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Some aspects of nitrogen heterocyclic chemistry

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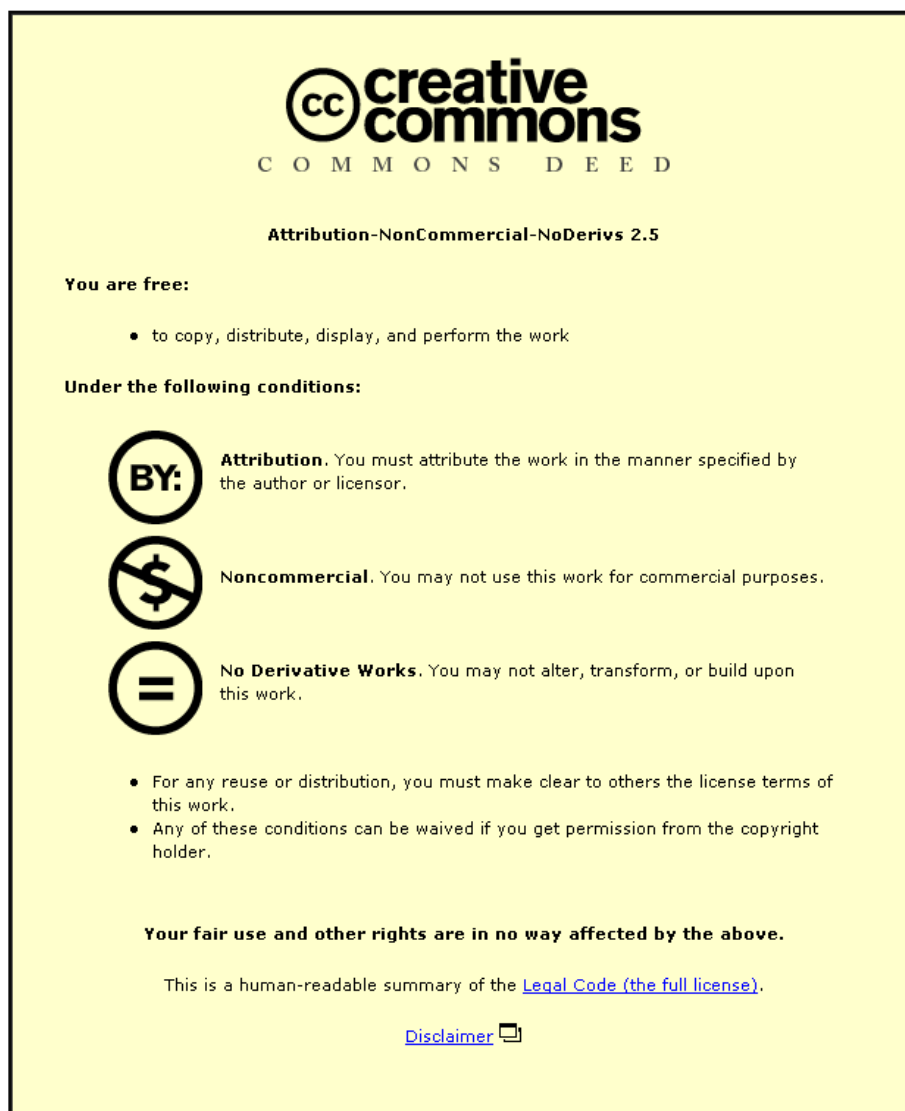
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Abstract

Chapter One reviews the use of scandium and lanthanide trifluoromethanesulfonates (triflates) in organic synthesis. Their ability to act as Lewis acids and so promote a wide variety of reactions are illustrated. In particular the review highlights the advantages of scandium and lanthanide triflates over more conventional Lewis acids, such as aluminium(III) chloride.

Chapter Two describes the use of scandium and lanthanide triflates in the reaction of acetals with amines to produce imines. The extension of this methodology to the synthesis of nitrogen-containing heterocycles such as isoindolones, isoquinolinones and β -carboline derivatives are elaborated on. Some limitations of the methodology and the problems encountered with its application to the synthesis of enamines are covered.

Chapter Three reports our approach to a novel synthesis of β -carboline derivatives. The formylation of indole-3-acetic acid derivatives in the 2-position proved difficult and several approaches to this problem are discussed. The attempted cyclisation of imines prepared from 2-formyl- and 2-acetyl-3-indolyl acetic acid compounds are also covered.

Chapter Four describes a modified Clauson-Kaas pyrrole procedure using trimethylsilyl triflate. The selection of reaction conditions in an effort to optimise the procedure are discussed.

Chapter Five provides full experimental procedures and analytical data for the reactions described in Chapters Two, Three and Four.

Some Aspects of Nitrogen Heterocyclic Chemistry

by

Michael Thomas Simcox

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

for the award


of

Doctor of Philosophy

of

Loughborough University

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Abbreviations

Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	<i>t</i> -butoxycarbonyl
BOM	<i>t</i> -butoxymethyl
b.p.	boiling point
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bu	butyl
de	diastereomeric excess
dec.	decomposed
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Et	ethyl
HFIP	hexafluoroisopropanol
Im	imidazole
IR	infrared
LDA	lithium diisopropylamine
Ln(OTf) ₃	lanthanide trifluoromethanesulfonate
Me	methyl
MOM	methoxymethyl
m.p.	melting point
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
Ph	phenyl
<i>i</i> Pr	isopropyl
r.t.	room temperature
TBDMS	<i>t</i> -butyldimethylsilyl
TBDPS	<i>t</i> -butyldiphenylsilyl
THP	tetrahydropyran
Tf	triflate or trifluoromethanesulfonate
THF	tetrahydrofuran
TMS	trimethylsilyl
TS	4-toluenesulfonyl

Chapter 1

Rare Earth Metal Triflates in Organic Synthesis

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1.1 Introduction

Lewis acids have been successfully used to catalyse a large number of chemical reactions. These have including several key carbon-carbon bond forming reactions, such as the aldol, Diels-Alder and Friedel-Crafts reactions. Their ability to provide high yields and selectivities under mild conditions have attracted considerable interest.

However, despite the impressive range of Lewis acid-promoted reactions that have been developed there are still some disadvantages associated with their use.

A major drawback of most Lewis acids is that their reactions have to be carried out under anhydrous conditions.¹ The presence of any significant amount of water stops the reaction. This is because most Lewis acids react immediately with water, rather than the substrates, and are decomposed or deactivated. This has restricted the use of Lewis acids. The fact that water decomposes most Lewis acids also makes it impossible to recover or reuse the catalyst because the majority of reactions using Lewis acids require an aqueous work-up.

The inability of Lewis acids to tolerate water can also cause difficulties with some substrates. The solubility or stability of some substrates make them difficult to use under anhydrous conditions. For example formaldehyde has to be generated as a gas immediately prior to its use in most hydroxymethylation reactions.

Another problem that can occur in certain reactions is that a catalytic amount of the Lewis acid is insufficient for the reaction to reach completion. For example during Friedel-Crafts acylation the Lewis acid is removed from the reaction by coordination to the aromatic ketones produced, so a stoichiometric amount is required.

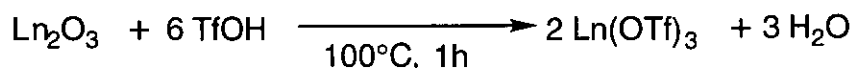
In recent years several groups have demonstrated that lanthanide compounds can act as Lewis acids.² In particular the lanthanide triflates, $\text{Ln}(\text{OTf})_3$, are strong Lewis acids because of the powerful electron withdrawing effect of the trifluoromethanesulfonate group. Similarly scandium(III) triflate, $\text{Sc}(\text{OTf})_3$, has also proved to be a notably efficient catalyst.³ This review will

examine the use of both lanthanide and scandium triflates in organic synthesis. The review will emphasise the advantages that their use has over more traditional Lewis acids and the progress made in surmounting the problems detailed above which hinder the wider application of Lewis acids in organic synthesis.

1.2 Preparation and Properties

Hydrolysis of the lanthanide triflates is postulated to be slow based on their hydration energies and their hydrolysis constants.⁴ These properties are demonstrated by the fact that lanthanide triflates have been prepared in aqueous solution. By contrast most Lewis acids have to be prepared under anhydrous conditions.

Lanthanide triflates are prepared by adding an excess of the lanthanide (III) oxide to an aqueous solution of trifluoromethanesulfonic acid (TfOH) (50% v/v) and heating to 100°C for up to 1 h.⁵ Filtration to remove unreacted oxide and evaporation of water gives the hydrate, the crystal structures of which have been reported,⁵ which is then dried by heating under vacuum at 200°C. **Scheme 1.1.**



Scheme 1.1

Scandium appears in group III of the periodic table and has chemical properties which lie between those of aluminium and those of the lanthanides, although they more closely resemble those of aluminium.⁶ Sc(OTf)₃ has been prepared from scandium(III) oxide (Sc₂O₃) by the same procedure used to prepare lanthanide triflates.⁷

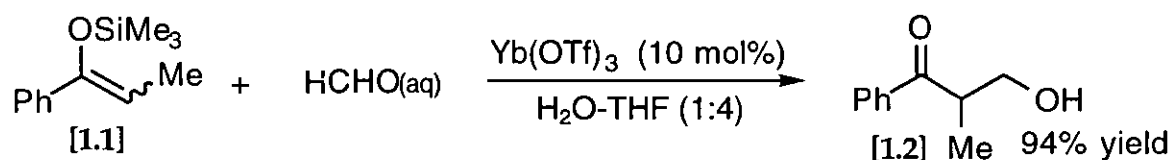
Both scandium and lanthanide triflates exhibit strong affinity for oxygen. This enables them to coordinate with oxygen atoms and allows them to catalyse a number of chemical reactions where the activation of oxygen is important. The fact that scandium and lanthanide triflates are stable in aqueous media offers the potential that they could act as water-tolerant Lewis acids. Several groups have investigated the possibilities of utilising scandium and lanthanide triflates in this way.

1.3 Rare Earth Metal Triflate Catalysed Reactions

1.3.1 Aldol Reactions

Kobayashi and co-workers have studied the ability of scandium and lanthanide triflates to catalyse aldol reactions in aqueous media.

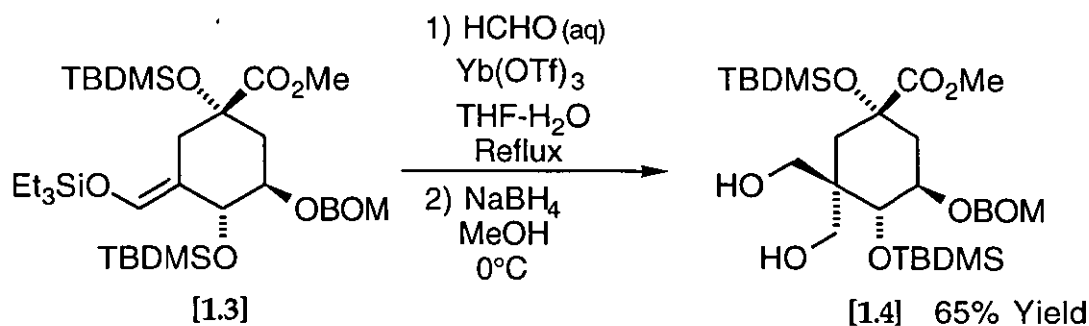
Initially the hydroxymethylation reactions of various silyl enol ethers with commercial aqueous formaldehyde solution using ytterbium triflate, Yb(OTf)₃, were examined.⁸ The reactions proceeded smoothly to give the aldol adducts in high yields. The best results were achieved when a mixed commercial formaldehyde solution-THF solvent system was used in the presence of a catalytic amount of Yb(OTf)₃. For example the silyl enol ether of propiophenone [1.1] gave the product [1.2] in 94% yield, Scheme 1.2.



Scheme 1.2

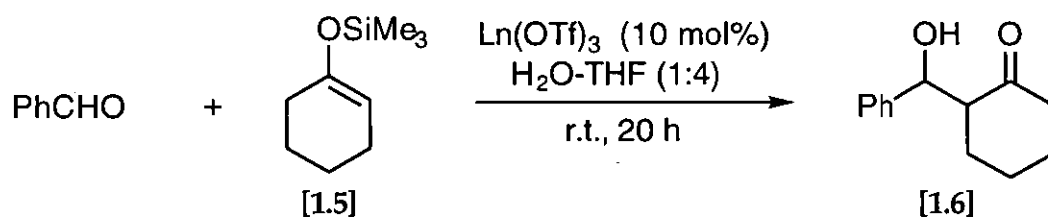
Previously hydroxymethylation required the generation of dry gaseous formaldehyde by the thermal depolymerisation of solid paraformaldehyde or from trioxane. Whereas commercial formaldehyde is easy to handle and stable even at room temperature. These reactions were carried out under extremely mild conditions and worked well with sterically hindered silyl enol ethers giving high diastereoselectivities. No poly-hydroxymethylated products were observed and the reactions were regiospecific as silyl enol ethers avoid the problems of double bond migration. As little as 1 mol% of Yb(OTf)₃ was required to catalyse the reaction, although the best results were achieved using 10 mol% of catalyst.

The utility of this methodology was demonstrated by its success in forming the spiro center in the desired product [1.4] from the silyl enol ether [1.3] in good yield, Scheme 1.3.⁹ By contrast when the reaction was attempted using activated hydroxymethyl equivalents with TiCl₄ or ZnCl₂ elimination of the C-4 TBDMSO group occurred to give the α,β -unsaturated aldehyde.



Scheme 1.3

Kobayashi screened a range of lanthanide triflates as catalysts in a model reaction of 1-trimethylsiloxycyclohexane [1.5] with benzaldehyde, **Scheme 1.4**.¹⁰ Most of the lanthanide triflates proved effective, but the yield of the aldol adduct [1.6] was significantly lower for lanthanum triflate La(OTf)_3 , praseodymium triflate Pr(OTf)_3 , europium triflate Eu(OTf)_3 and thulium triflate Tm(OTf)_3 , **Table 1.1**.



Scheme 1.4

Ln(OTf)_3	Yield%	Ln(OTf)_3	Yield%
La(OTf)_3	8	Dy(OTf)_3	73
Pr(OTf)_3	28	Ho(OTf)_3	47
Nd(OTf)_3	83	Er(OTf)_3	52
Sm(OTf)_3	46	Tm(OTf)_3	20
Eu(OTf)_3	34	Yb(OTf)_3	91
Gd(OTf)_3	89	Lu(OTf)_3	88

Table 1.1

The effect that altering the counter anion of the ytterbium salt had on the model reaction (**Scheme 1.4**) was studied.¹¹ Less nucleophilic anions such as OTf^- and ClO_4^- were found to catalyse the reactions effectively, but more

nucleophilic anions such as Cl⁻ and OAc⁻ gave only low yields. Ytterbium salts with less nucleophilic counter anions are more cationic, this indicates that the high Lewis acidity of the lanthanide triflates is required for the reaction to proceed efficiently.

