH), 141.42

(q), 149.12 (q), 150.75 (q), 157.14 (CH).

N-4-Methoxybenzilideneaniline 215[157]

215
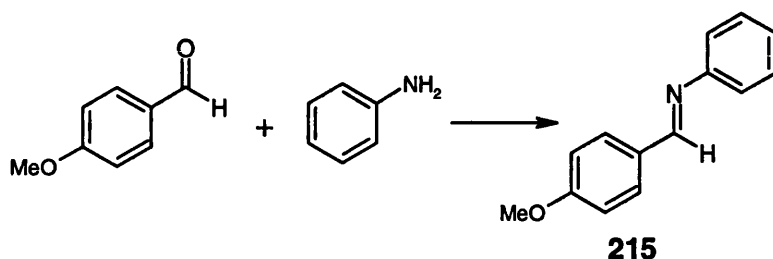
N-p-Methoxybenzaldehyde (5 mmol) was reacted with aniline using the general

procedure to provide *N*-4-methoxybenzilideneaniline as a white crystalline solid

(isolated yield 93 %, 0.98 g). The data for *N*-4-methoxybenzilideneaniline was

consistent with that found in the literature, V_{max} (Nujol)/cm⁻¹: 3060.5, 2838.6, 1624.1,

1614.8, 1512.5, 1485.6, 1422.2, 1310.7, 1253.0, 1164.9, 1030.9, 833.6. δ_H (400 MHz,

CDCl₃): 3.86 (s, 3H), 6.96-7.01 (m, 2H), 7.18-7.22 (m, 3H), 7.36-7.40 (m, 2H), 7.83-

7.87 (m, 2H), 8.37 (s, 1H). δ_C (400 MHz, CDCl₃): 55.44 (CH₃), 114.07 (CH), 114.20

(CH), 120.74 (CH), 125.42 (CH), 128.96 (CH), 129.93 (CH), 152.16 (q), 159.50 (q),

162.03 (CH), 164.38 (q).

N-2-Fluorobenzilideneaniline 213[158]
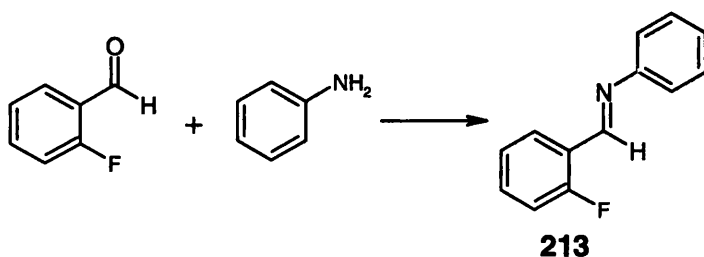
213

N-2-Fluorobenzaldehyde (5 mmol) was reacted with aniline using the general procedure to provide *N*-2-fluorobenzilideneaniline as a white crystalline solid (isolated yield 98 %, 0.98 g). The data for *N*-2-fluorobenzilideneaniline was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 3063.6, 2916.4, 1623.9, 1591.6, 1579.0, 1490.6, 1458.0, 1368.8, 1278.8, 1240.4, 1206.7, 1095.8, 761.2. δ_H (400 MHz, $CDCl_3$): 7.09-7.15 (m, 1H), 7.22-7.28 (4H), 7.38-7.48 (m, 3H), 8.16-8.22 (m, 1H), 8.78 (s, 1H). δ_C (400 MHz, $CDCl_3$): 116.00 (CH), 116.21 (CH), 121.20 (CH), 124.68 (CH), 126.50 (CH), 128.08 (CH), 129.38 (CH), 133.10 (CH), 152.10 (CH), 153.63 (q), 161.74 (q), 164.26 (q).

N-2-Fluorobenzilidenebenzylamine[159]
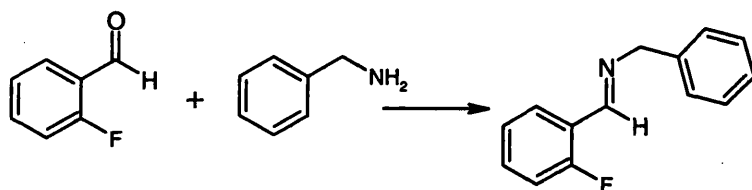
N-2-Fluorobenzaldehyde (5 mmol) was reacted with benzylamine using the general procedure to provide *N*-2-fluorobenzilidenebenzylamine as a white crystalline solid (isolated yield 97 %, 1.03 g). The data for *N*-2-fluorobenzilidenebenzylamine was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 3029.0, 2889.5, 2833.5, 1640.8, 1613.6, 1485.3, 1459.3, 1378.8, 1279.0, 1233.7, 1099.6, 759.9. δ_H (270 MHz, $CDCl_3$): 4.83 (s, 2H), 7.03-7.23 (m, 4H), 7.30-7.42 (m, 5H), 8.02 (dt, 1H, J= 1.73, 6.1 Hz). δ_C (400 MHz, $CDCl_3$): 65.46 (CH_2), 115.48 (CH), 123.61 (CH), 124.20 (CH), 126.91 (CH), 127.73 (CH), 127.84 (CH), 128.37 (CH), 132.18 (CH), 138.92 (q), 154.97 (CH), 160.83 (q), 163.33 (q)

N-Benzilidene-2-hydroxylaniline 225[100]

225
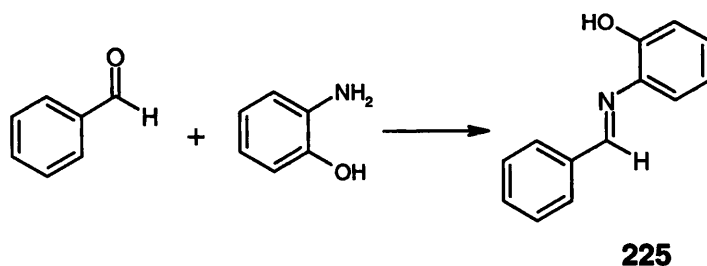
Benzaldehyde (5 mmol) was reacted with 2-amino phenol using the general procedure to provide *N*-benzilidene-2-hydroxylaniline as a white crystalline solid (isolated yield 91 %, 0.90 g). The data for *N*-benzilidene-2-hydroxylaniline was consistent with that found in the literature, V_{max} (thin film)/cm^{-1}: 3423.9, 2922.1, 2853.9, 1625.4, 1594.1, 1482.2, 1468.7, 1450.6, 1379.6, 1250.8, 1168.1, 1026.3, 765.7. δ_H (270 MHz, CDCl$_3$): 6.87-6.94 (dt, 1H, J = 1.4, 6.4 Hz), 7.00-7.04 (dd, 1H, J = 1.3, 6.8, 1.5), 7.17-7.25 (m, 3H), 7.29-7.53 (m, 3H), 7.90-7.94 (m, 2H), 8.70 (s, 1H). δ_C (300 MHz, CDCl$_3$): 115.46 (CH), 116.33 (CH), 120.53 (CH), 129.24 (CH), 129.28 (CH), 129.36 (CH), 132.10 (CH), 135.92 (q), 136.25 (q), 152.78 (q), 157.56 (CH).

6.6 Imine Aldol

General Procedure for the Imine Aldol Reaction

To a stirring suspension of In(OTf)$_3$ (0.5 mol %) in DCM (5 ml) was added the imine (1 mmol) in acetonitrile (10 ml) at room temperature. The reaction mixture was allowed to stir for 5 minutes then the silyl enolate (1.2 mmol) was added dropwise. After 8 hours or when TLC showed the reaction to be complete, the reaction was quenched with sodium hydrogen carbonate (3 x 5 ml) and extracted with ethyl acetate. The organic layers were dried over magnesium sulphate, filtrated and concentrated *in vacuo* to afford the crude product. Further purification by column

chromatography (petroleum ether 40-60: ethyl acetate, 95:5) gave the corresponding product.

Trimethylsiloxy-1-methoxy propene (Aldrich)
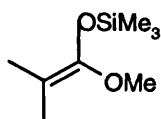
δ_H (270 MHz, CDCl$_3$): 0.18 (s, 9H), 1.49 (s, 3H), 1.54 (s, 3H), 3.47 (s, 3H). δ_C (400 MHz, CDCl$_3$): 0.00 (SiMe$_3$), 33.40 (CH$_3$), 38.05 (CH$_3$), 56.47 (CH$_3$), 90.87 (q), 149.41 (q).

Methyl 3-anilino-2, 2-dimethyl-3-phenylpropioniate 208[160]
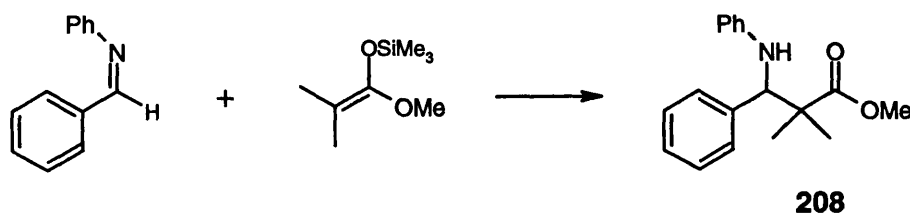
208

N-Benzilideneaniline (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene (1.2 mmol) using the general procedure to provide methyl 3-anilino-2,2-dimethyl-3-phenylpropioniate as a white crystalline solid (isolated yield 72 %, 0.20 g). The data for methyl 3-anilino-2, 2-dimethyl-3-phenylpropioniate was consistent with that found in the literature, v_{max} (thin film)/cm^{-1}: 3361.1, 2981.1, 2923.8, 1716.1, 1600.8, 1498.3, 1435.1, 1308.6, 1252.2, 1134.5, 1078.1, 802.5. δ_H (270 MHz, CDCl$_3$): 1.16 (s, 3H), 1.27 (s, 3H), 3.66 (s, 3H), 4.49 (s, 1H), 4.80 (bs, 1H), 6.47-6.51 (m, 2H), 6.59-6.62 (m, 1H), 7.01-7.04 (m, 2H), 7.26-7.29 (m, 5H). δ_C (400 MHz, CDCl$_3$): 21.10 (CH$_3$), 24.94 (CH$_3$), 52.48 (CH$_3$), 64.75 (CH), 113.77 (CH), 117.65 (CH), 127.83 (CH), 128.38 (CH), 128.66 (CH), 129.40 (CH), 146.94 (q).