Lanthanide triflates have proved to be effective in activating a number of aldehydes for aldol reactions with silyl enol ethers in aqueous media. The reactions produce the *syn* product with moderate selectivity, 20-46% de. Particularly impressive was the ability to catalyse reactions with substrates, such as salicylaldehyde and 2-pyridinecarboxaldehyde, which are normally problematic. Salicylaldehyde contains a free hydroxyl group which is incompatible with Lewis acids and 2-pyridinecarboxaldehyde generally deactivates Lewis acids because of coordination of the acid to the pyridine nitrogen. Both gave the aldol adducts in high yield.

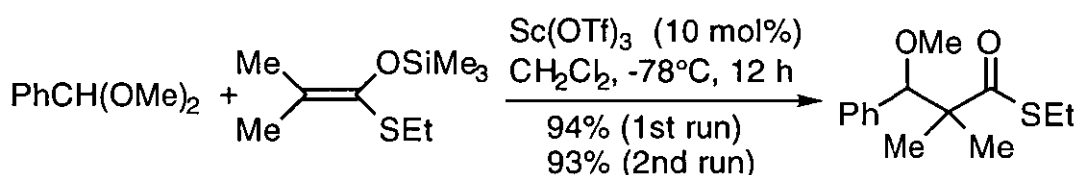
The amount of water present in the water-THF mixture has a profound effect on the yield. A study of the model reaction, **Scheme 1.4**, showed that the highest yields were obtained when 10-20 mol% of water was present.¹¹ When the amount of water increased beyond this level the yield decreased, at very high levels of water hydrolysis of the silyl enol ether competed with the desired aldol reaction. Although even when the reaction was carried out in 100% water solution an 18% yield of the aldol adduct was obtained. When THF alone was used only 10% of the product was formed. The authors proposed that the activity of THF coordinated Yb(OTf)₃ as a Lewis acid is low and that the most active Yb species for this reaction contains some water coordinated to the Yb(OTf)₃.

Lanthanide triflates are unable to catalyse reactions with ketene silyl acetals in aqueous media.¹² This is because hydrolysis of the ketene silyl acetal proceeds faster than the desired aldol reaction. However in organic solvents, such as dichloromethane, the reactions give the aldol products in high yields. In addition lanthanide triflates have also converted acetals into their corresponding aldol-type adducts.

Lanthanide triflates are more soluble in water than in organic solvents such as dichloromethane. After extraction of the product with dichloromethane the Ln(OTf)₃ is recoverable in almost quantitative yield on removal of water from the aqueous layer. This recovered catalyst is equally effective in

promoting aldol reactions. For example the reaction (**Scheme 1.2**) of the silyl enol ether of propiophenone [1.1] with formaldehyde using Yb(OTf)₃ gave the product [1.2] in 94% yield. The recycled Yb(OTf)₃ gave a 91% yield and the 3rd use a 93% yield. Lanthanide triflates are expected to solve some severe environmental problems induced by Lewis acid-promoted reactions in industrial chemistry.¹³

Scandium triflate shares the unique characteristics displayed by the lanthanide triflates. For example, Sc(OTf)₃ has proved to be an efficient Lewis acid catalyst in both organic and aqueous media. It has been successfully employed to catalyse the aldol reaction of aldehydes and acetals with silyl enol ethers and ketene silyl acetals. Scandium triflate was found to have a much higher catalytic activity than the lanthanide triflates in these reactions.¹⁴ This has enabled reactions in the presence of Sc(OTf)₃ to be carried out successfully at low temperatures such as -78°C. Furthermore Sc(OTf)₃ was almost quantitatively recoverable from the aqueous layer after work up of the reaction and the recovered catalyst was reused without loss of catalytic activity, for example **Scheme 1.5**.



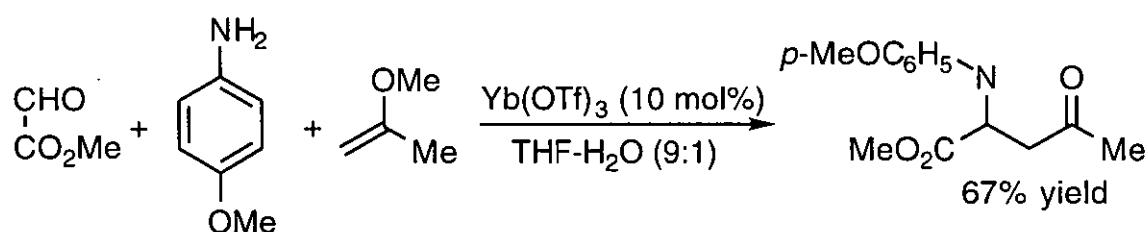
Scheme 1.5

More recently both Yb(OTf)₃ and Sc(OTf)₃ have been reported to catalyse aldol reactions in the absence of organic solvents using micellar conditions.¹⁵ The reactions are sluggish in pure water but show remarkably improved reactivity in the presence of a small amount of surfactant, such as sodium dodecylsulfate (0.2 equivalents). Scandium triflate was more reactive than Yb(OTf)₃ producing higher yields and required much shorter reaction times. The mechanism of this reaction is still under investigation.

Ytterbium enolates have been prepared by the sequential addition of a ketone and a tertiary amine to Yb(OTf)₃.¹⁶ The ytterbium enolates smoothly underwent cross-aldol additions to aldehydes with moderate to high *anti* selectivity (40-98% de). The existence of the ytterbium enolate was confirmed by trapping with chlorotrimethylsilane to afford the silyl enol ether.

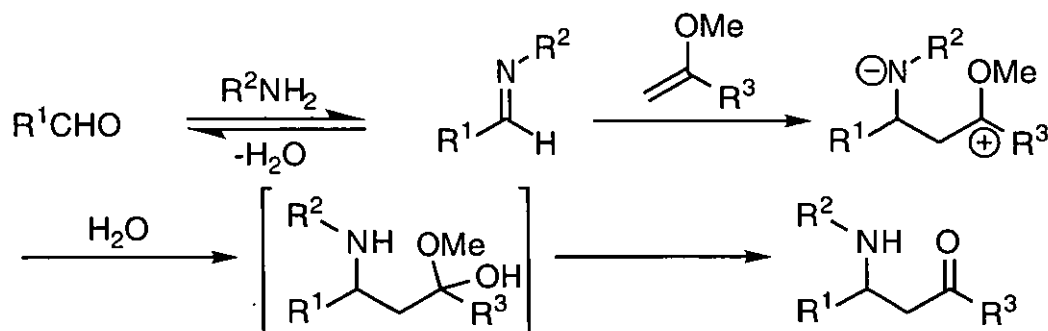
1.3.2 Mannich-type Reactions

Kobayashi has reported a novel Mannich-type reaction which allows β -amino ketones to be prepared in good yields by simply mixing an aldehyde, an amine and a vinyl ether with a catalytic amount of $\text{Yb}(\text{OTf})_3$.¹⁷ The reactions were stirred at room temperature for up to 24 h until complete and the catalyst could be recovered and reused without loss of activity. The utility of the procedure was demonstrated by its success with methyl glyoxylate, **Scheme 1.6**, and phenylglyoxal monohydrate. Mannich reactions of these aldehydes often give low yields because of the instability of their imines, and in some cases troublesome treatments are necessary for their use.



Scheme 1.6

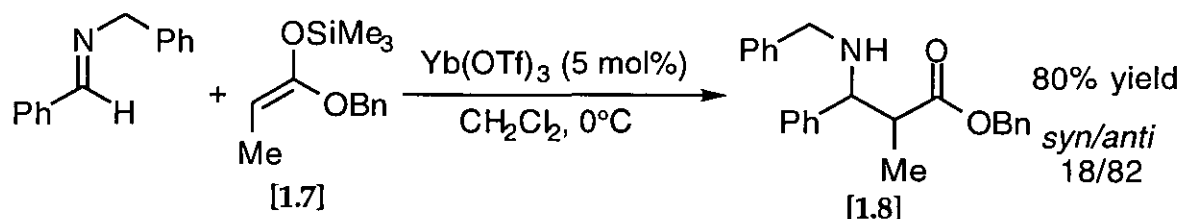
The authors proposed a possible mechanism for the reaction, **Scheme 1.7**. Initial imine formation was followed by addition of the vinyl ether, both reactions proceeded smoothly in aqueous solution.



Scheme 1.7

The Mannich-type reaction was also catalysed efficiently by $\text{Sm}(\text{OTf})_3$, $\text{Tm}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$.

Lanthanide triflates have also been used to activate imines to nucleophilic attack from ketene silyl acetals to give β -amino esters in high yield.¹⁸ The reactions proceeded with just 5 mol% of catalyst which could be recovered and reused. Yb(OTf)₃, Y(OTf)₃ and Sc(OTf)₃ were all used successfully with Sc(OTf)₃ being the most active. In reactions with the silyl enolate derived from benzyl propionate [1.7] the *anti* adduct [1.8] was obtained in reasonable selectivity (64% de), **Scheme 1.8**



Scheme 1.8

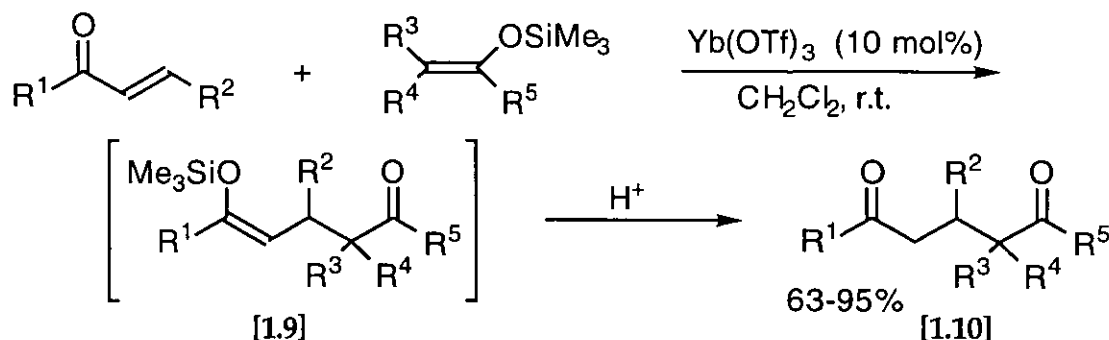
Lanthanide triflates catalyse the Mannich-type reaction of silyl enolates with *N*-(α -aminoalkyl)benzotriazoles,¹⁹ which behave as masked imines.²⁰ This produces the β -amino ketones or esters in high yields with no detectable side reactions. The reactions display high *anti* diastereoselectivities regardless of the geometry of the silyl enolates.

1.3.3 Reactions With Michael Acceptors

The Michael reaction of silyl enol ethers with α,β -unsaturated carbonyl compounds has been catalysed efficiently by Lewis acids.²¹ However the catalysts could not be recovered after the reactions were completed.

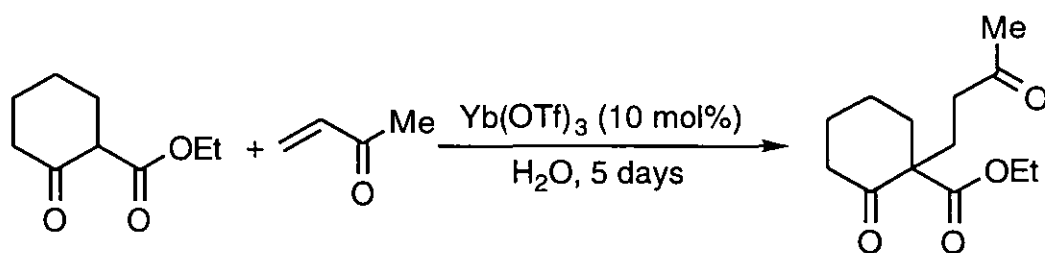
Lanthanide triflates are efficient reusable catalysts for the Michael reaction producing the 1,5-dicarbonyl compounds in good yields after an acid work up.²² The reactions proceeded under extremely mild conditions with as little as 1 mol% of catalyst present. Silyl enolates prepared from ketones, esters and thioesters all gave the desired products, without any 1,2-addition products being observed. All the lanthanide triflates screened (Ln(OTf)₃; Ln = La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, Er, Tm, Yb and Lu) worked well and they could be recovered almost quantitatively and reused without loss of activity. Scandium triflate proved equally efficient and displayed the same advantages as the lanthanide triflates.¹⁴ The reactions were carried out successfully in both organic and aqueous solvents resulting in high yields. The products

could be isolated as the synthetically useful silyl enol ether [1.9] if the crude adduct was worked up without acid, or acidified to give the 1,5-dicarbonyl compounds [1.10] in good yield, **Scheme 1.9**.



Scheme 1.9

Feringa investigated the use of $Yb(OTf)_3$ to catalyse Michael additions of β -ketoesters in water.²³ Both cyclic and acyclic β -ketoesters gave the desired Michael adducts in quantitative yield without hydrolysis of the ester functionality and in most examples no further purification was necessary after work-up. The reactions were carried out under mild conditions but required stirring for up to 5 days to give quantitative yields, **Scheme 1.10**. In several examples the β -ketoesters were present as suspensions, indicating that solubility did not influence the conversion. Attempting the reactions in organic solvents, such as THF, dioxane and dichloromethane, resulted in little or no reaction despite the presence of $Yb(OTf)_3$.

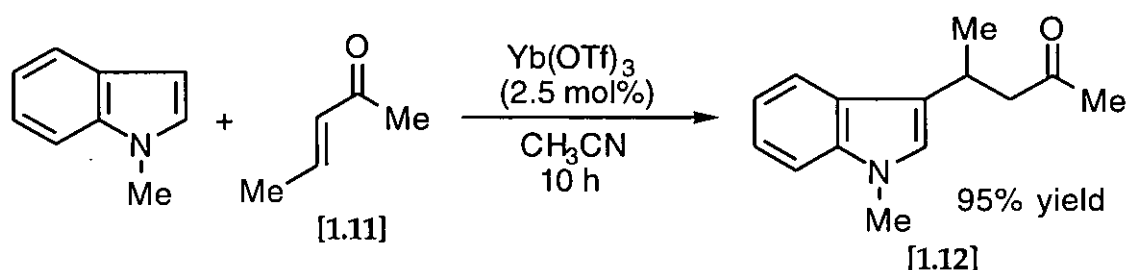


Scheme 1.10

When alternative Michael acceptors to methyl vinyl ketone were tested the results were disappointing. Of the electron deficient Michael acceptors that were tested only acrolein gave the 1,4-addition product, with acrylonitrile, ethyl acrylate and ethyl propiolate only starting materials were recovered. A number of α,β -unsaturated enones with different substituents were also

examined. It was found that only β -unsubstituted enones gave the desired product. The reduced reactivity of β -substituted α,β -unsaturated enones is not unexpected as these compounds often require more forcing conditions in conjugate addition reactions.²⁴

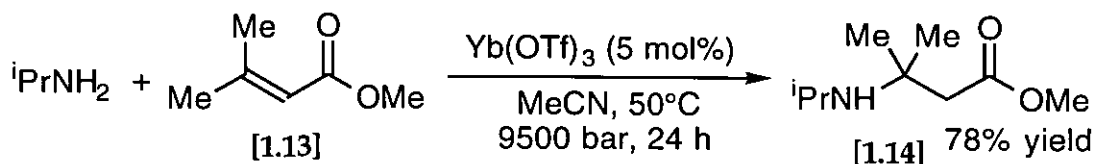
Ytterbium triflate has been reported to catalyse the alkylation of indoles in the 3-position with Michael acceptors.²⁵ For example *trans*-3-penten-2-one [1.11] reacts with 1-methylindole to yield the adduct [1.12] in excellent yield, Scheme 1.11.