HPLC: OJ Chiralpak column, 99 Hex: 1 IPA, 1ml/min, rt, 254nm, t= 13.41, 16.93 mins. Chirophos/ AgClO$_4$: t = 13.43, 16.93, 0% e.e. Prophos/ AgClO$_4$: t = 13.17,

16.53, 0% e.e. Josiphos/ AgClO₄: t = 13.40, 16.74, 0% e.e. DIOP/ AgClO₄: t = 13.54,

16.98, 0% e.e. *R* – BINAP/ In(OTf)₃: t = 13.08, 16.33, 0% e.e. Chirophos/ In(OTf)₃: t =

13.88, 17.38, 0% e.e

Methyl 3-anilino-2,2-dimethyl-3-cinnamylpropioniate 210[100]

210

Trans-cinnamaldehyde (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene

(1.2 mmol) using the general procedure to provide methyl 3-anilino-2,2-dimethyl-3-

cinnamylpropioniate as a white crystalline solid (isolated yield 53 %, 0.16 g). The

data for methyl 3-anilino-2,2-dimethyl-3-cinnamylpropioniate was consistent with that

found in the literature. V_{max} (Nujol)/cm⁻¹: 3419.0, 3061.3, 2978.8, 1725.2, 1687.1,

1597.6, 1448.8, 1433.6, 1299.8, 1254.6, 1224.5, 1193.7, 1128.4, 1002.2. δ_H (300

MHz, CDCl₃): 1.17 (s, 3H), 1.22 (s, 3H), 3.22-3.30 (m, 1H), 3.52-3.59 (m, 1H), 3.67

(s, 3H), 3.76-3.83 (m, 1H), 7.16-7.31 (m, 6H), 7.40-7.58 (m, 3H), 7.87 (d, 2H). δ_C (400

MHz, CDCl₃): 22.04 (CH₃), 25.21 (CH₃), 40.34 (CH₃), 48.31 (CH), 52.25 (CH), 127.22

(CH), 128.28 (CH), 128.38 (CH), 128.88 (CH), 129.76 (CH), 133.30 (q). *m/z* (EI)

(Found: *M+* 311.2, Expected *M*, 311.2). CHN (Found: C, 77.3; H, 7.22; N, 4.5.

C₂₀H₂₃NO₂ requires C, 77.4; H, 7.4; N, 4.5 %).

Methyl 3-anilino-2,2-dimethyl-3-(2-fluoro)phenylpropioniate 214
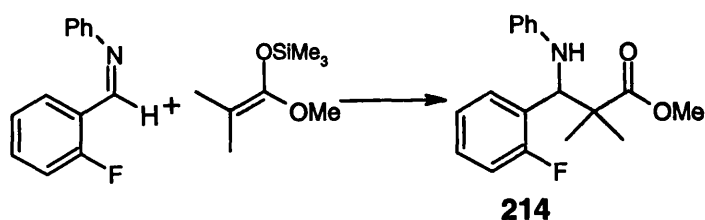
214

N-2-Fluorobenzilideneaniline (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene (1.2 mmol) using the general procedure to provide methyl 3-anilino-2,2-dimethyl-3-(2-fluoro)phenylpropioniate as a brown oil (isolated yield 65 %, 0.20 g).

V_{max} (Nujol)/cm^{-1}: 3406.1, 2976.5, 1728.9, 1602.8, 1516.4, 1469.8, 1341.6, 1258.0, 1185.7, 1134.2, 1011.4, 856.3. δ_H (270 MHz, CDCl$_3$): 1.19 (s, 3H), 1.34 (s, 3H), 3.62 (s, 3H), 4.84 (s, 1H), 4.90 (bs, 1H), 6.52-6.64 (m, 3H), 6.91-7.10 (m, 4H), 7.17-7.27 (m, 2H). δ_C (400 MHz, CDCl$_3$): 20.66 (CH$_3$), 24.76 (CH$_3$), 47.36 (CH$_3$), 52.15 (CH), 57.32, 113.10 (CH), 115.01 (CH), 115.24 (CH), 117.46 (CH), 123.98 (CH), 128.84 (CH), 129.00 (CH), 130.27 (CH), 146.48 (q), 159.90 (q), 176.65 (q).*m/z* (EI) (Found: *M+* 302.2, Expected *M*, 302.2). CHN (Found: C, 70.8; H, 6.6; N, 4.5. C$_{18}$H$_{20}$FNO$_2$ requires C, 70.8; H, 6.6; N, 4.7 %).

Methyl 3-anilino-2,2-dimethyl-3-(*p*)-nitrophenylpropioniate 212
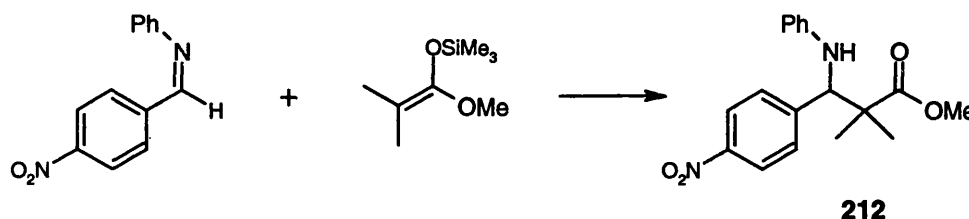
212

N-4-Nitrobenzilideneaniline (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene (1.2 mmol) using the general procedure to provide methyl 3-anilino-2,2-dimethyl-3-(4)-nitrophenylpropioniate as a brown oil (isolated yield 63 %, 0.21 g).

V_{max} (thin film)/cm^{-1}: 3416.1, 3055.4, 2983.8, 1729.0, 1602.3, 1518.0, 1472.0, 1434.3, 1347.0, 1265.5, 1193.8, 1139.1, 1014.4, 863.9. δ_H (400 MHz, CDCl$_3$): 1.19 (s, 3H), 1.33 (s, 3H), 3.67 (s, 3H), 4.59 (s, 1H), 4.90 (bs, 1H), 6.42-6.48 (m, 2H), 7.46-7.5 (m, 2H), 8.14-8.19 (m, 2H). δ_C (400 MHz, CDCl$_3$): 21.26 (CH$_3$), 24.58 (CH$_3$), 46.88 (q), 52.36 (CH$_3$), 53.47 (q), 64.21 (q), 113.23 (q), 117.92 (CH), 123.92 (CH), 129.03 (CH), 129.07 (CH), 146.00 (q), 147.28 (q), 176.03 (q). *m/z* (EI) (Found: *M+* 328.0, Expected

M, 328.0). CHN (Found: C, 65.70; H, 6.11; N, 8.54. $C_{18}H_{20}N_2O_4$ requires C, 65.9; H, 6.1; N, 8.5%).

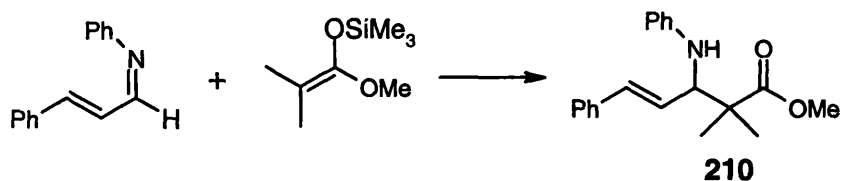## Methyl 3-anilino-2,2-dimethyl-3-(4)-methoxyphenylpropioniate 216
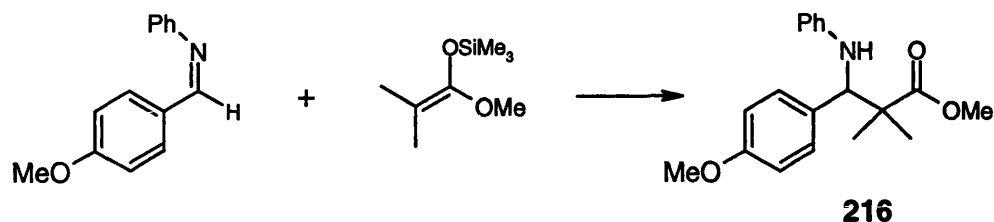
216

N-4-Methoxybenzilideneaniline (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene (1.2 mmol) using the general procedure to provide methyl 3-anilino-2,2-dimethyl-3-(p)-methoxyphenylpropioniate as a white crystalline solid (isolated yield 57 %, 0.18 g). V_{max} (thin film)/cm^{-1}: 3408.6, 2950.8, 2836.7, 1726.6, 1602.7, 1510.5, 1463.5, 1433.5, 1316.2, 1284.0, 1248.1, 1178.4, 1136.3, 1032.8, 834.3. δ_H (400 MHz, CDCl$_3$): 1.15 (s, 3H), 1.25 (s, 3H), 3.64 (s, 3H), 3.75 (s, 3H), 4.44 (s, 1H), 4.75 (bs, 1H), 6.48-6.57 (m, 3H), 6.79-6.85 (m, 2H), 7.02-7.09 (m, 2H), 7.16-7.22 (m, 2H). δ_C (400 MHz, CDCl$_3$): 20.79 (CH$_3$), 24.56 (CH$_3$), 47.16 (q), 52.07 (CH$_3$), 55.15 (CH$_3$), 63.81 (CH), 113.29 (CH), 117.09 (CH), 128.84 (CH), 129.11 (CH), 131.01 (CH), 146.82 (q), 158.65 (q), 176.86 (q). m/z (EI) (Found: $M+$ 313.2, Expected M, 313.1). CHN (Found: C, 72.6; H, 7.3; N, 4.4. $C_{19}H_{23}NO_3$ requires C, 72.8; H, 7.3; N, 4.5 %).

Methyl 3-(2-hydroxy)anilino-2,2-dimethyl-3-phenylpropioniate 226[100]
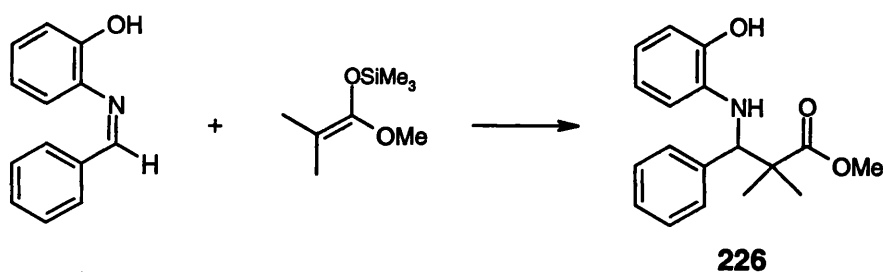
226

N-Benzilidene-2-hydroxylaniline (1 mmol) was reacted with trimethylsiloxy-1-methoxy propene (1.2 mmol) using the general procedure to provide methyl 3-(2-hydroxy)anilino-2,2-dimethyl-3-phenylpropioniate as a white crystalline solid (isolated yield 63%, 0.19 g). The data for methyl 3-anilino-2,2-dimethyl-3-(4)-methoxyphenylpropioniate was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3416.9, 3056.2, 2982.1, 1726.9, 1595.5, 1513.0, 1265.5, 1143.4, 819.4. δ_H (270 MHz, CDCl$_3$): 1.18 (s, 3H), 1.25 (s, 3H), 3.66 (s, 3H), 4.53 (s, 1H), 5.20 (bs, 1H), 6.27-6.70 (m, 4H), 7.23-7.29 (m, 5H). δ_C (400 MHz, CDCl$_3$): 19.9, 24.2, 47.3, 52.3, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0.

2-(Phenyl-phenylamino-methyl)-cyclohexanone 218[161]
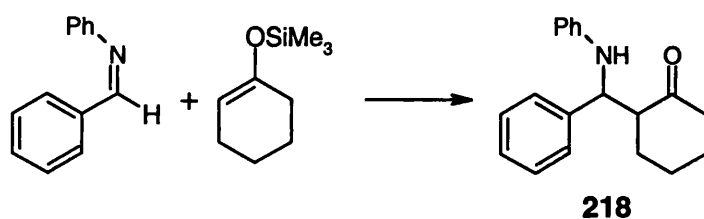
218

N-Benzilideneaniline (1 mmol) was reacted with 1-cyclohexenyloxy-trimethylsilane (1.2 mmol) using the general procedure to provide 2-(phenyl-phenylamino-methyl)-cyclohexanone as a white crystalline solid (isolated yield 51 %, 0.14 g). The data for 2-(phenyl-phenylamino-methyl)-cyclohexanone was consistent with that found in the literature, V_{max} (thin film)/cm^{-1}: 3366.0, 3027.9, 2931.5, 2862.8, 1702.3, 1676.3, 1602.0, 1498.8, 1447.7, 1313.5, 1259.2, 1142.7, 1070.2, 1028.0, 909.8, 821.2. δ_H (400 MHz, CDCl$_3$): 1.54-1.67 (m, 3H), 1.82-1.98 (m, 1H), 2.19 (s, 2H), 2.24-2.38 (m, 1H), 2.40-2.48 (m, 1H), 2.73-2.84 (m, 1H), 4.55 (bs, 1H), 4.8 (d, 1H, J = 4.3 Hz), 6.52-6.56 (m, 3H), 7.02-7.10 (m, 2H), 7.18-7.23 (m, 1H), 7.28-7.32 (m, 2H), 7.33-7.39 (m, 2H). δ_C (400 MHz, CDCl$_3$): 24.92 (CH$_2$), 27.07 (CH$_2$), 28.75 (CH$_2$), 42.44 (CH$_2$), 56.61 (CH), 57.27 (CH), 113.94 (CH), 117.54 (CH), 126.84 (CH), 127.11 (CH), 127.36 (CH), 128.20 (CH), 128.84 (CH), 141.37 (q), 147.28 (q), 211.00 (q).

2-(2-Fluorophenyl-phenylamino-methyl)-cyclohexanone 219
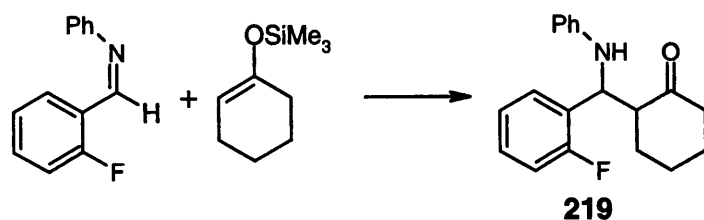
N-2-Fluorobenzilideneaniline (1 mmol) was reacted with 1-cyclohexenyloxy-trimethylsilane (1.2 mmol) using the general procedure to provide 2-(2-fluorophenyi-phenylamino-methyl)-cyclohexanone as a white crystalline solid (isolated yield 45 %, 0.13 g). V_{max} (thin film)/cm^{-1}: 3370.6, 3036.9, 2938.1, 2865.1, 1706.5, 1684.8, 1614.5, 1602.0, 1498.0, 1484.3, 1453.5, 1257.4, 1231.1, 1143.0, 1098.6, 1070.9, 910.3. δ_H (270 MHz, CDCl$_3$): 1.50-1.80 (m, 4H), 1.82-2.06 (m, 2H), 2.14-2.2 (m, 1H), 2.28-2.46 (m, 2H), 2.90-3.00 (m, 1H), 4.6-4.7 (bs, 1H), 5.10-5.14 (d, 1H), 6.56-6.68 (m, 3H), 6.98-7.2 (m, 5H), 7.46-7.5 (m, 1H). δ_C (400 MHz, CDCl$_3$): 24.81 (CH$_2$), 27.37 (CH$_2$), 29.32 (CH$_2$), 42.59 (CH$_2$), 55.30 (CH), 69.37 (CH), 113.72 (CH), 115.04 (CH), 117.43 (CH), 117.81 (CH), 129.04 (CH) 143.92 (q), 147.86 (q). m/z (EI) (Found: M+ 297.2, Expected M, 297.2). CHN (Found: C, 76.8; H, 6.83; N, 4.70. C$_{19}$ H$_{19}$ FNO$_2$ requires C, 76.8; H, 6.79; N, 4.7 %).

2-(4-Nitrophenyl-phenylamino-methyl)-cyclohexanone 220
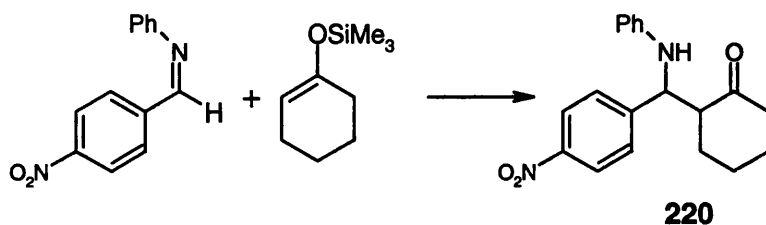
N-*p*-Nitrobenzilideneaniline (1 mmol) was reacted with 1-cyclohexenyloxy-trimethylsilane (1.2 mmol) using the general procedure to provide 2-(4-Nitrophenyl-phenylamino-methyl)-cyclohexanone as a brown oil (isolated yield 49 %, 0.16 mg).

V_{max} (thin film)/cm^{-1}: 3386.3, 3053.2, 2937.4, 2863.1, 1705.9, 1601.0, 1515.8, 1449.5,

1435.2, 1344.7, 1264.1, 1179.9, 1141.9, 1109.5, 1014.0, 854.7. δ_H (400 MHz, CDCl$_3$):

1.24 –1.26 (m, 1H), 1.54 –2.50 (m, 8H), 2.80 –2.90 (m, 1H), 4.7 –4.8 (bs, 1H), 6.48 –

6.52 (m, 2H), 6.64 –6.72 (m, 1H), 7.06 –7.12 (m, 2H), 7.54 –7.62 (m, 2H), 8.14 –8.20

(m, 2H). δ_C (400 MHz, CDCl$_3$): 24.47 (CH$_2$), 27.07 (CH$_2$), 27.75 (CH$_2$), 41.36 (CH$_2$),

53.81 (CH), 55.36 (CH), 113.64 (CH), 118.91 (CH), 127.05 (CH), 127.19 (CH),

127.29 (CH), 128.61 (CH), 128.24 (CH), 144.91 (q), 146.33 (q), 201.70 (q). m/z (EI)

(Found: $M+$ 324.2, Expected M, 324.2). CHN (Found: C, 68.3; H, 6.2; N, 7.9. C$_{19}$ H$_{20}$

N$_2$ O$_3$ requires C, 70.4; H, 6.2; N, 8.6 %).

2-(4-Methoxyphenyl-phenylamino-methyl)-cyclohexanone 221
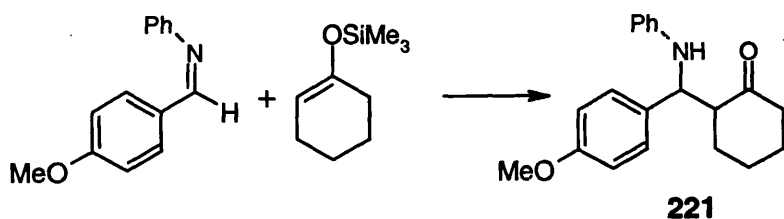
221

N-4-Methoxybenzilideneaniline (1 mmol) was reacted with 1-cyclohexenyloxy-
trimethylsilane (1.2 mmol) using the general procedure to provide 2-(4-
methoxyphenyl-phenylamino-methyl)-cyclohexanone as a white crystalline solid

(isolated yield 42 %, 0.13 g). V_{max} (thin film)/cm^{-1}: 3366.6, 3026.5, 2864.4, 1702.6,

1658.3, 1601.2, 1555.8, 1509.1, 1466.7, 1451.9, 1418.1, 1314.0, 1392.8, 1250.6,

1163.7, 1025.4, 966.9. δ_H (270 MHz, CDCl$_3$): 1.51-1.70 (m, 4H), 1.80-2.00 (m, 4H),

2.28-2.37 (m, 1H), 3.78 (s, 3H), 4.57 (d, 1H, J = 7.0 Hz), 4.7 (bs, 1H), 6.51-6.66 (m,

3H), 6.81-6.86 (m, 2H), 7.04-7.09 (m, 2H), 7.25-7.29 (m, 2H). δ_C (400 MHz, CDCl$_3$):

Sample not run for long enough. m/z (EI) (Found: $M+$ 309.2, Expected M, 309.2).