Scheme 1.11

The structure of the Michael acceptor proved to be a critical factor in the success of the reaction. For example cyclohex-2-en-1-one gave only a 38% yield with 1-methylindole even after stirring for 7 days. The yields were also drastically reduced upon substitution at the β -carbon and many Michael acceptors failed to give any product. These included phenyl vinyl sulfone, ethyl cinnamate, methyl acrylate, acrylonitrile and several α,β -unsaturated aldehydes.

Ytterbium triflate has been used to catalyse the conjugate addition of amines with α,β -unsaturated esters to give β -aminoesters.²⁶ For example benzylamine is reported not to react with ethyl crotonate in dichloromethane at room temperature, but addition of Yb(OTf)₃ gave, after stirring for 15 h, a 92% yield of the conjugate addition product. High pressure has also been reported to improve these reactions,²⁷ Jenner has combined both methods to enable sterically hindered substrates to be converted to β -aminoesters.²⁸ The utility of the combined method is demonstrated by the reaction of methyl 3,3-dimethyl acrylate [1.13] with *iso*-propylamine, Scheme 1.12. No β -amino-ester [1.14] was formed at atmospheric pressure, but at 9500 bar without Yb(OTf)₃ the yield was 45% and when both high pressure and catalysis were used the yield increased to 78%.



Scheme 1.12

The yields of β -aminoester were variable depending on the substrate employed, but in all cases high pressure and $\text{Yb}(\text{OTf})_3$ catalysis combined gave a higher yield than use of either of the methods alone.

1.3.4 Friedel-Crafts Reactions

Friedel-Crafts alkylation and acylation reactions are key processes in organic chemistry.²⁹ Unfortunately, both processes suffer from disadvantages which hinder their use.

In Friedel-Crafts alkylations when the incoming alkyl group is electron releasing the initial product becomes activated to further alkylation, so poly-alkylated species are sometimes observed. Alkylation of substituted arenes containing functionality such as $-\text{OH}$, $-\text{OR}$ and $-\text{NH}_2$ can be inhibited because these groups readily coordinate to the Lewis acid, thereby reducing the desired coordination between the alkylating agent and the catalyst. The presence of electron-withdrawing groups deactivate the aromatic ring to alkylation which is why nitrobenzene cannot be alkylated under normal conditions.³⁰

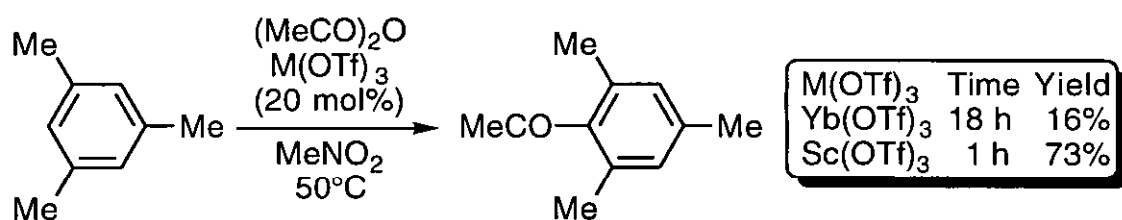
Friedel-Crafts acylations require greater than stoichiometric amounts of conventional Lewis acids such as AlCl_3 or BF_3 , because the catalyst coordinates to the aromatic ketone produced. This causes problems particularly in industrial processes because large amounts of residues derived from the catalyst remain after the usual aqueous work up.³¹

The Friedel-Crafts acylations of substituted benzenes with acid chlorides or anhydrides were found to proceed smoothly requiring only a catalytic amounts of lanthanide triflate.³² When acetic anhydride, acetonitrile or nitromethane were used as the solvent the reaction was homogeneous and the acylation reaction proceeded readily, with nitromethane giving the best results. When nitrobenzene or dichloromethane were used the reaction

mixture was heterogeneous and the yields were poor. Quantitative acylation was achieved when 20 mol% of $\text{Yb}(\text{OTf})_3$ was used, although 5 mol% still produced the acylation product in good yield.

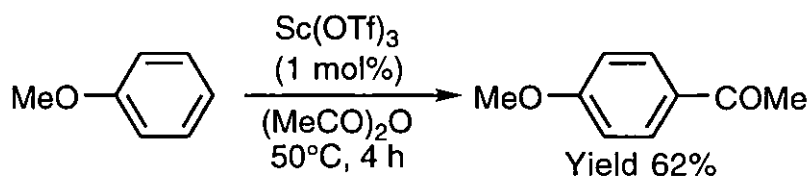
Benzene failed to be acylated under these conditions but methylthio- and dimethylamino- substituted benzenes gave the acylation product in high yield. Methyl substituted aromatics were also effective, for example *m*-xylene was converted to dimethylacetophenone in moderate yield. The catalyst was recoverable in almost 90% yield from the aqueous layer and could be used again.

Scandium triflate was found to be a more active catalyst for Friedel-Crafts acylations than lanthanide triflates. In the acetylation of mesitylene $\text{Sc}(\text{OTf})_3$ afforded a much higher yield in a much shorter reaction time than when $\text{Yb}(\text{OTf})_3$ was used, **Scheme 1.13**.



Scheme 1.13

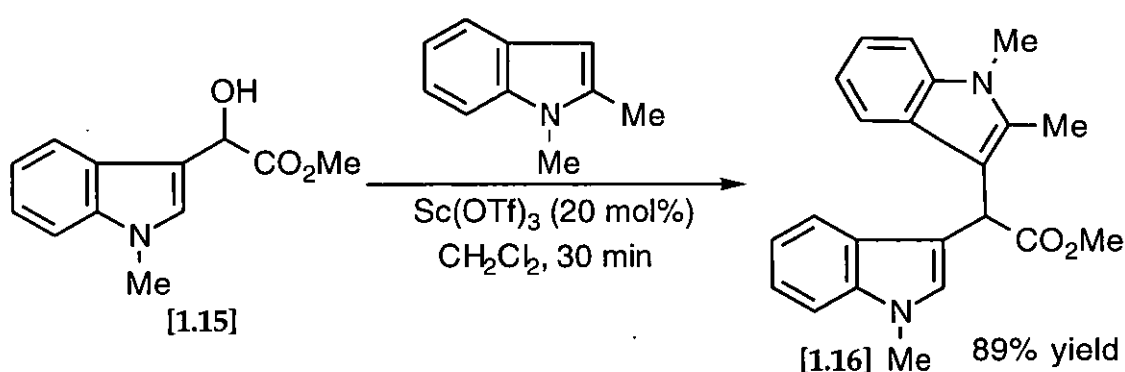
With $\text{Sc}(\text{OTf})_3$ it was possible to use as little as 1 mol% of the Lewis acid and still achieve a good yield of acylated product, **Scheme 1.14**.³³ The best yields were obtained when 20 mol% of $\text{Sc}(\text{OTf})_3$ was employed.



Scheme 1.14

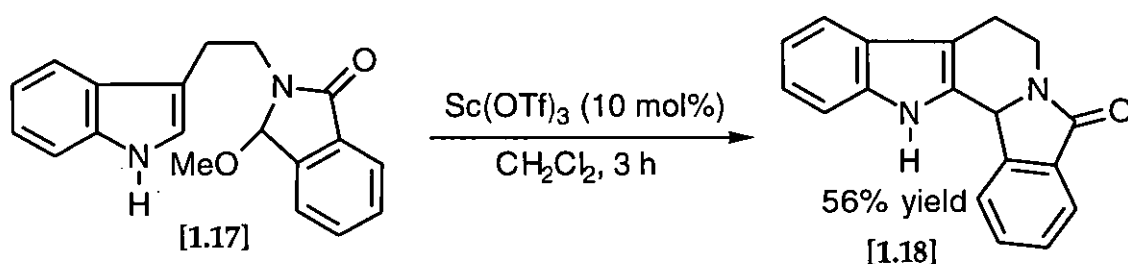
The catalyst can be recovered and re-cycled without loss of activity. One limitation is that less reactive aromatics such as benzene and toluene fail to give acylation products under $\text{Sc}(\text{OTf})_3$ catalysis.

Friedel-Crafts alkylation reactions have also been reported for a range of aromatics using either benzyl alcohols or indole carbinols as the alkylating agent, instead of the more troublesome alkyl halides.³⁴ Heaney reported that alkylation of methyl 1-methyl-3-indolyl- α -hydroxy-acetate [1.15] with 1,2-dimethylindole gave the product [1.16] in excellent yield, **Scheme 1.15**, and that the $\text{Sc}(\text{OTf})_3$ could be successfully recycled.^{34(a)}



Scheme 1.15

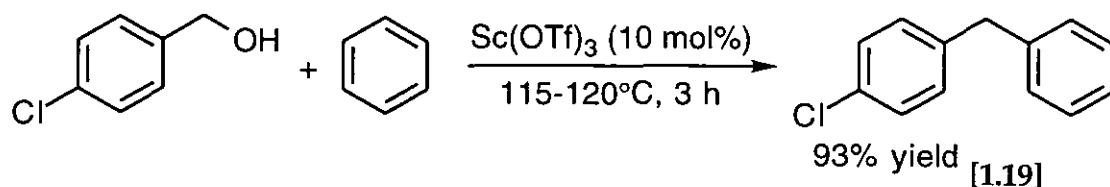
Scandium triflate has also been employed to catalyse Pictet-Spengler type cyclisations of acyliminium ions. For example α -methoxyisoindolone [1.17] was converted into the β -carboline derivative [1.18] in the presence of $\text{Sc}(\text{OTf})_3$ (10 mol%), **Scheme 1.16**.



Scheme 1.16

Fukuzawa has demonstrated that $\text{Sc}(\text{OTf})_3$ is an efficient catalyst for alkylation of aromatics with various benzyl alcohol derivatives.^{34(b)} For example benzene reacted with 4-chlorophenylmethanol to give the

diarylmethane [1.19] in excellent yield, **Scheme 1.17**. However, both 4-nitro and 4-hydroxyphenylmethanol failed to give benzylated products under these conditions.

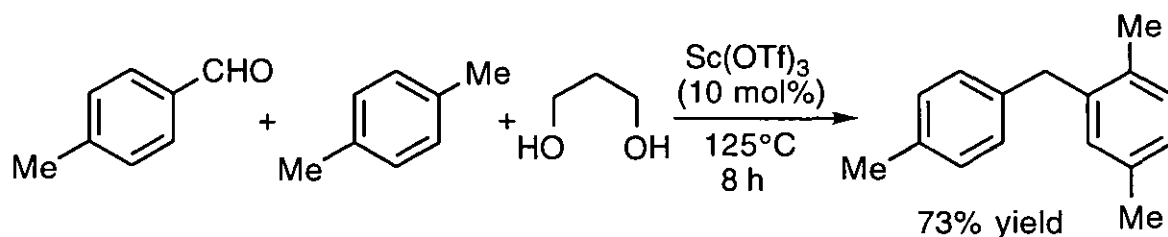


Scheme 1.17

The isomer distribution when substituted arenes were used showed an *ortho-para* preference, consistent with typical electrophilic aromatic substitutions.³⁵

The procedure was extended to the Friedel-Crafts allylation of benzene with allylic alcohols.^{34(b)} The allyl benzene derivatives were formed in good yields with reactions occurring at the less substituted allylic carbon site. The reactions preferentially gave the *trans* isomer and the stereochemistry was found to be time independent, indicating kinetic control.

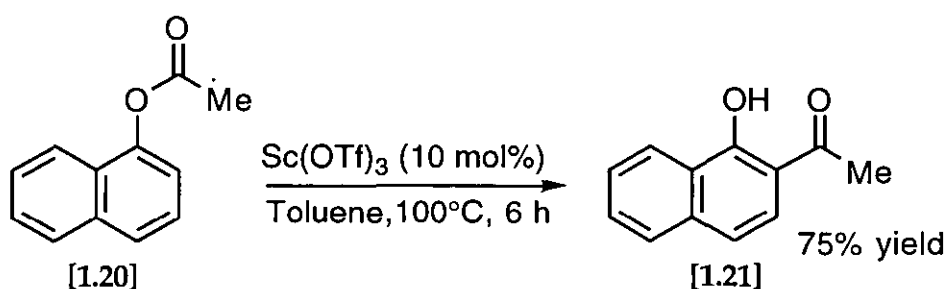
Scandium triflate also catalyses the Friedel-Crafts benzylation of aromatic compounds with arenecarbaldehydes and propane-1,3-diol.³⁶ The reaction produces, *via* a clean redox process, diarylmethanes in good yields, **Scheme 1.18**. The reaction is postulated to proceed via the acetal, and isotopic-labelling experiments have confirmed that the diol acts as the hydride source. When lanthanide triflates such as Y(OTf)₃, Nd(OTf)₃, Sm(OTf)₃ and Yb(OTf)₃, were used instead of Sc(OTf)₃ the reaction failed to produce any of the desired product. With substituted arenes the expected *ortho-para* preference was observed.



Scheme 1.18

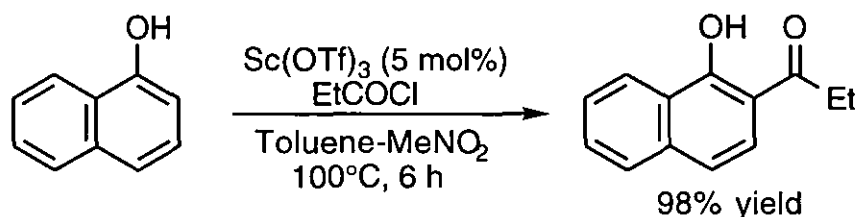
1.3.5 Fries Rearrangements

The Fries rearrangement is a method for preparing hydroxyarylketones which has been used both industrially and on a lab scale.³⁷ Unfortunately the reaction requires a greater than stoichiometric amount of Lewis acid because most Lewis acids are deactivated by the free hydroxy group of the products. However, the Fries rearrangement of acyloxy naphthalenes to hydroxynaphthyl ketones have been catalysed with a catalytic amount of $\text{Sc}(\text{OTf})_3$.³⁸ 1-Naphthyl acetate [1.20] was converted into 1-hydroxy-2-acetonaphthone [1.21] in good yield using only 10 mol% of $\text{Sc}(\text{OTf})_3$, **Scheme 1.19**. By comparison other Lewis acids such as $\text{Yb}(\text{OTf})_3$, TiCl_4 , AlCl_3 , SnCl_4 and $\text{BF}_3 \cdot \text{OEt}_2$ all yield less than 10% of the desired product when used catalytically. Indeed when an excess (140 mol%) of AlCl_3 was used the yield was only 61%.³⁹



Scheme 1.19

This methodology has recently been extended to a one pot 2-acylation reaction of both phenol and 1-naphthol derivatives using acyl chlorides.⁴⁰ It is assumed that the scandium triflate (5 mol%) catalyses both the initial ester formation and the *in-situ* Fries rearrangement, **Scheme 1.20**. This procedure was found to give higher yields than the Fries rearrangement using acyloxy derivatives.