CHN (Found: C, 77.56; H 7.40; 4.99%. C$_{20}$H$_{23}$NO$_2$ requires C, 77.67; H, 7.44; N, 4.53

%).

6.7 Imino Ene

6.7.1 Intramolecular Imino Ene

Preparation of 3-Methyl Citronellal 235[162]

235
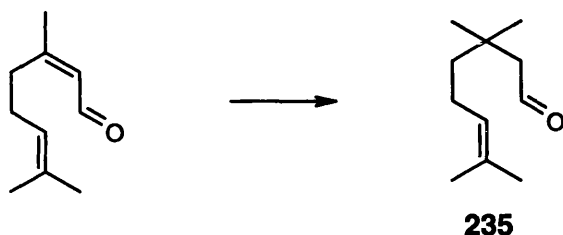
To a slurry of 4.0 g of cuprous iodide (21 mmol) in 200 ml of ether at 0 °C under nitrogen was added 32 ml of methyllithium (1.3 M in hexane, 42 mmol). After stirring at 0 °C for 10 minutes, the solution was cooled to −78 °C and 3.04 g of citral (20 mmol) in 20 ml of ether was added drop-wise at this temperature. The resulting mixture was stirred at −78 °C for 10 min and at −20 °C for 4 hours. The reaction mixture was poured onto cold-saturated NH_4Cl solution and extracted with ether. The organic extracts were combined, dried, concentrated, and purified by column chromatography on silica gel (9: 1 petrol: ethyl acetate) to provide 3-methylcitronellal as a colourless oil (75 % yield, 2.53 g). The data for 3-methylcitronellal was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 1722.3. δ_H (270 MHz, $CDCl_3$): 1.06 (s, 6H), 1.32-1.37 (m, 2H), 1.60 (s, 3H), 1.67 (s, 3H), 1.92-2.00 (q, 2H, J = 7.3, 9.97 Hz), 2.27-2.28 (m, 2H), 5.06-5.10 (t, 1H, J = 5.9, 7.2 Hz), 9.83-9.86 (t, 1H). δ_C (270 MHz, $CDCl_3$): 17.49 (CH_3), 22.65 (CH_2), 25.59 (CH_3), 27.18 (CH_3), 27.37 (CH_3), 33.44 (q), 42.64 (CH_2), 54.65 (CH_2), 124.22 (CH), 131.48 (q), 203.54 (CH). m/z (EI) (Found: M+ 169.1 , Expected M, 169.1)

N-(5-Dimethyl-5-hexenylidine)benzylamine 236[163]

236
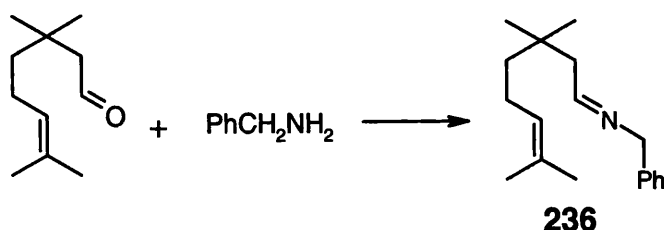
Benzylamine (5 mmol) was reacted with 3-methyl citronellal using the general procedure for preparing imines to provide N-(5-dimethyl-5-hexenylidine) benzylamine as a off-white crystalline solid (isolated yield 98 %, 1.26 g). The data for N-(5-dimethyl-5-hexenylidine)benzylamine *was* consistent with that found in the literature.

V_{max} (thin film)/cm^{-1}: 2965.0, 2926.7, 1669.2, 1454.3, 1385.1, 1265.6, 1157.6, 1027.7.

δ_H (270 MHz, CDCl$_3$): 0.95 (s, 6H), 1.25-1.32 (m, 2H), 1.56 (s, 3H), 1.65 (s, 3H), 1.94-2.03 (m, 2H), 2.23 (d, 2H, J = 5.5Hz), 4.60 (s, 2H), 5.05-5.10 (m, 1H), 7.24-7.35 (m, 5H), 7.83-7.87 (t, 1H, J = 5.8, 5.5 Hz). δ_C (270 MHz, CDCl$_3$): 17.23 (CH$_3$), 22.37 (CH$_2$), 25.39 (CH$_3$), 27.07 (CH$_3$), 33.23 (q), 42.30 (CH$_2$), 47.13 (CH$_2$), 65.05 (CH), 124.49 (CH), 126.51 (CH), 127.58 (CH), 128.09 (CH), 128.69 (CH), 130.70 (CH), 139.05 (q), 164.33 (q). m/z (EI) (Found: M+ 258.1, Expected M, 258.1)

Cyclisation of N-(5-Dimethyl-5-hexenylidine)benzylamine 237[163]

237
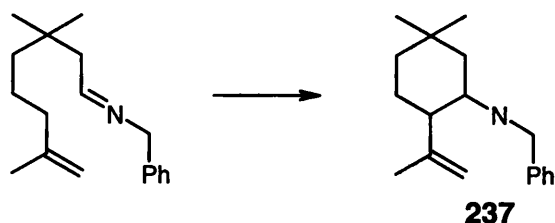
To a stirred solution of N-(5-dimethyl-5-hexenylidine)benzylamine (1 mmol) in dichloromethane was added tin tetrachloride (4 mmol), After 24 hours the reaction was quenched with water and 20 % sodium hydroxide solution (3x5 ml) and extracted with diethyl ether. The organic layer was further washed with 10%

hydrochloric acid and extracted with diethylether and reduced *in vacuo*. The crude product was purified by column chromatography (9:1, petrol: ethylacetate) to provide a white crystalline solid (isolated yield 19 %, 0.05 g) The data *was* consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3054.4, 2986.6, 2929.9, 1722.6, 1648.9, 1583.5, 1511.3, 1421.8, 1364.6, 1218.3, 1179.9, 1075.0, 896.0. δ_H (270 MHz, CDCl$_3$): 0.91 (s, 3H), 0.96 (s, 3H), 1.22-1.28 (m, 2H), 1.43-1.48 (m, 1H), 1.53 (d, 3H, J = 0.7Hz), 1.84-1.94 (m, 4H), 2.49-2.57 (dt, 1H, J =6.8, 3.8 Hz), 3.57-3.62 (d, 1H, J =13.2 Hz), 3.83-3.88 (d, 1H, J = 13 Hz), 4.78 (s, 2H), 7.23-7.31 (m, 5H). δ_C (400 MHz, CDCl$_3$): 18.59 (CH$_3$), 25.03 (CH$_3$), 27.18 (CH$_2$), 31.23 (q), 33.29 (CH$_3$), 38.71 (CH$_2$), 44.54 (CH$_2$), 50.83 (CH$_2$), 52.42 (CH$_3$), 112.61 (CH$_2$), 126.80 (CH), 128.04 (CH), 128.24 (CH), 128.32 (CH), 130.86 (CH), 140.53 (q), 147.13 (q). *m/z* (EI) (Found: *M+* 258.2, Expected *M*, 258.2)

6.7.2 Activated Imines

General Procedure for the Synthesis of *N*-Trimethyl silyl Imines

To a cold solution (0 °C) of hexamethyldisilazane (1.2 mmol) under an inert atmosphere of nitrogen was added dropwise (2.5 M *n*-butyllithium in hexanes (1 mmol). The aldehyde (1 mmol) was then added to the cold LiHMDS solution, and the reaction was stirred at 0 °C for 30 min. The reaction was then brought to room temperature, and the products were purified by vacuum distillation, although purification is not necessary.

N-(Trimethylsilyl)benzaldimine 238[112]

238
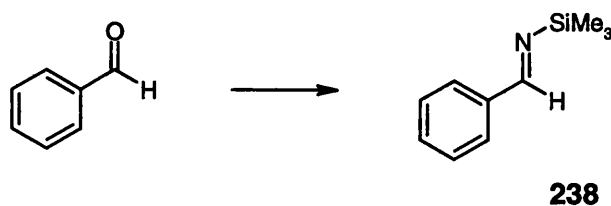
Benzaldehyde (1 mmol) was reacted with LiHMDS solution using the general procedure to provide N-(trimethylsilyl)benzaldimine as a straw-yellow oil (isolated yield 61 %, 0.11 g). The data for N-(trimethylsilyl)benzaldimine was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 1650.1. δ_H (270 MHz, CDCl$_3$): 0.29 (s, 9H), 7.44-7.47 (m, 3H), 7.81-7.84 (m, 2H), 9.01 (s, 1H). δ_C (400 MHz, CDCl$_3$): 3.80 (CH$_3$), 128.43 (CH), 128.52 (CH), 131.26 (CH), 138.79 (q), 168.55 (CH). m/z (EI) (Found: M+ 178.1, Expected M, 178.1)

N-(4-Trimethylsilyl)-furaldimine 240[112]

240
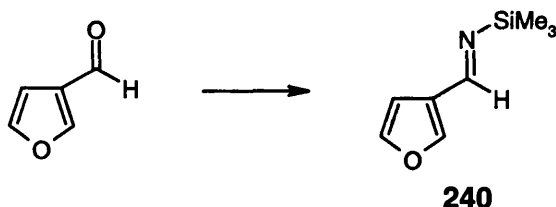
Furaldehyde (1 mmol) was reacted with LiHMDS solution using the general procedure to provide N-(4-trimethylsilyl)-furaldimine as a brown oil (isolated yield 56 %, 0.094 g). The data for N-(4-trimethylsilyl)-furaldimine was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 1643.2. δ_H (270 MHz, CDCl$_3$): 0.35 (s, 9H), 6.58-6.60 (m, 1H), 6.92-6.93 (d, 1H, J = 3.3 Hz), 7.37-7.64 (m, 1H), 8.78 (s, 1H).