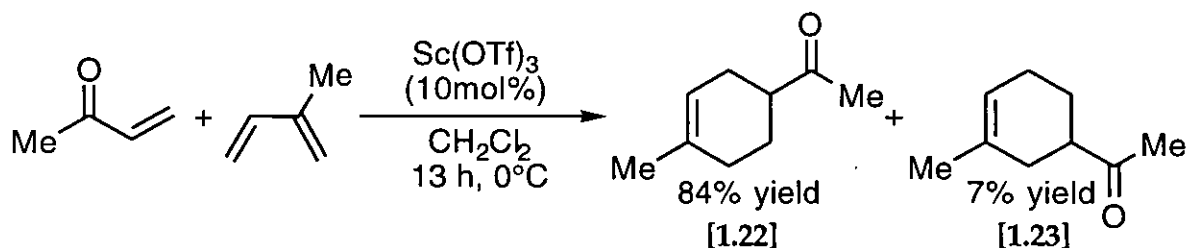
Scheme 1.20

1.3.6 Diels-Alder Reactions

The Diels-Alder reaction is one of the most important synthetic methods in organic chemistry. However many Diels-Alder reactions require high temperatures, thus limiting the substrates that can be employed in these reactions. Lewis acid catalysis have allowed the reactions to proceed under milder conditions but they are often accompanied by diene polymerisation and when carbonyl containing dienophiles are used excess amounts of the catalyst are often necessary.⁴¹

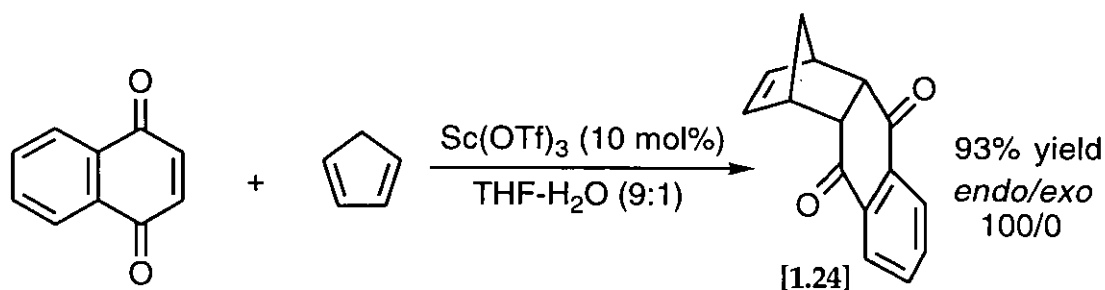
Both $\text{Yb}(\text{OTf})_3$ and $\text{Y}(\text{OTf})_3$ have proved capable of catalysing Diels-Alder reactions of carbonyl containing dienophiles with cyclopentadiene.²² A catalytic amount of lanthanide triflate gave the adducts in high yields, and the catalyst could be recycled successfully.

Scandium triflate has also been applied to the Diels-Alder reaction of carbonyl containing dienophiles with both cyclic and acyclic dienes affording the adducts in good yield at 0°C .^{7,42} Scandium triflate was clearly more effective than the lanthanide triflates in promoting the Diels-Alder reaction. The model reaction of methyl vinyl ketone with isoprene gave only a trace amount of the product when $\text{Yb}(\text{OTf})_3$ or $\text{Y}(\text{OTf})_3$ were used. However with $\text{Sc}(\text{OTf})_3$ (10 mol%) the reaction yielded 91% of the Diels-Alder adducts [1.22] and [1.23], **Scheme 1.21**.⁷



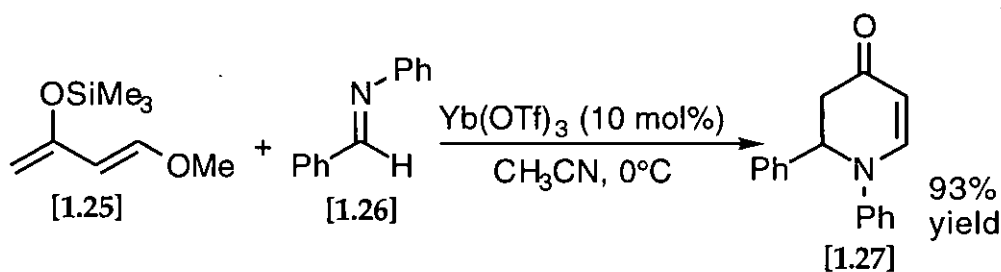
Scheme 1.21

The Diels-Alder reactions were carried out successfully in aqueous media affording the adduct with high *endo* selectivity (68-100%). Thus, naphthoquinone reacted with cyclopentadiene to give the corresponding adduct [1.24] with high yield and selectivity, **Scheme 1.22**. It was again possible to recover and reuse the catalyst under these reaction conditions.



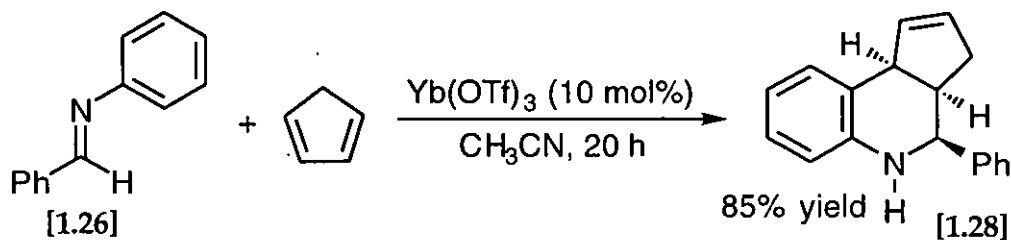
Scheme 1.22

Lanthanide triflate catalysis has also been applied to the imino Diels-Alder reaction of imines with dienes or alkenes, which has been recently reviewed by Kobayashi.⁴³ Although other Lewis acids often promote these reactions, greater than stoichiometric amounts of the Lewis acid were required due to strong coordination of the acids to nitrogen atoms.⁴⁴ The reaction of Danishefsky's diene [1.25] and the imine [1.26] with $\text{Yb}(\text{OTf})_3$ (10 mol%) gave the tetrahydropyridine derivative [1.27] in excellent yield, Scheme 1.23.¹⁸



Scheme 1.23

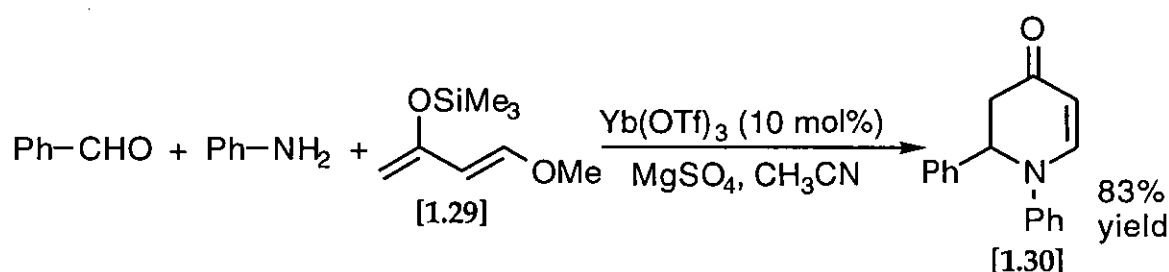
When the same imine [1.26] was reacted with cyclopentadiene the Diels-Alder reaction went by an alternative route.¹⁸ The imine acted as an azadiene and one of the double bonds of cyclopentadiene as a dienophile resulting in the tetrahydroquinoline product [1.28], Scheme 1.24.⁴⁵



Scheme 1.24

Scandium triflate and some of the lanthanide triflates such as $\text{Er}(\text{OTf})_3$ and $\text{Tm}(\text{OTf})_3$ gave better yields than $\text{Yb}(\text{OTf})_3$. Tetrahydroquinoline derivatives were also formed in high yields when a vinyl sulfide, a vinyl ether and a silyl enol ether were used as dienophiles.^{43,46} Interestingly when ketene silyl acetals were used in the reaction imino aldol products were formed and no cyclisation products were observed.⁴⁶

Kobayashi has developed an efficient one-pot three component coupling procedure between aldehydes, amines and alkenes to afford pyridine and quinoline derivatives.⁴⁷ Both $\text{Yb}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$ catalysed the imine formation and successive imino Diels-Alder reaction to give the desired products in good yields. For example, $\text{Sc}(\text{OTf})_3$ (10 mol%) and benzaldehyde were treated successively with aniline and Danishefsky's diene [1.29] to give the tetrahydropyridine derivative [1.30], **Scheme 1.25**. The $\text{Sc}(\text{OTf})_3$ retained its activity in the presence of both the amine and the water produced in the imine formation. When one equivalent of other Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ and ZnCl_2 were used to promote the same reaction much lower yields were observed (23% and 12% respectively).



Scheme 1.25

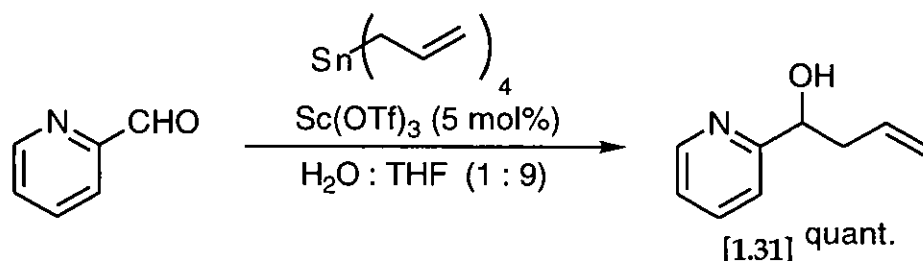
Impressively, the reaction worked efficiently with phenylglyoxal monohydrate whose imine is known to be highly hygroscopic and its purification by distillation or chromatography is very difficult due to its instability.^{45(a)} It was also possible to use commercial formaldehyde solution directly in the three component reaction. Recently Wang reported the lanthanide promoted aqueous aza Diels-Alder reaction of chiral aldehydes, prepared from carbohydrates, with benzylamine hydrochloride and cyclopentadiene.⁴⁸ The nitrogen-containing heterocyclic adducts were subsequently transformed into azasugars. Ytterbium triflate has also catalysed the hetero Diels-Alder reaction of a thiabutadiene with a chiral dienophile,

which gave the desired adduct in excellent yield with good π -facial selectivity.⁴⁹

1.3.7 Allylation Reactions

The addition of allyl organometallics to carbonyl compounds to give homoallylic alcohols has been used extensively in organic synthesis.⁵⁰ Allylation of both aldehydes and ketones using tetraallyltin under the influence of catalytic $\text{Sc}(\text{OTf})_3$ gave the homoallylic alcohols in high yield.⁵¹ The reactions were carried out successfully in both organic, CH_3CN or CH_2Cl_2 , and aqueous media, $\text{H}_2\text{O}/\text{THF}$ (1:9) or $\text{H}_2\text{O}/\text{EtOH}$ (1:9).

Use of aqueous conditions enabled unprotected sugars to be used directly, the allylated adducts obtained are intermediates in the synthesis of higher sugars.⁵² Other challenging substrates such as 2-pyridine-carboxaldehyde, which reacts with the Lewis acid rather than with the nucleophile under general Lewis acid conditions, also gave the homoallylic alcohol [1.31] in excellent yield, **Scheme 1.26**.



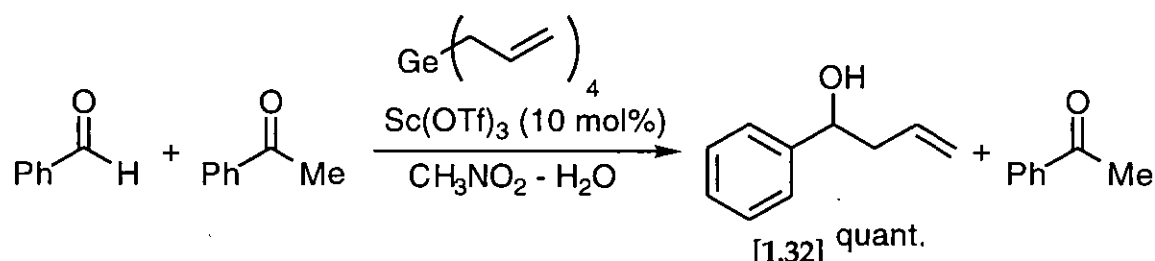
Scheme 1.26

Other reagents have proved to be effective in the allylation of carbonyl compounds. Ytterbium triflate catalyses the reaction of both aliphatic and aromatic aldehydes using the less reactive allyltributyltin as the allylating agent.⁵³ Allyltrimethylsilane has also been employed as the allylating agent in the allylation of aldehydes in the presence of as little as 2 mol% $\text{Sc}(\text{OTf})_3$.⁵⁴

Although little attention has been paid to germanium compounds,⁵⁵ they offer the advantage of being less toxic than organotin compounds.⁵⁶ Recently the $\text{Sc}(\text{OTf})_3$ promoted allylation of carbonyl compounds with tetraallylgermane in aqueous media has been reported.⁵⁷ The amount of water present strongly influenced both the yield and the rate of the reaction.

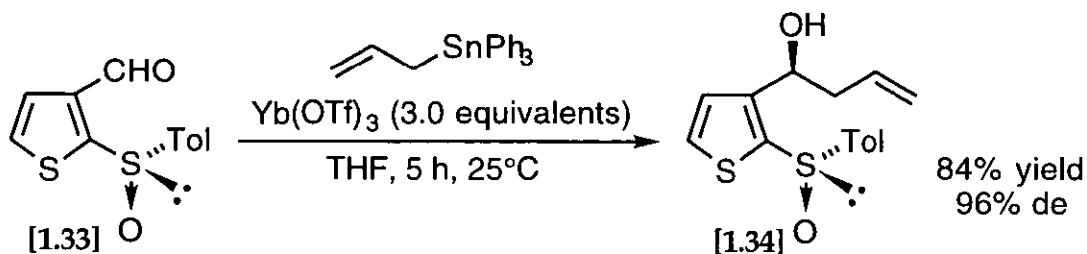
As the ratio of water increased the yield improved although the reaction rate slowed. The optimum conditions were when 30-40 equivalents based on $\text{Sc}(\text{OTf})_3$ were employed. Above this level water began to retard the reaction, reducing both the rate and the yield of the reaction. As with the corresponding tin reagent the tetraallylgermane was capable of transferring more than one of the allyl groups, however the reaction time had to be increased and the yield was lower in this case.

This reaction system also exhibited very high chemoselectivity towards aldehydes, this has been achieved in only a few previous examples.⁵⁸ Competitive allylation between benzaldehyde and acetophenone (1:1) gave exclusively the allylation product from benzaldehyde [1.32] in excellent yield, **Scheme 1.27**.



Scheme 1.27

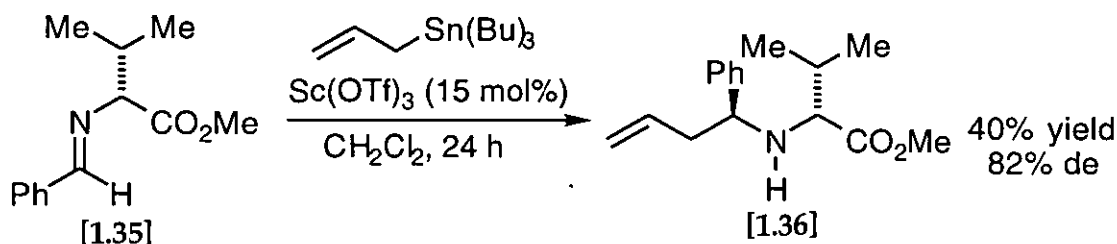
Arai has used an optically active sulfoxide substituent as a chiral auxiliary in the allylation of a thiophenecarbaldehyde with allyltriphenylstannane.⁵⁹ The allylation of [1.33] using $\text{Yb}(\text{OTf})_3$ gave the product [1.34] in excellent yield and diastereoselectivity at ambient temperature, **Scheme 1.28**. Other Lewis acids such as SnCl_4 , TiCl_4 , $\text{Sm}(\text{OTf})_3$ and $\text{Nd}(\text{OTf})_3$ gave lower stereoselectivity even when the reactions was carried out at low temperature.



Scheme 1.28

The addition of allyltributylstannane to imines promoted by either lanthanide or scandium triflates gave the corresponding homoallylic amines.⁶⁰ The yields achieved varied greatly, although the only side products observed were hydrolysed and unreacted imine. Both the structure of the imine and the amount of the catalyst employed were important factors in determining the yield. The group attached directly to the nitrogen played a crucial role, with aromatic groups being the most effective substituents. A catalyst loading of 15 mol% was sufficient in most cases, although higher loadings were sometimes required.

The imine derived from glyoxylic acid was converted into the homoallylic aminoester, without any attack of the allylating species on the ester group, resulting in a precursor of non-proteogenic aminoacids. Chiral imines were allylated yielding the desired product with good stereoselectivity, albeit in moderate yield. The imine [1.35], derived from benzaldehyde and *S*-valine methyl ester afforded the *S,S*-diastereoisomer [1.36], chelation between the imine and Sc(OTf)₃ accounts for the stereoselectivity, **Scheme 1.29**.



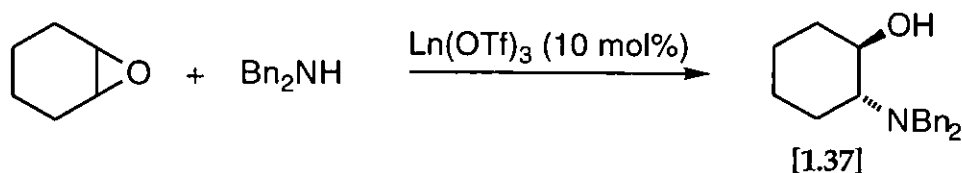
Scheme 1.29

1.3.8 Ring Opening Reactions

The ring opening of epoxides with amines is the most direct and simplest route to the synthesis of β -amino alcohols. However, the low nucleophilicity of amines requires elevated temperatures. Sterically bulky amines in particular display low reactivity and regiocontrol can be difficult.⁶¹ The use of metal amides has allowed some of these problems to be overcome,⁶² but an efficient direct ring opening of epoxides with amines is desirable.

The Yb(OTf)₃ catalysed reaction of cyclohexene oxide with dibenzylamine proceeded smoothly giving the *trans*-2-(*N,N*-dibenzylamino)

cyclohexanol [1.37] in a 99% yield after refluxing in THF for 12 h , **Scheme 1.30**.⁶³



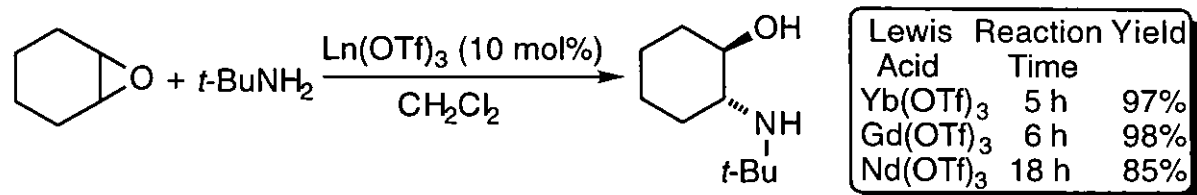
Scheme 1.30

In trial investigations using this reaction, **Scheme 1.30**, Yb salts other than the triflate proved much less effective. A disappointing 65% yield was obtained with YbCl_3 , whilst none of the β -amino alcohol [1.37] was observed with YbF_3 , $\text{Yb}(\text{OPri})_3$, $\text{Yb}(\text{NBn}_2)_3$ and $\text{Yb}(\text{CN})_3$. A study of the effectiveness of several lanthanides showed that the triflates of La, Pr, Sm, Eu, Dy, Er and Yb all efficiently gave the product [1.37] in greater than 95% yield. Only the triflates of Nd (70%yield), Gd (45%) and Ho (88%) gave less satisfactory results. The effect of reducing the amount of $\text{Yb}(\text{OTf})_3$ was also investigated, 5 mol% of $\text{Yb}(\text{OTf})_3$ gave a 98% yield. Impressively 1 mol% still gave a 75% yield indicating the remarkably high catalytic activity of $\text{Yb}(\text{OTf})_3$ in this reaction.

The $\text{Yb}(\text{OTf})_3$ catalysed ring opening of a range of epoxides with several different amines was achieved in good to high yields. The ring opening proceeded with complete *anti* selectivity and preferential attack at the least hindered carbon of asymmetric epoxides. Even with tri- and tetra-substituted epoxides good yields could be obtained by using an excess of amine (2-3 equivalents) and increasing both the reaction time and the catalyst loading (20 mol%).

The authors also reported that the ring opening can be accomplished in the absence of any catalyst when high pressure is used. For example the product [1.37] was formed in 90% yield when the reactants were stirred at room temperature under a pressure of 10 kbar although a longer reaction time of 6 days was required. Combining both high pressure and catalysis proved more effective than using either method independently.

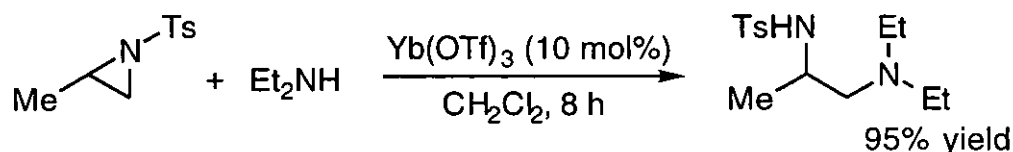
Crotti and co-workers have reported the aminolysis of epoxides by stirring at room temperature in a non protic solvent (dichloromethane or toluene) using lanthanide triflates.⁶⁴ Whilst $\text{Gd}(\text{OTf})_3$ gave comparable yields to $\text{Yb}(\text{OTf})_3$, $\text{Nd}(\text{OTf})_3$ was less efficient even with increased reaction times. **Scheme 1.31**.



Scheme 1.31

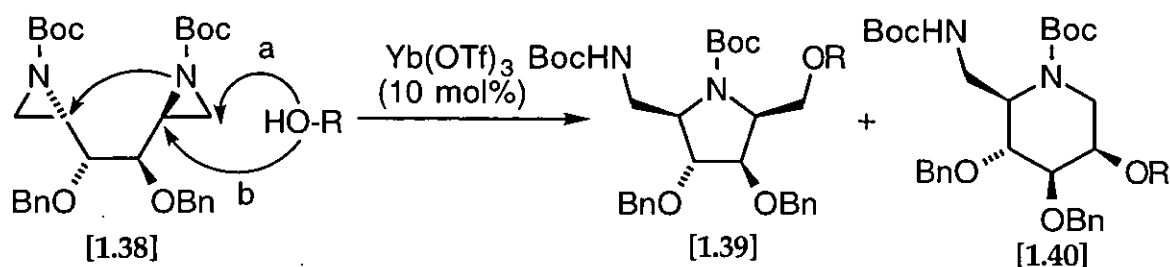
With a tetrasubstituted epoxide a higher catalyst loading of 50 mol% and longer reaction time, 24 h, was required. Reactions under these conditions displayed complete *anti* selectivity and high regioselectivity for attack at the least hindered carbon of the epoxide.

In analogous fashion to epoxides nitrogen-protected aziridines were smoothly converted to 1,2-diamines by refluxing in CH_2Cl_2 with a catalytic amount of $\text{Yb}(\text{OTf})_3$.⁶⁵ The use of *N*-protected aziridines (e.g. tosyl, benzyl or Boc) was essential since unprotected aziridines may themselves act as nucleophiles leading to oligomers or polymers. Again attack of the nucleophile at the least hindered carbon was favoured, **Scheme 1.32**, although in some cases significant amounts of the other regioisomers were produced. With the more sterically demanding tri-substituted aziridines the reaction was slower and unidentified polymers were produced as by-products. Other catalysts which proved effective in opening aziridines were $\text{La}(\text{OTf})_3$, $\text{Sm}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$ and $\text{Pr}(\text{OTf})_3$.



Scheme 1.32

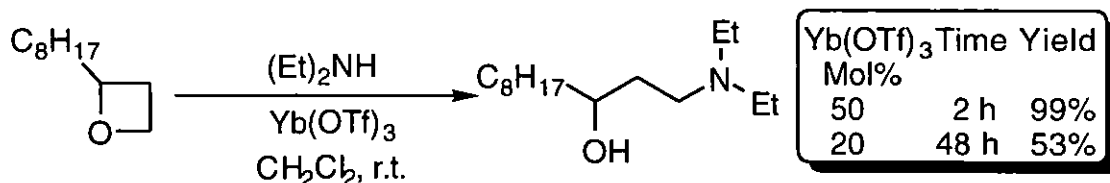
Dur  ault has extended this methodology to the synthesis of azasugars using the C₂ symmetrical bis-aziridine [1.38].⁶⁶ The Yb(OTf)₃ catalysed opening of [1.38] using allylic alcohol or water can take place at either C-1 or C-2 and it proceeds with S_N1 characteristics. Attack at C-1 (path a) provides, after nitrogen intramolecular cyclisation, the tetrasubstituted pyrrolidine [1.39] of D-gluco configuration, while attack at C-2 (path b) leads to the piperidine [1.40] of D-mano configuration via a 6-*exo-tet* process. The nitrogen intramolecular cyclisation step is almost exclusively a 5-*exo* process, **Scheme 1.33**.



Scheme 1.33

With both allylic alcohol and water attack at C-2 leading to the piperidine [1.40] was favoured. The piperidine [1.40] was obtained in a 50-55% yield as opposed to the pyrrolidine [1.39] which was isolated in 27% yield in both cases. By contrast when BF₃-OEt₂ was used the reaction with allylic alcohol displayed no regioselectivity and gave a lower overall chemical yield.

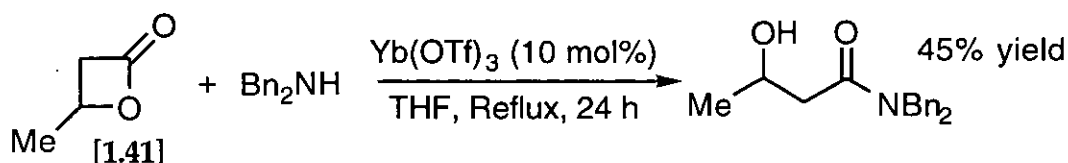
The lanthanide(III) triflate catalysed ring opening procedures developed have been applied to several other strained heterocyclic systems. Crotti has shown that Ln(OTf)₃ catalyse the reaction of 4-membered ring oxetanes with amines to give γ-amino alcohols.⁶⁷ A high catalyst loading of 50 mol% was found to be necessary for optimum results, **Scheme 1.34**. The reaction exclusively formed the γ-amino alcohol produced by attack of the nucleophile at the least hindered carbon. By contrast a 4-membered ring nitrogen analogue, 1-tosylazetidine, failed to react with amines under these conditions.^{65(b)}



Scheme 1.34

Among the $\text{Ln}(\text{OTf})_3$ tested, the order of effectiveness was found to be $\text{Yb}(\text{OTf})_3 > \text{Gd}(\text{OTf})_3 \gg \text{Nd}(\text{OTf})_3$. Particularly noteworthy was the success of $\text{Yb}(\text{OTf})_3$ in catalysing the aminolysis of 2-phenyloxetane to give greater than 90% yield of ring opened products after stirring for 2 h. Previous methods using LiClO_4 or LiBF_4 gave much poorer yields even after heating to 80°C for 48 h. Unfortunately with this substrate a mixture of regioisomers are formed, although the regioisomer formed by nucleophilic attack at the less substituted carbon α - to the oxetane oxygen is still the main product.

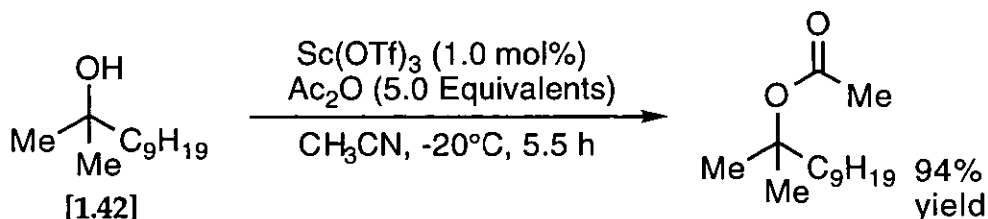
Yamamoto has also shown that $\text{Yb}(\text{OTf})_3$ catalyses the ring opening of the β -lactone [1.41] although the yield was slightly disappointing, **Scheme 1.35**.



Scheme 1.35

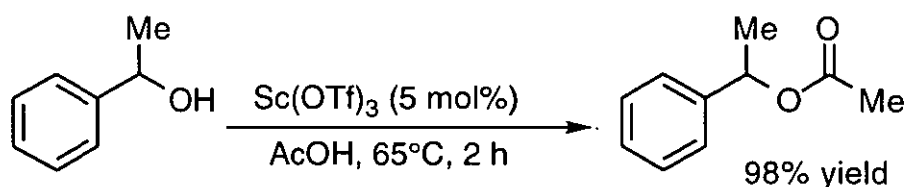
1.3.9 Acylation and Esterification Reactions

Yamamoto has shown $\text{Sc}(\text{OTf})_3$ to be one of the most effective catalysts available for the acylation of alcohols with acid anhydrides, as little as 0.1 mol% $\text{Sc}(\text{OTf})_3$ was required for primary alcohols.⁶⁸ The very mild conditions employed allowed sterically hindered alcohols such as 2-methyl-2-dodecanol [1.42] to be converted successfully, the common elimination side-products were effectively prevented by the use of low temperature, **Scheme 1.36**. For more acid sensitive allylic and benzylic tertiary alcohols use of acetic anhydride as the solvent at low temperature allowed the desired acetate to be formed in good yield (>68%), with only minimal formation of primary acetates produced by 1,3-migration of the acetoxy group (<15%).