Ethylglyoxalate 242[124]

242
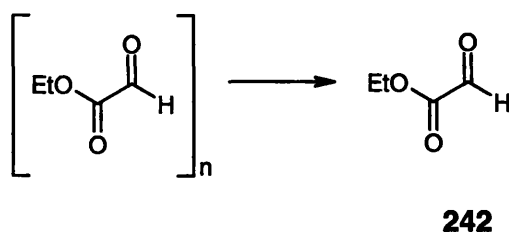
Ethylglyoxalate/ toluene solution (1:1 v/v) was heated to 115 °C and allowed to reflux for 4 hours to provide a straw-yellow coloured solution. For data purposes the ethylglyoxalate solution was distilled using short-path distillation equipment and

ethylglyoxalate was found to distil over at 140-150 °C as a thick colourless oil. The data for ethylglyoxalate was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 1752.4. δ_H (270 MHz, CDCl$_3$): 1.23 (t, 3H, J = 7.0Hz), 4.22 (q, 2H, J = 7.1 Hz), 9.24 (s, 1H).

General Procedure for the Synthesis of N-Tosyl Imines

To a refluxing mixture of aldehyde (1 mmol) and toluene (15 ml) was added 4-tolene sulphonylisocyanate drop-wise (1 mmol). The reaction mixture was stirred for a further 8 hours at reflux. The reaction mixture was allowed to cool to room temperature and concentrated. The crude product was recrystalised from ethyl acetetate to give the corresponding N-tosyl Imine.

N-Ethyl N-(4-Toluenesulphonyl)iminoacetate 244[124]

244
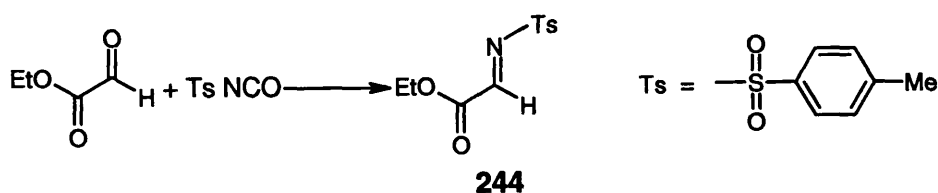
Ethylglyoxalate (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using the general procedure to provide N-Ethyl N-(4-Toluenesulphonyl)iminoacetate as a colourless oil. The data for N-Ethyl N-(4-Toluenesulphonyl)iminoacetate was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 1633.2. δ_H (270 MHz, CDCl$_3$): 1.32-1.37 (t, 3H, J = 7.2, 7.1 Hz), 2.46 (s, 3H), 4.33-4.41 (q, 2H, J = 7.2, 7.2 Hz), 7.37-7.40 (d, 2H, J = 8.0 Hz), 7.84-7.87 (d, 2H, J =8.3 Hz), 8.26 (s, 1H). δ_C (270 MHz, CDCl$_3$): 13.8 (CH$_3$), 21.62 (CH$_2$), 63.13 (CH$_2$), 128.83 (CH), 130.03 (CH), 132.27 (CH), 146.01 (q), 160.00 (q), 161.14 (q).

N-(4-Toluenesulphonyl)benzaldimine 245[115]
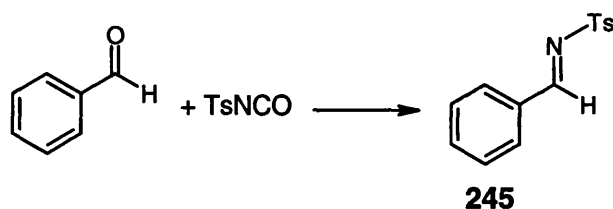
245

Benzaldehyde (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using the general procedure to provide N-(4-toluenesulphonyl)benzaldimine as a straw yellow crystalline solid (isolated yield 79%, 1.02 g). The data for N-(4-toluenesulphonyl)benzaldimine was consistent with that found in the literature. M.p 91-92 °C. V_{max} (Nujol)/cm^{-1}: 3358.8, 3262.2, 3066.7, 1650.0, 1598.3, 1575.0, 1450.6, 1323.3, 1223.6, 1154.8, 1088.8, 999.8, 867.4, 817.4. δ_H (400 MHz, CDCl$_3$): 2.44 (s, 3H), 7.31-7.47 (m, 2H), 7.49-7.62 (m, 3H), 7.80-7.94 (m, 4H), 9.04 (s, 1H). δ_C (300 MHz, CDCl$_3$): 22.04 (CH$_3$), 126.80 (CH), 128.48 (CH), 128.86 (CH), 129.55 (CH), 130.04 (CH), 130.22 (CH), 130.53 (CH), 131.70 (CH), 132.74 (q), 135.37 (CH), 135.47 (q), 145.05 (q), 170.61 (CH). m/z (EI) (Found: M+ 260.1, Expected M, 260.1)

N-(4-Toluenesulphonyl)-4-bromobenzaldimine[164]
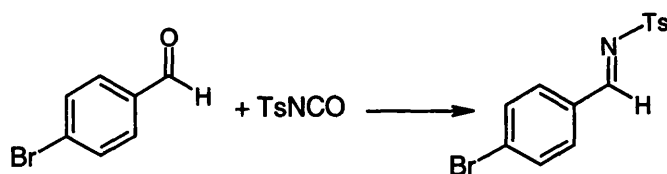
4-Bromobenzaldehyde (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using the general procedure to provide N-(4-toluenesulphonyl)-p-bromobenzaldimine as a light brown crystalline solid (isolated yield 79 %, 1.33 g). The data for N-(trimethylsilyl)-4-bromobenzaldimine was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}: 3055.1, 2986.6, 2922.4, 1608.7, 1587.9, 1559.9, 1483.5, 1398.0, 1346.6, 1265.9, 1161.0, 1089.8, 1066.1, 871.1. δ_H (270 MHz, CDCl$_3$): 2.44 (s, 3H),

7.30-7.37 (d, 2H, J = 7.9 Hz), 7.62-7.83 (m, 4H), 7.87-7.90 (d, 2H, J = 8.3 Hz), 9.00

(s, 1H). δ_C (300 MHz, CDCl$_3$): 22.07 (CH$_3$), 128.54 (CH), 130.26 (CH), 130.64 (q),

131.37 (CH), 131.61 (q), 132.78 (CH), 132.83 (CH), 132.97 (CH), 135.23 (q), 145.20

(q), 169.21 (CH).

N-(4-Toluenesulphonyl)-2-napthaldimine 246[165]

246

2-Napthaldehyde (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using

the general procedure to provide N-(4-toluenesulphonyl)-2-napthaldimine as a straw-

yellow crystalline solid (isolated yield 85 %, 1.31 g). The data for N-(4-

toluenesulphonyl)-2-napthaldimine was consistent with that found in the literature,

V_{max} (Nujol)/cm^{-1}: 3060.1, 2958.0, 1627.6, 1588.4, 1567.8, 1439.2, 1365.8, 1320.5,

1158.3, 1089.1, 846.6, 829.5. δ_H (400 MHz, CDCl$_3$): 2.44 (s, 3H), 7.36-7.38 (d, 2H, J

= 6.8 Hz), 7.55-7.66 (m, 2H), 7.86-7.97 (m, 5H), 8.02-8.04 (dd, 1H, J = 1.7, 7.3, 1.3

Hz), 8.34 (s, 1H), 9.18 (s, 1H). δ_C (300 MHz, CDCl$_3$): 22.06 (CH$_3$), 124.47 (CH),

127.65 (CH), 128.45 (CH), 128.51 (CH), 129.56 (CH), 129.89 (CH), 130.47 (q),

133.00 (q), 135.64 (q), 136.54 (CH), 136.90 (CH), 145.00 (q), 170.45 (CH).

N-(4-Toluenesulphonyl)-3,5-dichlorobenzaldimine 247[166]
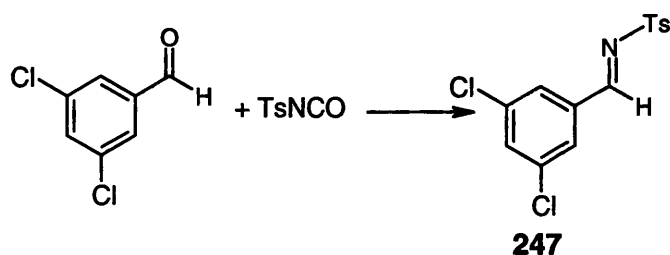
247

3,5 Dichlorobenzaldehyde (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using the general procedure to provide N-(4-toluenesulphonyl)-3,5-dichlorobenzaldimine as a white crystalline solid (isolated yield 80 %, 1.31 g). The data for N-(4-toluenesulphonyl)-3,5-dichlorobenzaldimine consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}:1629.7 δ_H (270 MHz, CDCl$_3$): 2.45 (s, 3H), 7.38-7.39 (m, 5H), 7.89-7.93 (d, 2H, J = 8.3 Hz), 9.40 (s, 1H).

N-(4-Toluenesulphonyl)-trans-cinnamaldimine 248[112]
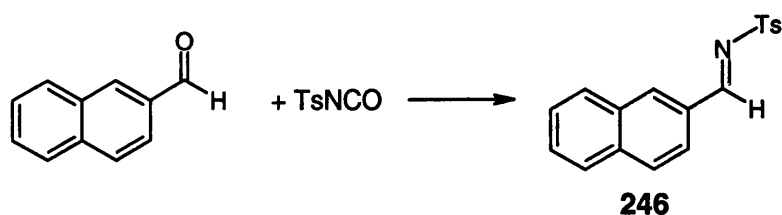

248
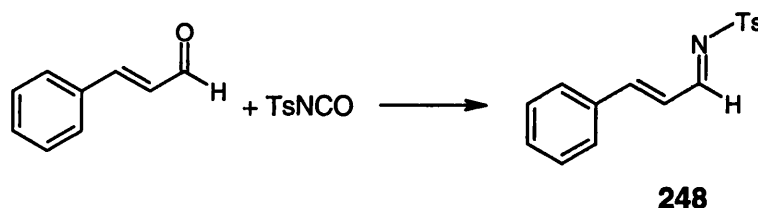
Trans cinnamaldehyde (5 mmol) was reacted with 4-toluene sulphonyl isocyanate using the general procedure to provide N-(4-toluenesulphonyl)-trans cinnamaldimine as a white crystalline solid (isolated yield 90 %, 1.28 g). The data for N-(4-toluenesulphonyl)-trans cinnamaldimine consistent with that found in the literature. mp 110-111 $^{\circ}$C, V_{max} (Nujol)/cm^{-1}: 3358.4, 3262.7, 1620.7, 1580.8, 1450.3, 1319.6, 1156.0, 1089.9, 858.1. δ_H (270 MHz, CDCl$_3$): 2.43 (s, 3H), 6.91-7.00 (dd, 1H, J =9.3, 6.4, 9.4 Hz), 7.24-7.60 (m, 9H), 7.84-7.87 (d, 1H, J = 5.9 Hz), 8.75-8.79 (d, 1H, J = 9.3 Hz)

1-Methylenetetralin 253[123]

253
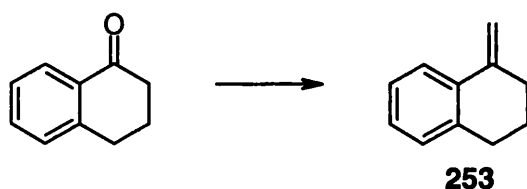
To a solution of 1-tetralone (5 mmol) in anhydrous ether (25 ml) under argon were added methyltriphenylphosphonium bromide (5mmol) followed by potassium tert-

butoxide (5 mmol). The mixture was stirred for 20 h at room temperature and the ether was removed under reduced pressure. The residue was extracted with pentane and filtered through Celite and further reduced in *vacuo*. The resulting crude product was purified by column chromatography with pentane as eluent to give 1-methylenetetralin as a colourless oil (75 % yield, 0.55 g) The data for tetralin consistent with that found in the literature. V_{max} (thin film)/cm^{-1}: 3066.0, 2932.1, 1684.4, 1627.8, 1484.8, 1302.6, 1264.5, 1046.5, 944.8. δ_H (300 MHz, CDCl$_3$): 1.85-1.90 (m, 2H), 2.51-2.60 (m, 2H), 2.82-2.91 (m, 2H), 4.96 (s, 1H), 5.44 (s, 1H), 7.11-7.19 (m, 3H), 7.63-7.71 (m, 1H). δ_C (300 MHz, CDCl$_3$): 24.30 (CH$_2$), 30.95 (CH$_2$), 33.74 (CH$_2$), 108.33 (CH$_2$), 124.69 (CH), 126.37 (CH), 128.06 (CH), 129.67 (CH), 135.19 (q), 137.76 (q), 143.91 (q).

6.7.3 Imino-ene products

General Procedure for the Inter-molecular Imino-Ene Reaction

The activated imine was added o a stirring suspension of In(OTf)$_3$ (0.5 mol %) in DCM (5 ml) was added the imine (in excess) in DCM (5 ml) at room temperature. The reaction mixture was allowed to stir for 5 minutes then the ene substrate (1.2 mmol) was added dropwise. After 8 hours or when TLC showed the reaction to be complete, the reaction was quenched with sodium hydrogen carbonate (3x5 ml) and extracted with ethyl acetate. The organic layers dried over magnesium sulphate, filtrated and concentrated in *vacuo* to afford the crude product. Further purification by column chromatography (petrolum ether 40-60: ethyl acetate, 90:10) gave the corresponding product.

3-Cyclohex-1-enyl-2-(toluene-4-sulfonylamino)-propionic Acid Ethyl Ester[124]
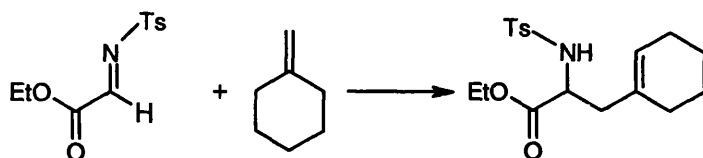
N-Ethyl *N*-(4-toluenesulphonyl)iminoacetate (1 mmol) was reacted with methylene cyclohexane using the general procedure to provide 3-cyclohex-1-enyl-2-(toluene-4-sulfonylamino)-propionic acid ethyl ester as a white crystalline solid (isolated yield 88 %, 0.31 g). The data for 3-cyclohex-1-enyl-2-(toluene-4-sulfonylamino)-propionic acid ethyl ester was consistent with that found in the literature. V_{max} (Nujol)/cm^{-1}:

3339.2, 2931.6, 1741.7, 1598.3, 1329.4, 1167.2, 1091.6. δ_H (270 MHz, CDCl$_3$): 1.10 (t, 3H, J = 7.1, 7.1 Hz), 1.47-1.63 (m, 4H), 1.79-1.84 (m, 2H), 1.94 (bs, 2H), 2.26-2.30 (m, 2H), 2.41 (s, 3H), 3.89-4.01 (m, 3H), 4.96-5.00 (d, 1H, J = 9Hz), 5.43 (s, 1H), 7.27-7.30 (d, 2H, J = 8.2Hz), 7.71-7.74 (d, 2H, J = 8.2 Hz). δ_C (400 MHz, CDCl$_3$): 13.96 (CH$_3$), 21.97 (CH$_2$), 22.61 (CH$_2$), 25.25 (CH$_2$), 27.80 (CH$_2$), 42.07 (CH$_2$), 54.34 (CH$_3$), 61.38 (CH), 126.59 (CH), 129.55 (CH), 143.67 (q).

InBr$_3$ imino ene yield 14%

4-Phenyl-2-(toluene-4-sulphonylamino)-pent-4-enoic Acid Ethyl Ester[124]
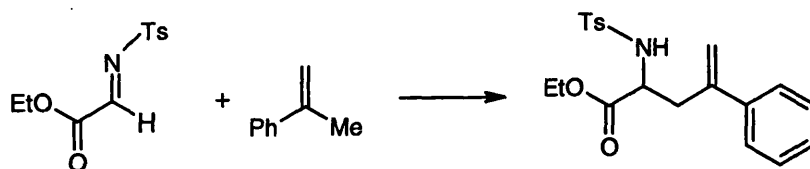
N-Ethyl *N*-(4-toluenesulphonyl)iminoacetate (1 mmol) was reacted with α-methyl styrene using the general procedure to provide 4-phenyl-2-(toluene-4-sulphonylamino)-pent-4-enoic acid ethyl ester as a white crystalline solid (isolated yield 55 %, 0.20 g). The data for 4-phenyl-2-(toluene-4-sulphonylamino)-pent-4-enoic acid ethyl ester was consistent with that found in the literature, V_{max} (Nujol)/cm$^-$

[1]: 3349.6, 2961.1, 2929.8, 1732.2, 1346.7, 1178.2, 1021.9. δ_H (300 MHz, CDCl$_3$):

0.98 (t, 3H), 2.36-2.40 (s, 3H), 2.93-2.98 (m, 2H), 3.62-3.80 (m, 2H), 3.97-4.01 (m,

1H), 5.09 (s, 1H), 5.33 (s, 1H), 7.21-7.36 (m, 7H), 7.61-7.63 (d, 2H, J = 9.2 Hz). δ_C

(400 MHz, CDCl$_3$): 13.84 (CH$_3$), 21.38 (CH$_2$), 38.92 (CH$_2$), 54.57 (CH$_2$), 61.37 (CH$_3$),

116.87 (CH), 125.98 (CH), 127.04 (CH), 127.16 (CH), 129.37 (CH), 129.46 (CH),

130.84 (CH), 1339.06 (CH), 141.37 (q), 147.28 (q), 171.00 (q).

2,4-Diphenyl-4-methoxycarbonylamino-1-butene 250[121]

250
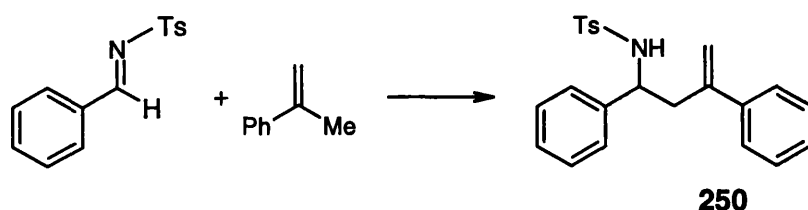
N-(4-toluenesulphonyl)benzaldimine (1 mmol) was reacted with α-methyl styrene

using the general procedure to provide 2,4-diphenyl-4-methoxycarbonylamino-1-

butene as a straw-yellow oil (isolated yield 69 %, 0.26 g). The data for 2,4-diphenyl-

4-methoxycarbonylamino-1-butene was consistent with that found in the literature.