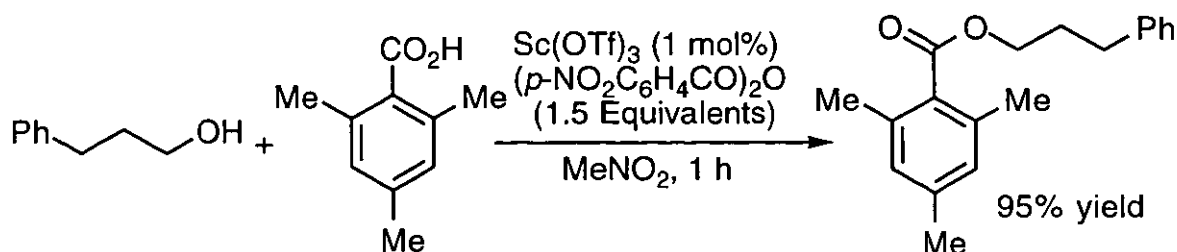
Scheme 1.36

However, the use of anhydrides is inherently wasteful since half of every anhydride molecule is lost as a carboxylic acid. Barrett has reported the direct acylation of alcohols with acetic acid, the Fischer esterification, in the presence of a catalytic quantity of Sc or lanthanide triflates.⁶⁹ This method is both economically and environmentally advantageous and the catalysts are readily recycled without loss of activity. Primary, secondary and tertiary alcohols were all acylated in up to quantitative yields, although in some cases elevated temperatures were required, **Scheme 1.37**. Trial reactions with phenylethyl alcohol demonstrated that Sc(OTf)₃ was a more effective catalyst than the lanthanides triflates.



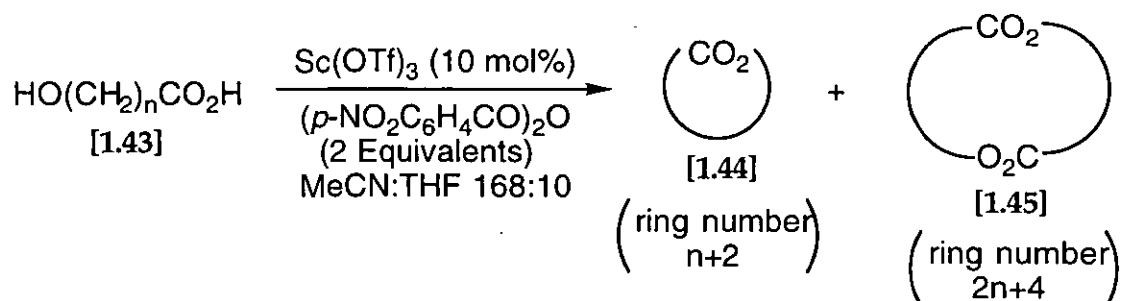
Scheme 1.37

The esterification of alcohols with mixed anhydrides, prepared beforehand, has been reported.⁷⁰ Recently Yamamoto extended this methodology with a convenient esterification procedure between alcohols and carboxylic acids using *p*-nitrobenzoic anhydride in the presence of Sc(OTf)₃. A mixed anhydride was formed between the carboxylic acid and the *p*-nitrobenzoic anhydride which reacted *in-situ* with the alcohol to give the product in good yield and high chemoselectivity. The reaction gave excellent results for primary and secondary alcohols but with tertiary alcohols the ester produced gradually eliminated the acyloxy group under the same conditions. Both aliphatic and aromatic acids such as 2,4,6-trimethylbenzoic acid were used successfully, **Scheme 1.38**.



Scheme 1.38

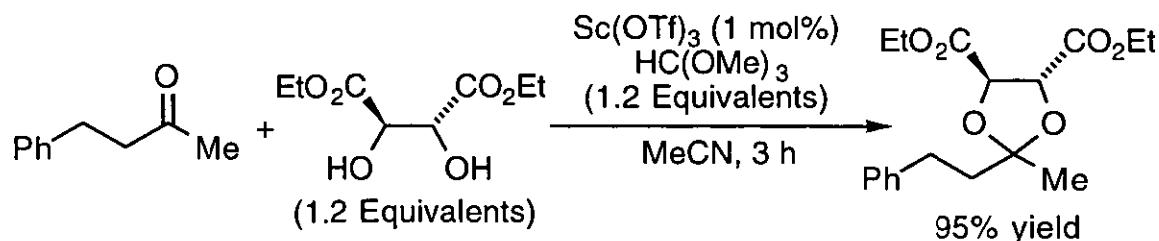
This method proved especially effective for the selective macrolactonisation of ω -hydroxy carboxylic acids [1.43] giving medium and large ring lactones [1.44] with negligible amounts (less than 5%) of the dimeric cyclic ester (diolide) [1.45] produced, **Scheme 1.39**.⁷¹ Other methods for the preparation of 8- to 12-membered lactones gave poor yields accompanied by large quantities of diolides.



Scheme 1.39

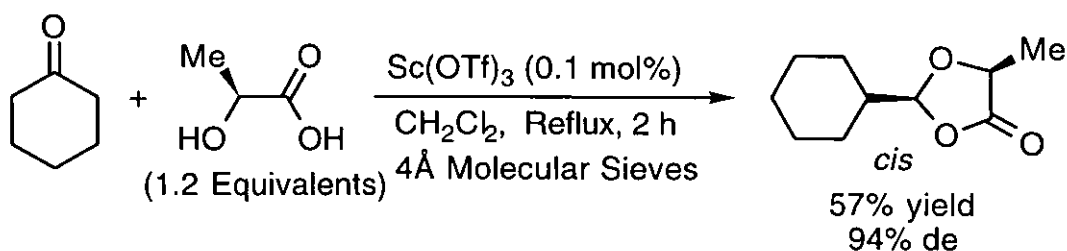
1.3.10 Acetalization Reactions

Yamamoto reported the acetalizations of ketones with trimethyl orthoformate catalysed by scandium triflate.⁷² Cyclic acetals were also obtained *via* an *in-situ* acetal-exchange reaction of ketones, diols and trimethyl orthoformate in the presence of 1 mol% of $\text{Sc}(\text{OTf})_3$, **Scheme 1.40**.



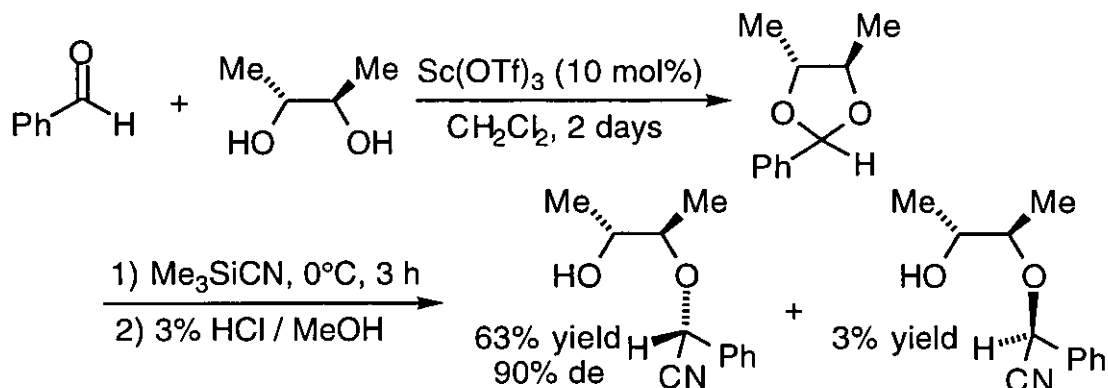
Scheme 1.40

Similarly 1,3-dioxolanones and 1,3-dioxanones were successfully prepared by the condensation of aldehydes or ketones and α - or β -hydroxy carboxylic acids in the presence of $\text{Sc}(\text{OTf})_3$ with azeotropic removal of the water produced. The products were produced in good to excellent yields and showed high diastereoselectivity favouring the *cis* isomer, **Scheme 1.41**.



Scheme 1.41

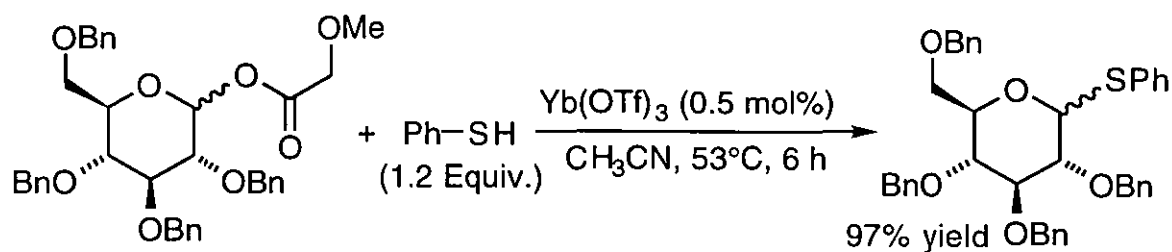
Fukuzawa has demonstrated the direct preparation of chiral acetals from aldehydes and diols using $\text{Sc}(\text{OTf})_3$.⁷³ The successive addition of trimethylsilyl cyanide, without isolation of the acetals, resulted in a one-pot silylcyanation procedure. The sequential reactions were both catalysed by $\text{Sc}(\text{OTf})_3$. Aliphatic aldehydes produced the cyanohydrin ethers with moderate stereoselectivity (50-56% de) but with benzaldehyde high selectivity was achieved (90% de) **Scheme 1.42**.



Scheme 1.42

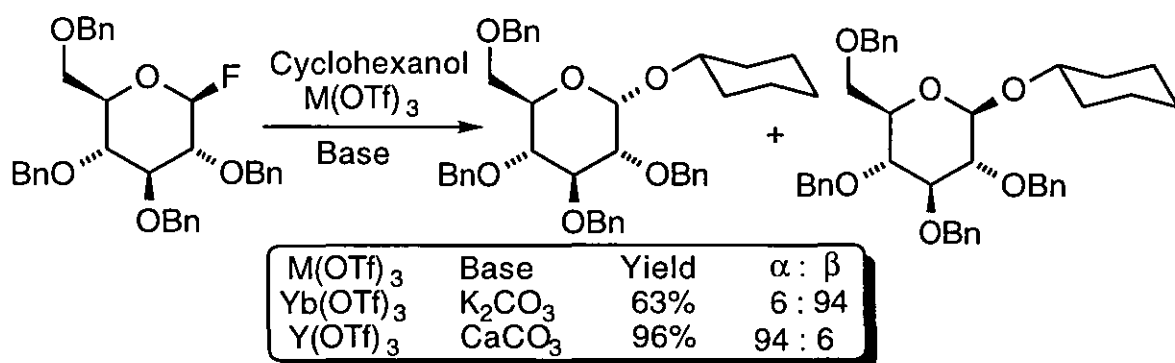
1.3.11. Glycosylation Reactions

Stereoselective glycosylation is one of the most important reactions in carbohydrate chemistry. Inanaga showed that lanthanoid triflates promote the reaction of 1-O-methoxyacetyl sugars with both alcohols and thiols yielding the corresponding glycosides, **Scheme 1.43**.⁷⁴ This work was expanded to include the use of 1-hydroxy sugars which were cross-coupled with alcohols in the presence of a catalytic amount of methoxyacetic acid and $\text{Yb}(\text{OTf})_3$ to give the glycosides.⁷⁵ Most of the yields were quantitative with $\alpha:\beta$ ratios of 75:25.



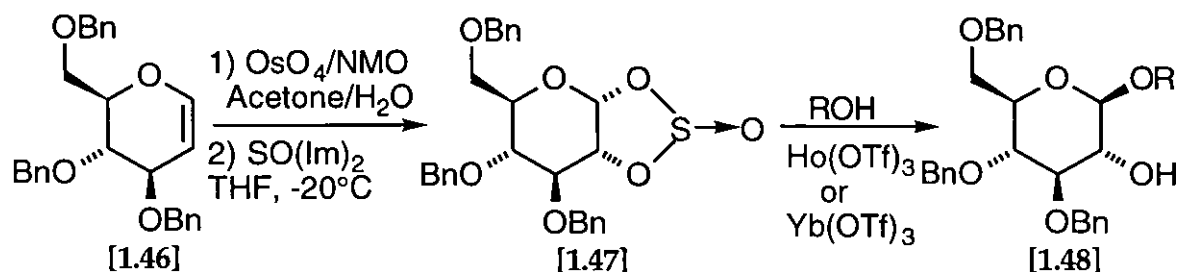
Scheme 1.43

Glycosyl fluorides are often employed as glycosyl donors in the synthesis of complex sugar chains. Lanthanide triflates catalyse their reaction with glycosyl acceptors.⁷⁶ Correct choice of lanthanide triflate and the reaction conditions enabled either the α - or β -product to be obtained selectively, **Scheme 1.44**. Use of Lewis acid additives such as zinc chloride or barium perchlorate significantly reduced the reaction times and improved the yield.



Scheme 1.44

Cyclic sulfites [1.47] were formed by treating the glycol [1.46] with osmium tetroxide and *N*-methylmorpholine *N*-oxide monohydrate, (NMO), producing the *cis*-diol, followed by reaction with thionyl diimidazole, **Scheme 1.45**. The benzyl protected sulfite [1.47], when treated with either allyl, benzyl or cyclohexyl alcohol in the presence of $\text{Yb}(\text{OTf})_3$ or $\text{Ho}(\text{OTf})_3$ stereoselectively produced the β -glycoside [1.48].⁷⁷

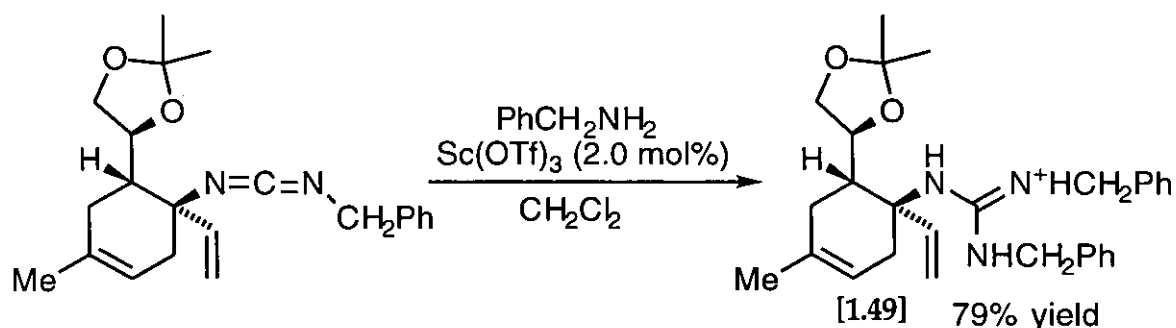


Scheme 1.45

Ytterbium triflate in nitromethane catalyses the reaction of peracylated sugars with trimethylsilyl azide to form glycosyl azides.⁷⁸ The yields are similar to those with other Lewis acids and the catalyst is reuseable.

1.3.12 Other Reactions

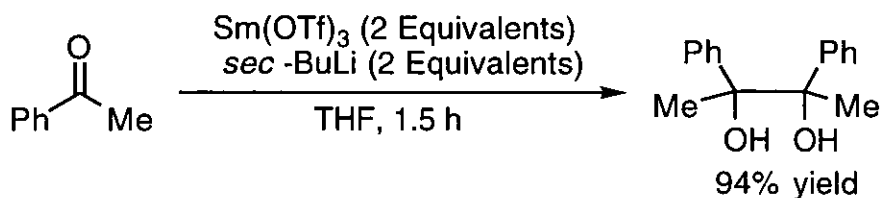
Isobe has demonstrated the use of $\text{Sc}(\text{OTf})_3$ in catalysing the addition of benzylamine to carbodiimides to give dibenzyl guanidines.⁷⁹ This reaction provided the key intermediate [1.49] in a synthesis of the guanidinium ring of (-)-tetrodotoxin, Scheme 1.46. By contrast, most Brønsted and Lewis acid catalysts deactivate the amine nucleophile and so fail to give the desired product.



Scheme 1.46

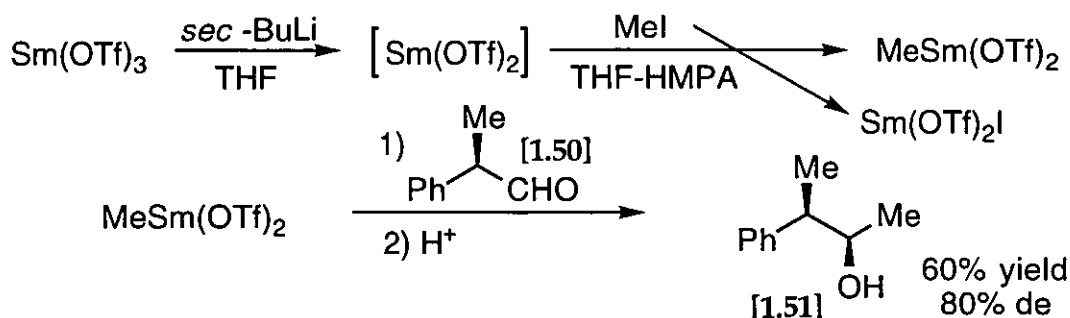
Alkyl and aryllanthanum triflates, $\text{RLa}(\text{OTf})_2$ were prepared from $\text{La}(\text{OTf})_3$ and organolithium reagents. Reacting these organolanthanum triflates with tertiary amides gave the corresponding alkyl or arylketones in good yields.⁸⁰ Alcohols were formed when the related organoytterbium triflates were added to aldehydes or ketones.⁸¹ These reagents were particularly effective in achieving non-chelation controlled (Felkin-Anh) addition to alkoxy-substituted aldehydes and ketones.

Fukuzawa prepared $\text{Sm}(\text{OTf})_2$ from $\text{Sm}(\text{OTf})_3$ and *sec*-butyllithium in THF at room temperature.⁸² Its reducing ability was demonstrated by its successful promotion of pinacol coupling reactions of carbonyl compounds. Aldehydes and aromatic ketones gave the corresponding pinacols in high yields, with aliphatic ketones the reactions were slower and only moderate yields were observed, typically 55%, **Scheme 1.47**. Analogous $\text{Sm}(\text{OTf})_2$ and $\text{Yb}(\text{OTf})_2$ reagents for pinacol coupling were prepared by treating $\text{Sm}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$ with ethylmagnesium bromide.⁸³



Scheme 1.47

The $\text{Sm}(\text{OTf})_2$ mediated Grignard-type reaction of alkyl, allyl and benzyl halides with aldehydes and ketones produced the secondary or tertiary alcohols in moderate to good yields, **Scheme 1.48**. This method proved superior to the samarium(II) diiodide mediated Grignard-type reactions. With $\text{Sm}(\text{OTf})_2$ the methyl, ethyl and allyl iodides gave the desired adducts, whereas when SmI_2 was used the alkylsamarium intermediates proved unstable, and the allyl halides underwent a Wurtz-type coupling.⁸⁴ For example, 2-phenylpropanol [1.50] and butyl iodide afforded the Cram product [1.51] in good yield and with higher selectivity than that achieved using either SmI_2 , MeMgI or MeLi , **Scheme 1.48**.⁸⁵

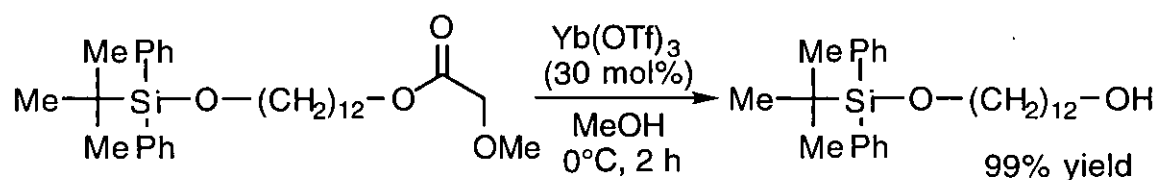


Scheme 1.48

When α - or β -halo esters were reacted with carbonyl compounds under these conditions the corresponding β -hydroxy esters or γ -lactones were produced in a type of samarium-Reformatsky reaction.⁸⁶ Whilst addition of aldehydes or ketones to $\text{Sm}(\text{OTf})_2$ and (iodomethyl)trimethylsilane yielded the corresponding alkenes in a samarium-Peterson type reaction.^{86,87}

Barrett showed that $\text{Yb}(\text{OTf})_3$ (1-10 mol%) catalyses the nitration of simple aromatic compounds with one equivalent of 69% nitric acid in good yields.⁸⁸ None of the dinitrated derivatives were observed and the only by-product was water. The catalyst was readily recycled without loss of activity.

The selective deprotection of methoxyacetates in methanol, in the presence of other hydroxy protecting groups such as, acetate, benzoate, THP, TBDMS and TBDPS, is catalysed by $\text{Yb}(\text{OTf})_3$ **Scheme 1.49**.⁸⁹

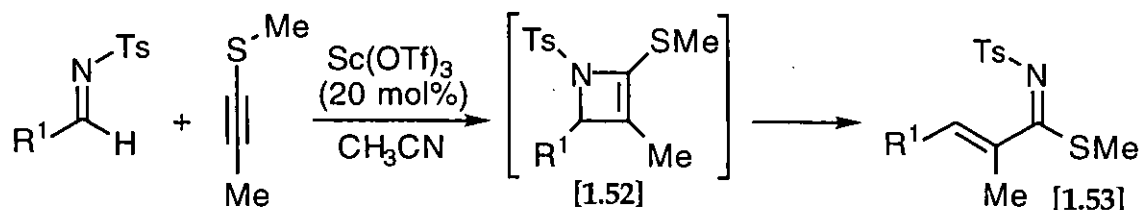


Scheme 1.49

The reaction is believed to be activated by the formation of a 5-membered chelate with Yb, with steric factors also influencing the rate of the catalytic alcoholysis. Sugar derivatives, secondary, tertiary and aromatic esters are all cleaved under non-basic conditions providing the alcohols in high yields.

Lanthanide triflates efficiently catalyse both the reactions of imines with cyanotrimethylsilane (TMSCN) and the three component-coupling reactions of aldehydes, amines and TMSCN producing the α -amino nitriles in high yields.⁹⁰

Recently a novel reaction of *N*-tosylimines with alkynyl sulfides catalysed by $\text{Yb}(\text{OTf})_3$ or $\text{Sc}(\text{OTf})_3$ was reported.⁹¹ The reactions are postulated to proceed via a [2 + 2] cycloaddition to form azetaine intermediates [1.52],⁹² which are unstable and immediately fragment to the α,β -unsaturated thioimides [1.53] in good yield, **Scheme 1.50**.



Scheme 1.50

Lanthanide triflates catalyse the reaction of indoles with aldehydes or ketones in aqueous solution yielding the bisindolylmethane adduct.⁹³ Dysprosium triflate is the most effective catalyst, being readily recycled, and affording the products in excellent yields, 75-99%.

Ytterbium triflate catalyses the condensation of bulky and aromatic amines with ethyl acetoacetate providing the corresponding enamino esters in significantly improved yields to those achieved without a catalyst.⁹⁴

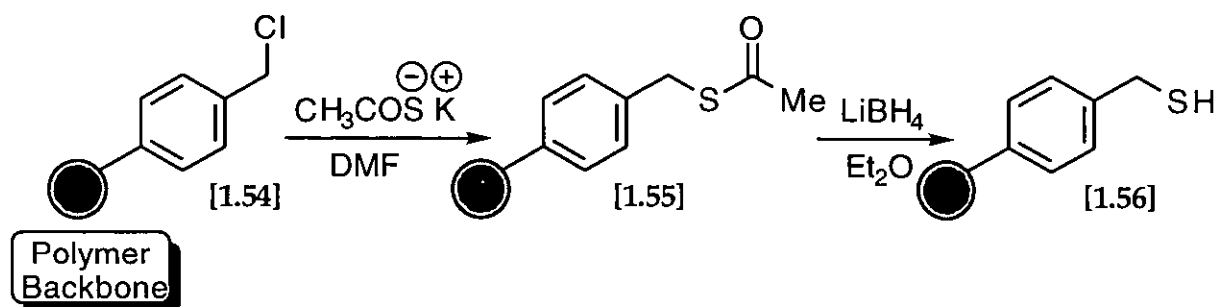
Catalytic quantities of lanthanide triflates promote the reaction between amines and nitriles forming the *N,N'*-disubstituted amidines in excellent yields, with primary diamines cyclic amidines are formed.⁹⁵

Scandium triflate has been shown to catalyse the decarbonylation of electron rich aromatic aldehydes such as 2,4,6-trimethoxy-benzaldehyde, in methanol,⁹⁶ and the cyclo-condensation of a hydroquinone with an allylic alcohol.⁹⁷ Scandium triflate also promotes a Meerwein-Ponndorf-Verley type reduction of aldehydes and ketones with isopropanol.⁹⁸ With electron rich aromatic carbonyl compounds, etherification of the product alcohol with isopropanol is a competing side reaction.

1.3.13 Combinatorial Synthesis

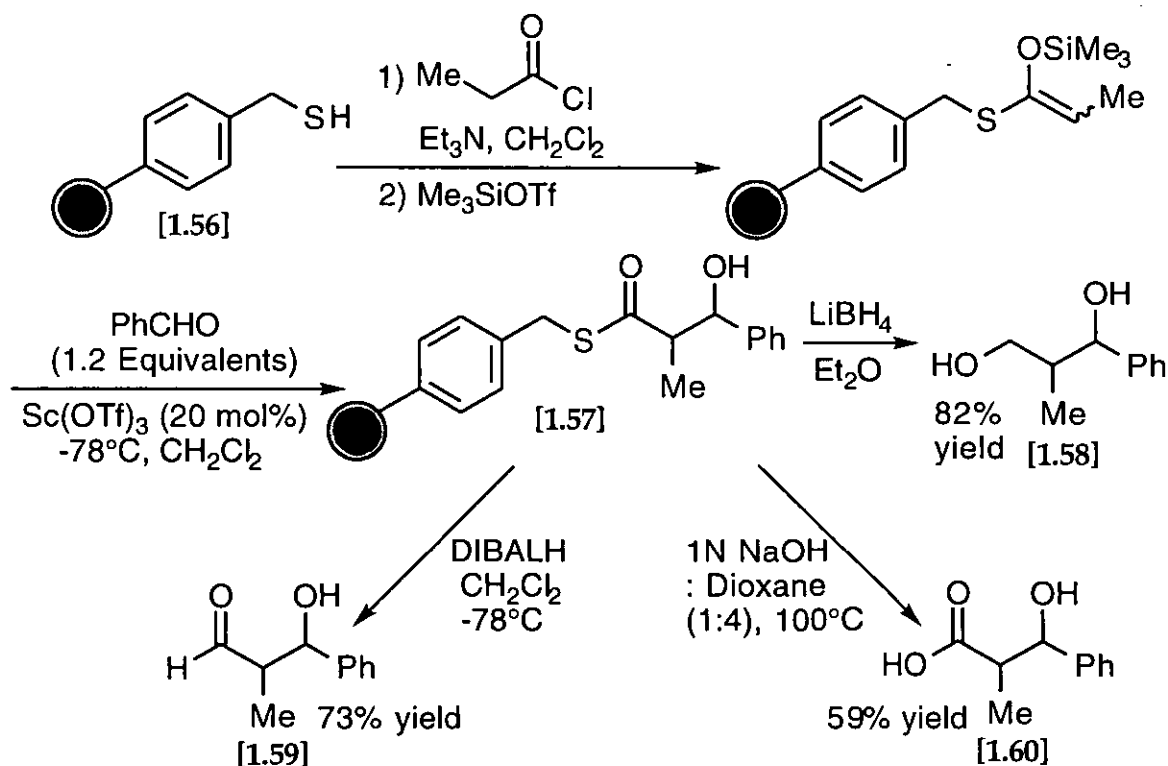
Combinatorial synthesis offers the prospect of an efficient approach to the synthesis of a large number of organic compounds and so has attracted much interest.⁹⁹ Silyl enol ethers are versatile reagents in organic synthesis,¹⁰⁰ and recently polymer-supported silyl enol ethers have been reported.¹⁰¹ Kobayashi treated chloromethyl copoly-(styrene-1% divinylbenzene) resin [1.54] with potassium thioacetate, **Scheme 1.51**. The resulting thioester [1.55] was reduced with lithium borohydride to yield the thiol [1.56]

which proved the most convenient precursor for the synthesis of immobilized silyl enol ethers.



Scheme 1.51

The thiol [1.56] was reacted with an acid chloride to give the corresponding thioketene silyl acetals, Scheme 1.52. Scandium triflate (20 mol%) efficiently catalysed the aldol reaction of the polymer-supported silyl enol ethers with aromatic, aliphatic, α,β -unsaturated and heterocyclic aldehydes.¹⁰² The solid phase $\text{Sc}(\text{OTf})_3$ -catalysed aldol reaction was demonstrated to be superior to the aldol reaction of a zinc enolate on solid phase with aldehydes under basic conditions.¹⁰³

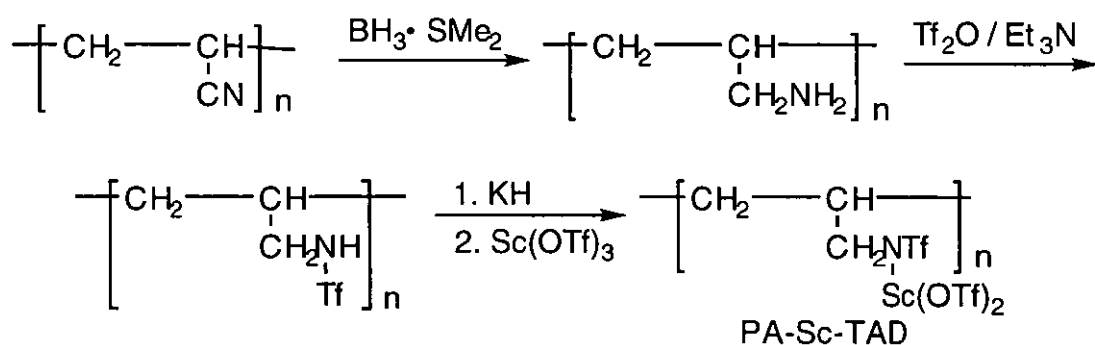


Scheme 1.52

The polymer-supported β -hydroxy thioesters such as [1.57] could be reduced to the free 1,3-diol [1.58] or the β -hydroxy aldehyde [1.59], or hydrolysed to the β -hydroxy carboxylic acid derivatives [1.60] depending on the reagent used to cleave the thioester, **Scheme 1.52**.