V_{max} (thin film)/cm^{-1}: 3275.2, 3028.4, 2921.8, 1598.2, 1493.7, 1444.3, 1323.3, 1157.7,

1092.7, 1057.6, 958.6. δ_H (300 MHz, CDCl$_3$): 2.39 (s, 3H), 2.89 (m, 2H), 4.19-4.22

(dd, 1H, J = 7.2, 12.9 Hz), 4.76 (bs, 1H), 4.98 (d, 1H, J = 1.0 Hz), 5.21 (d, 1H, J =

1.1Hz), 7.01-7.04 (m, 4H), 7.12-7.25 (m, 8H), 7.42 (d, 2H, J = 8.1 Hz). δ_C (400 MHz,

CDCl$_3$): 21.38(CH$_3$), 44.09(CH$_2$), 56.38(CH$_2$), 111.35 (CH), 126.10 (CH), 126.63

(CH), 127.08 (CH), 127.41 (CH), 127.66 (CH), 128.25 (CH), 128.42 (CH), 129.18

(CH), 136.97 (CH), 139.24(q), 140.66 (q), 142.90 (q), 143.72 (q).

2-(Toluene-4-sulphonylamino)-3-(3,4-dehydronapthalene-1-yl)-propionic Acid Ethyl Ester[124]

254
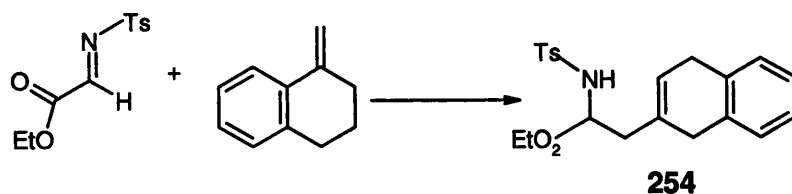
N-Ethyl *N*-(4-toluenesulphonyl)iminoacetate (1 mmol) was reacted with 1-methylene tetralin using the general procedure to provide 2-(toluene-4-sulphonylamino)-3-(3,4-dehydronapthalene-1-yl)-propionic acid ethyl ester as a white crystalline solid (isolated yield 45 %, 0.18 g). The data for 4-phenyl-2-(toluene-4-sulphonylamino)-pent-4-enoic acid ethyl ester was consistent with that found in the literature, V_{max} (Nujol)/cm^{-1}: 3349.6, 2961.1, 2929.8, 1732.2, 1346.7, 1178.2, 1021.9. δ_H (300 MHz, CDCl$_3$): 1.05 (t, 3H), 2.21 (q, 2H), 2.36 (s, 3H), 2.64 (t, 2H), 2.83 (m, 2H), 3.86 (q, 2H), 4.03 (q, 1H), 5.19 (d, 1H), 5.85 (m, 1H), 7.17-7.31 (m, 6H), 7.63 (d, 2H). δ_C (400 MHz, CDCl$_3$): 13.82 (CH$_3$), 21.31 (CH$_2$), 23.36 (CH$_2$), 28.11 (CH$_2$), 21.32 (CH$_2$), 29.67 (CH), 36.71 (CH), 54.59 (CH), 61.47 (CH$_3$) 122.21 (CH), 125.73 (CH), 127.02 (CH), 127.66 (CH), 129.33 (CH), 129.49 (CH), 130.84 (CH), 132.16 (CH), 136.47 (q), 144.28 (q), 171.40 (q).

7.0 Hetero Diels Alder

General Procedure for the Hetero-Diels Alder Reaction

To a stirring suspension of In(OTf)$_3$ (0.5 mol %) in DCM (4ml) was added the aldehyde (1 mmol) and amine (1 mmol) in DCM (6 ml) at room temperature. The reaction mixture was allowed to stir for 5 minutes then Danishefsky's diene (1.1 mmol) was added dropwise. After 30 minutes the reaction was quenched with sodium hydrogen carbonate (3x5 ml) and extracted with ethyl acetate. The organic layers dried over magnesium sulphate, filtrated and concentrated *in vacuo* to afford

the crude product. Further purification by column chromatography (petroleum ether

40-60: ethyl acetate, 90:10) gave the corresponding product.

1,2-Diphenyl-1,2,3,4-tetrahydropyridin-4-one 266[167]
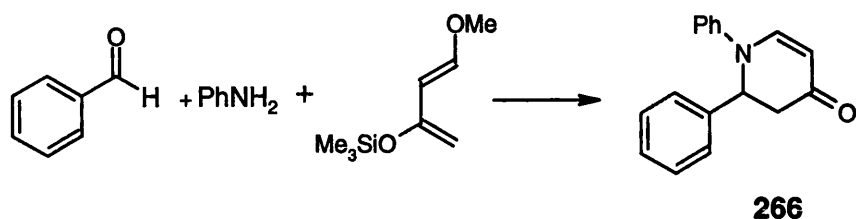
266

Banzaldehyde (1 mmol) and aniline (1 mmol) were reacted with Danishefsky's diene

using the general procedure to provide 1,2-diphenyl-1,2,3,4-tetrahydropyridin-4-one

as a white crystalline solid (isolated yield 51 %, 0.13 g). The data for 1,2-diphenyl-

1,2,3,4-tetrahydropyridin-4-one was consistent with that found in the literature, V_{max}

(thin film)/cm^{-1}: 3062.7, 2982.3, 1651.4, 1574.0, 1494.7, 1467.1, 1361.2, 1324.4,

1274.6, 1219.6, 1102.1, 969.3. δ_H (270 MHz, $CDCl_3$): 2.76-2.87 (m, 1H), 3.27-3.36

(dd, 1H, J = 1, 6 Hz), 5.25-5.35 (m, 2H), 6.85-6.87 (m, 2H), 7.00-7.16 (m, 3 H), 7.25-

7.39 (m, 5H), 7.67-7.72 (d, 1H, J = 7.9 Hz). δ_C (400 MHz, $CDCl_3$): 43.61 (CH_2), 61.92

(CH), 102.82 (CH), 115.84 (CH), 119.02 (CH), 124.99 (CH), 126.48 (CH), 127.45

(CH), 128.25 (CH), 129.36 (CH), 129.92 (CH), 131.22 (CH), 138.14 (q), 144.85 (q),

149.41 (CH), 191.10 (q).

1-Phenyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyridin-4-one 271

271
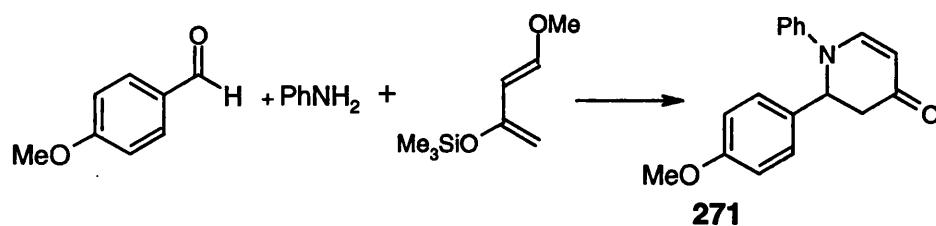
N-4-Methoxybenzaldehyde (1 mmol) and aniline (1 mmol) were reacted with Danishefsky's diene using the general procedure to provide 1-phenyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyridin-4-one as a white crystalline solid (isolated yield 71 %, 0.20 g). V_{max} (thin film)/cm^{-1}: 3066.7, 2836.7, 1646.4, 1578.1, 1511.2, 1363.1, 1301.8, 1250.8, 1217.9, 1180.3, 1036.6, 910.4, 830.1. δ_H (270 MHz, CDCl$_3$): 3.18-3.28 (d, 1H, J = 16.4 Hz), 3.70-3.79 (dd, 1H, J =5.9Hz), 4.23 (s, 3H), 5.7-5.8 (m, 2H), 7.28-7.34 (m, 2H), 7.48-7.8 (m, 7H), 8.10-8.16 (d, 1H, J = 7.9 Hz). δ_C (400 MHz, CDCl$_3$): 43.5 (CH$_2$), 55.1 (CH$_3$), 61.1 (CH), 102.46 (CH), 114.08 (CH), 118.40 (CH), 124.11 (CH), 127.06 (CH), 129.21 (CH), 129.52 (CH), 144.37 (q), 147.92 (CH), 158.76 (q), 190.01 (q). m/z (EI) (Found: $M+$ 309.2, Expected M, 309.2). CHN (Found: C, 75.9; H, 6.0; N, 4.8. C$_{18}$ H$_{17}$ NO$_2$ requires C, 77.4; H, 6.1; N, 5.0 %).

1-Phenyl-2-(2-fluorophenyl)-1,2,3,4-tetrahydropyridin-4-one 267

N-2-Fluorobenzaldehyde (1 mmol) and aniline were reacted with Danishefsky's diene using the general procedure to provide 1-phenyl-2-(2-fluorophenyl)-1,2,3,4-tetrahydropyridin-4-one as a straw yellow oil (isolated yield 84 %, 0.22 g). V_{max} (Nujol)/cm^{-1}: 3054.3, 2986.5, 1651.1, 1581.4, 1495.8, 1422.1, 1264.9, 1220.3, 1191.3, 1098.3, 896.0. δ_H (300 MHz, CDCl$_3$): 2.78-2.84 (m, 1H), 3.23-3.33 (dd, 1H, J =7.3, 9.1Hz), 5.29-5.32 (d, 1H, J =7.8 Hz), 5.58-5.61 (d, 1H, J =6.9 Hz), 7.02-7.51 (m, 9H), 7.71-7.74 (d, 1H, J = 7.7 Hz). δ_C (300 MHz, CDCl$_3$): 42.22 (CH$_2$), 56.59 (CH), 102.99 (CH), 116.57 (CH), 116.85 (CH), 118.78 (CH), 124.75 (CH), 124.80 (CH), 125.02 (CH), 125.09 (CH), 128.04 (CH), 130.01 (CH), 144.67 (q), 149.01 (CH),

158.54 (q), 161.80 (q), 190.60 (q). m/z (EI) (Found: $M+$ 268.1, Expected M, 268.1).

CHN (Found: C, 75.0; H, 5.2, N, 5.2. $C_{17} H_{14} FNO$ requires C, 76.4; H, 5.2; N, 5.2 %).

1-Phenyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydropyridin-4-one 270
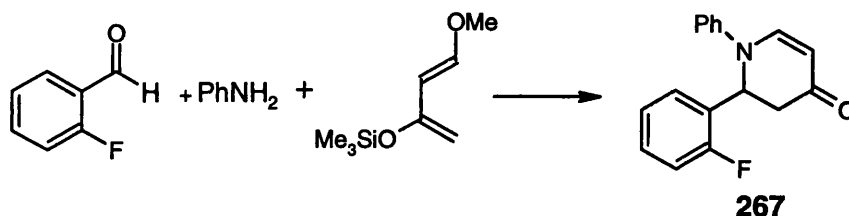

N-4-Nitrobenzaldehyde (1 mmol) and aniline (1 mmol) were reacted with Danishefsky's diene using the general procedure to provide 1-phenyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydropyridin-4-one as a brown crystalline solid (isolated yield 64 %, 0.19 g). The data for 1-phenyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydropyridin-4-one was consistent with that found in the literature[168]. V_{max} (Nujol)/cm^{-1}: 3055.1, 2982.5, 1643.9, 1573.9, 1519.4, 1494.1, 1466.1, 1346.2, 1299.1, 1208.8, 1104.2, 1040.0, 930.5, 855.9. δ_H (270 MHz, CDCl$_3$): 2.74-2.82 (m, 1H), 3.32-3.40 (dd, 1H, J =7,9,7Hz), 5.28-5.42 (m, 2H), 6.96-7.01 (m, 2H), 7.13-7.19 (m, 1H), 7.30-7.19 (m, 1H), 7.45-7.50 (m, 2H), 7.69-7.73 (dd, 1H, $J=$ 1,7,1Hz), 8.19-8.23 (m, 2H). δ_C (400 MHz, CDCl$_3$): 43.00 (CH$_2$), 61.31 (CH), 103.42 (CH), 118.41 (CH), 124.21 (CH), 127.18 (CH), 129.69 (CH), 144.01 (CH), 145.32 (q), 147.48 (q), 147.88 (CH), 188.83 (q). m/z (EI) (Found: $M+$ 295.2, Expected M, 295.2). CHN (Found: C, 69.2; H, 4.9; N, 9.6. $C_{17} H_{14} N_2 O_3$ requires C, 69.4; H, 4.8; N, 9.5 %).

1-Benzyl-2-(2-fluorophenyl)-1,2,3,4-tetrahydropyridin-4-one 268

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N-2-Fluorobenzaldehyde (1 mmol) and benzylamine (1 mmol) were reacted with Danishefsky's diene using the general procedure to provide 1-benzyl-2-(2-fluorophenyl)-1,2,3,4-tetrahydropyridin-4-one as a white crystalline solid (isolated yield 50 %, 0.14 g). V_{max} (thin film)/cm^{-1}: 3440.7, 3064.5, 3031.5, 2915.5, 1637.9, 1594.7, 1486.3, 1455.6, 1382.7, 1359.7, 1214.9, 1163.6, 1096.5, 910.8. δ_H (270 MHz, CDCl$_3$): 2.64-2.72 (dd, 1H, J = 6.3, 10.5, 6.3 Hz), 2.86-2.94 (dd, 1H, J = 7.4, 7.4, 7.4), 4.14-4.18 (d, 1H, J= 14.8 Hz), 4.37-4.41 (d, 1H, J= 15.2 Hz), 4.88-4.91 (t, 1H, J= 7.1, 6.6 Hz), 5.06-5.08 (d, 1H, J= 9.8 Hz), 7.04-7.19 (m, 4H), 7.30-7.39 (m, 6H). δ_C (400 MHz, CDCl$_3$): 41.84 (CH$_2$), 53.91 (CH), 57.64 (CH$_2$), 98.46 (CH), 115.91 (CH), 124.43 (CH), 124.95 (CH), 127.97 (CH), 128.00 (CH), 128.19 (CH), 128.84 (CH), 129.85 (CH), 135.57 (CH), 153.71 (CH), 158.89 (q), 161.34 (q), 189.65 (q). m/z (EI) (Found: M+ 282.2, Expected M, 282.2). CHN (Found: C, 75.7; H, 5.81; N, 4.9. C$_{18}$H$_{16}$FNO requires C, 76.8; H, 5.3; N, 5.0 %).

1-Phenyl-2-pyridyl-1,2,3,4-tetrahydropyridin-4-one 269

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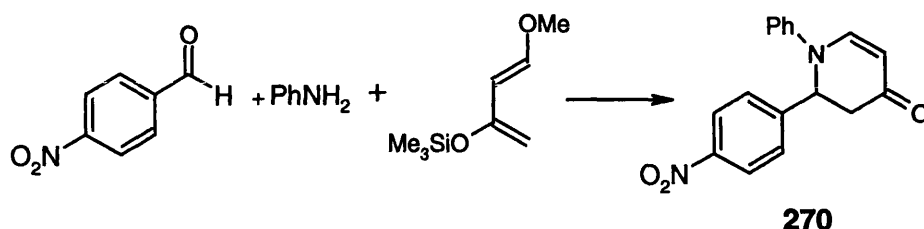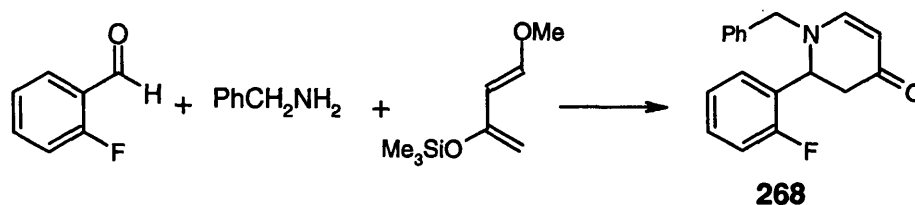N-Pyridinecarboxaldehyde (1 mmol) and aniline (1 mmol) were reacted with Danishefsky's diene using the general procedure to provide 1-phenyl-2-pyridyl-1,2,3,4-tetrahydropyridin-4-one as a brown crystalline solid (isolated yield 95 %, 0.24 g). V_{max} (thin film)/cm^{-1}: 3052.9, 2983.3, 1646.1, 1578.4, 1495.5, 1434.2, 1341.8, 1299.8, 1265.9, 1213.0, 1173.9, 1001.1, 929.7. δ_H (400 MHz, CDCl$_3$): 3.1-3.15 (m, 1H), 3.26-3.31 (dd, 1H), 5.29-5.32 (d, 1H), 5.35-5.37 (d, 1H), 7.0-7.06 (m, 2H), 7.1-7.34 (m, 4H), 7.58-7.64 (dt, 1H), 7.70-7.74 (dd, 1H), 8.63-8.65 (m, 1H). δ_C (400 MHz, CDCl$_3$): 41.50 (CH$_2$), 63.00 (CH), 103.41 (CH), 117.91 (CH), 120.32 (CH), 122.55 (CH), 124.18 (CH), 126.44 (CH), 129.49 (CH), 135.58 (CH), 136.69 (CH), 144.30 (q), 147.44 (CH), 150.04 (CH), 157.16 (CH), 190.20 (q). m/z (EI) (Found: $M+$ 251.2, Expected M, 251.2). CHN (Found: C, 74.2; H,5.6; N, 10.7 . C$_{16}$ H$_{14}$ N$_2$ O requires C, 76.8; H, 5.6, N, 11.2 %).

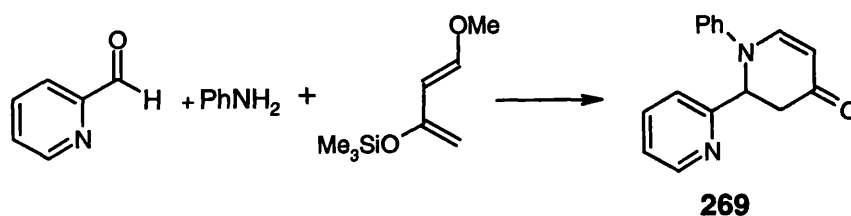## 1-Phenyl-2-furyl-1,2,3,4-tetrahydropyridin-4-one 272

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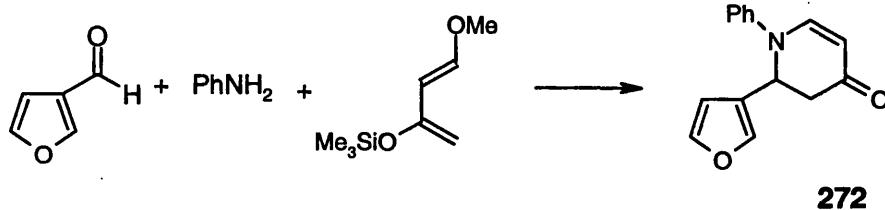
N-Furaldehyde (1 mmol) and aniline (1 mmol) were reacted with Danishefsky's diene using the general procedure to provide 1-phenyl-2-furyl-1,2,3,4-tetrahydropyridin-4-one as a dark brown oil (isolated yield 61 %, 0.15 g). The data for 1-Phenyl-2-furyl-1,2,3,4-tetrahydropyridin-4-one was consistent with that found in the literature[168], V_{max} (thin film)/cm^{-1}: 3053.3, 2983.1, 1648.4, 1579.3, 1494.7, 1433.2, 1340.4, 1265.9, 1175.6, 1014.3, 911.8. δ_H (270 MHz, CDCl$_3$): 2.84-2.92 (m, 1H), 3.12-3.20 (dd, 1H, 6.5, 9.9 Hz), 5.25-5.31 (m, 2H), 6.26-6.33 (m, 2H), 7.15-7.56 (m, 7H). δ_C (400 MHz,

CDCl$_3$): *m/z* (EI) (Found: *M+* 240.1, Expected *M*, 240.1). CHN (Found: C, 72.2; H, 5.6; N, 5.31. C$_{15}$ H$_{13}$ NO$_2$ requires C, 75.3; H, 5.4; N, 5.9 %).

CHAPTER 7

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CHAPTER 6. EXPERIMENTAL

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