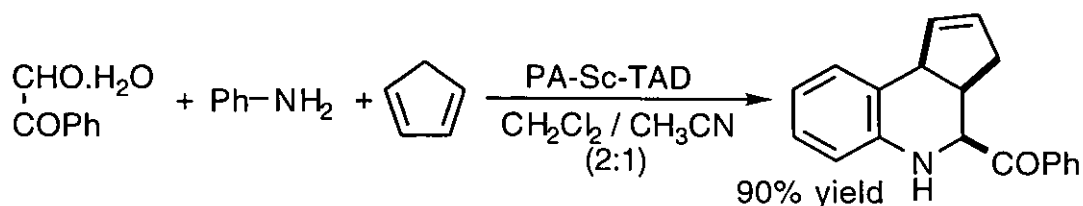
The resin bound silyl enol ethers also reacted with imines under $\text{Sc}(\text{OTf})_3$ catalysis to afford β -amino thioesters.¹⁰¹ Reduction gave the free amino alcohols in good yield. The success of $\text{Sc}(\text{OTf})_3$ catalysed reactions of these polymer-supported silyl enol ethers has enabled the preparation of several different compound libraries.

Kobayashi has reported using a polymer-supported scandium catalyst based on $\text{Sc}(\text{OTf})_3$, (polyallyl) scandium triflylamide ditriflate (PA-Sc-TAD), for combinatorial synthesis.¹⁰⁴ The catalyst PA-Sc-TAD was prepared in three steps from polyacrylonitrile, **Scheme 1.53**. Polymer-supported catalysts offer simplification of product workup, separation and isolation, however they frequently suffer from low reactivity, due to the insolubility of the catalyst. The catalyst PA-Sc-TAD is dispersed and partially soluble in a CH_2Cl_2 - CH_3CN mixed solvent system. On addition of hexane the dispersed catalyst re-assembles and can be recovered by filtration.



Scheme 1.53

This catalyst has been applied to the three component coupling reaction between aromatic amines, aldehydes and alkenes to form quinolines. As with $\text{Sc}(\text{OTf})_3$ the polymer supported catalyst was water tolerant and capable of reacting directly with substrates containing water of crystallisation, **Scheme 1.54**.



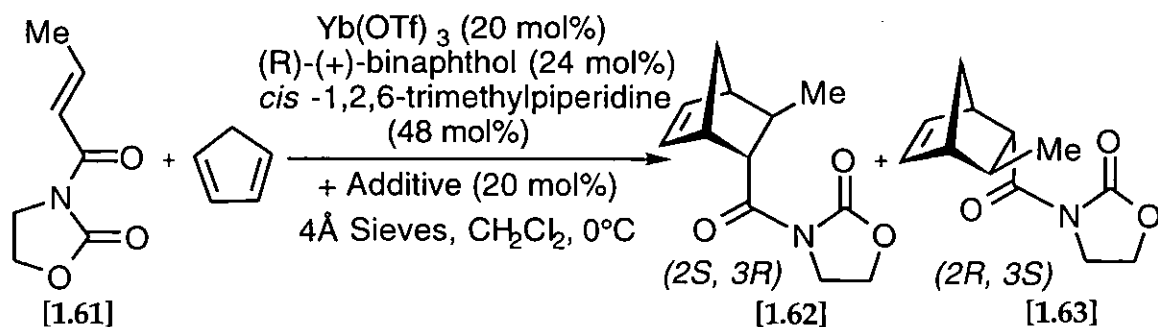
Scheme 1.54

The polymer catalyst also catalysed three component reactions between aldehydes, amines and silylated nucleophiles. Nucleophiles such as silyl enol ethers, ketene silyl acetals and cyanotrimethylsilane all reacted smoothly to afford the corresponding β -amino ketones, β -amino esters and α -amino nitriles in high yield.¹⁰⁵

It was possible to re-use the catalyst without loss of activity. The reactions were found to proceed slightly slower than they would if lanthanide triflates were used as the catalyst but gave comparable yields. Using PA-Sc-TAD allowed reactions on up to 100 milligram scale to proceed with a wide range of molecules yielding the desired products with high purities. Generally with more conventional polymer-supported substrates low loading levels preclude synthesis on this scale.

1.3.14 Asymmetric Catalysis

A Chiral Yb catalyst was prepared *in-situ* from $\text{Yb}(\text{OTf})_3$, (R)-(+)-binaphthol and a tertiary amine.¹⁰⁶ Its effectiveness was examined in a model reaction of 3-(2-butenoyl)-1,3-oxazolin-2-one [1.61] with cyclopentadiene. When triethylamine was used as the amine the *endo* adducts were formed (52% de) in low enantiomeric excess (33% ee). The amine used in preparing the chiral catalyst strongly influenced both the diastereo- and enantioselectivities, with bulky amines producing the best results. The enantioselectivity was found to improve when the amine was used in conjunction with 4Å molecular sieves and the temperature lowered to 0°C. For example with (*cis*-1,2,6-trimethylpiperidine) the enantioselectivity rose from 71%ee to 95%ee.



Scheme 1.55

Additive	yield(%)	<i>endo</i> / <i>exo</i>	[1.62] / [1.63]	ee(%)
 [1.64]	77	89/11	96.5/3.5	93
 [1.65]	83	93/7	9.5/90.5	81

Table 1.2

When the chiral Yb catalyst system was used in the model reaction, Scheme 1.55, with 3-acetyl-1,3-oxazolidin-2-one [1.64] (20 mol%) as the additive, the *endo* adduct [1.62] was obtained in high enantiomeric excess with the 2*S*, 3*R* absolute configuration, Table 1.2.¹⁰⁷ When the additive was changed to 3-phenylacetylacetone [1.65] (20 mol%), the reverse enantiofacial selectivity was observed and the *endo* adduct [1.63] with the 2*R*, 3*S* absolute configuration was favoured, Table 1.2. Thus the enantioselectivities were controlled by the choice of the achiral ligand, the same chiral source (*R*)-(+)-binaphthol was used to prepare both enantiomers. Traditional methods require both enantiomers of the chiral source in order to prepare both enantiomers of the product stereoselectively.¹⁰⁸ This is significant because in several examples the enantiomer of the chiral source is hard to obtain.

The selectivities are believed to be strongly dependant on the specific coordination number of Yb(III). The catalyst is postulated to contain two free binding sites, with site A being more readily available for coordination than site B. With 3-acetyl-1,3-oxazolidin-2-one [1.64] as the additive, then [1.64] or the dienophile [1.61] coordinates to site A under equilibrium conditions.

When the dienophile [1.61] is coordinated to site A the cyclopentadiene can attack from the *si* face. However, when 3-phenylacetylacetone [1.65] is the additive it occupies site A and forms a strong coordination bond to Yb(III). So the dienophile [1.61] has to coordinate to the second site, site B, which favours attack by the cyclopentadiene from the opposite *re* face.

The yields and selectivities for both catalytic systems were found to be strongly influenced by changing the lanthanide triflate. In both systems Yb(OTf)₃ was the most efficient, resulting in the best yields and highest selectivities.

The corresponding chiral scandium catalyst prepared from Sc(OTf)₃, (R)-(+)-binaphthol and 1,2,3-trimethylpiperidine also gave the Diels-Alder adducts in high yields.¹⁰⁹ The chiral Sc catalyst was more active than the chiral Yb catalyst and in some cases gave significantly improved chemical yields. Again the reactions favoured the *endo* adducts which were formed with excellent enantioselectivity. The products had the same configuration and similar stereoselectivity as was obtained using the chiral Yb catalyst with the 3-acetyl-1,3-oxazolidin-2-one [1.64] additive. However when the Sc catalyst was used with 3-phenylacetylacetone [1.65] as an additive no reverse enantioselectivity was observed. This result occurs because Sc can accommodate only seven ligands whereas the specific coordination numbers of Yb(III) allow it to have up to twelve ligands.¹¹⁰

The observed asymmetric induction can be rationalized by assuming an intermediate octahedral Sc(III)-dienophile complex, **Figure 1.1**. The axial chirality of (R)-(+)-binaphthol is transferred *via* the hydrogen bonds to the amine, the *re* face of the dienophile [1.61] is effectively shielded by the amine part, and a diene approaches [1.61] from the *si* face to afford the adduct in high enantioselectivity. This is consistent with the experimental results showing that amines employed in the preparation of the chiral catalysts strongly influenced the selectivities, and that bulky amines gave better selectivities.

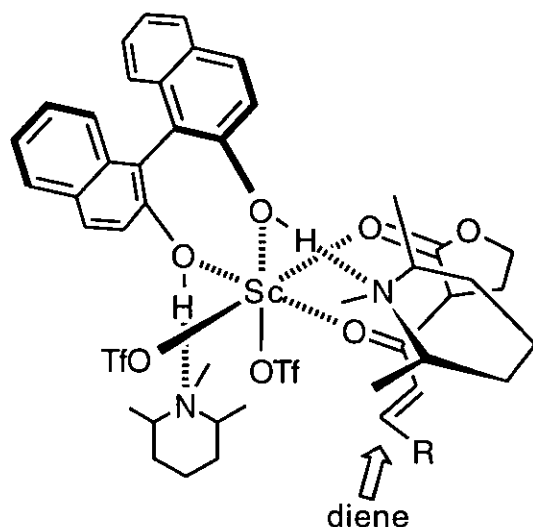
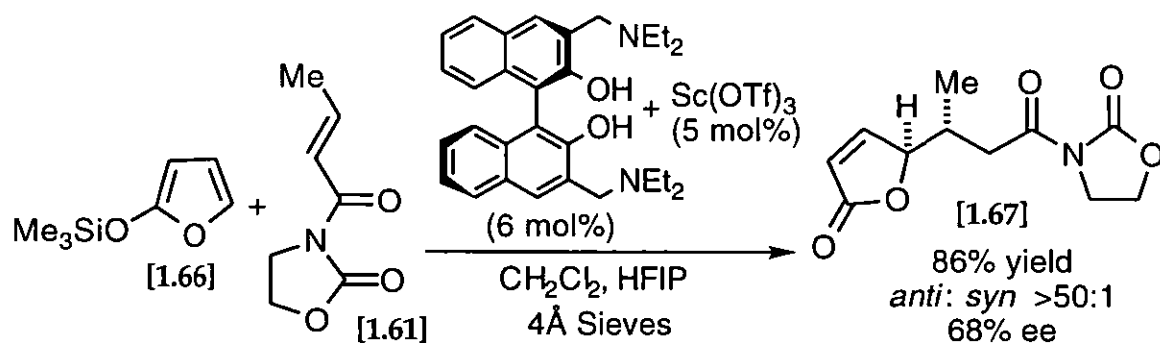


Figure 1.1

A chiral $\text{Sc}(\text{OTf})_3$ based catalyst has also been used in the addition of 2-(trimethylsilyloxy)furan [1.66] to Michael acceptors.¹¹¹ The best results were achieved with binaphthol derivatives containing tertiary aminomethyl groups at the 3,3'-carbons. It was anticipated that the conformation of the aminomethyl group would be fixed by intramolecular hydrogen bonding upon its coordination to $\text{Sc}(\text{OTf})_3$. When the reaction was carried out in dichloromethane the yield was moderate due to the formation of a Diels-Alder type side product, produced by Dieckmann condensation of the intermediate enolate. In order to limit this reaction, an additive hexafluoroisopropanol (HFIP) was added, which accelerates the quenching of the enolate but has poor coordinating ability. Under these conditions the reaction proceeded in good yield, with excellent diastereoselectivity and reasonable enantioselectivity. The absolute configuration of the major isomer [1.67] was determined to be *R,R* as shown, Scheme 1.56.



Scheme 1.56

1.4 Summary

This review has shown that scandium and lanthanide triflates are extremely versatile and efficient Lewis acids. They promote many reactions, frequently proving to be among the best methods available. In addition the rather unique properties displayed by scandium and lanthanide triflates provide important advantages over more conventional Lewis acids, ensuring continued interest in their application in chemistry.

Scandium and lanthanide triflates are stable to water and function as strong Lewis acids in aqueous media. They are easily recovered because they can tolerate an aqueous work-up and are reused without any loss of activity. They act as catalysts in several reactions where other Lewis acids require stoichiometric amounts. Their capacity to form strong but labile bonds enables them to activate a range of functional groups without remaining coordinated to the products. These factors have allowed them to promote reactions with substrates which are problematic under normal Lewis acid conditions.

Preliminary studies in Diels-Alder and Michael reactions suggests that they could be important catalysts for stereoselective synthesis. Their control of the stereochemistry by use of chiral ligands and additives is very promising.

The development of environmentally friendly clean-technology is an area of increasing importance in chemistry because of growing concern over pollution and the use of hazardous materials. Scandium and lanthanide triflates are potentially key reagents in the development of clean-technology. Their ability to carry out reactions in aqueous media with recycling of the catalyst reduces the quantity of waste materials and solvents to a minimum.

Chapter 2

Synthesis of Imines and Nitrogen Containing Heterocycles Using Rare Earth Metal Triflates

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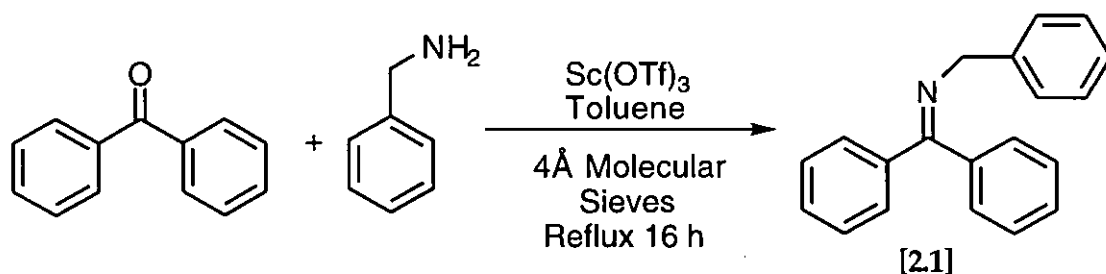
2.1 Introduction

As Chapter One has illustrated, the properties of $\text{Sc}(\text{OTf})_3$ make it a desirable catalyst and prompted a study of its suitability as a catalyst for the formation of imines. The success of $\text{Sc}(\text{OTf})_3$ as a Lewis acid catalyst in reactions involving amine nucleophiles,^{94,95} in particular the addition of benzylamine to carbodiimide derivatives,⁷⁹ suggested that it would be an ideal catalyst for promoting imine formation.

The use of Lewis acids to promote imine formation of hindered and unreactive ketones, such as aromatic ketones is well known.¹¹² Examples of imine formation catalysed by zinc chloride,¹¹³ thallium acetate¹¹⁴ and titanium tetrachloride^{115,116} have all been reported. However, Lewis acid chlorides have some disadvantages. In addition to being difficult to handle, they also require the use of a stoichiometric amount of the acid chloride and consequently the disposal of substantial quantities of insoluble residues. Often these disadvantages are avoided when $\text{Sc}(\text{OTf})_3$ is used.

2.2 Scandium Triflate as a Catalyst For Imine Formation

Initially the reaction of amines with ketones using $\text{Sc}(\text{OTf})_3$ as a catalyst was investigated. A less reactive aromatic ketone, benzophenone, was chosen to provide a difficult target. Benzylamine was employed because the methylene group provides a distinctive peak enabling the reaction to be followed by ^1H NMR. The benzylamine was refluxed with benzophenone in toluene for 16 h, using 5 mol% of $\text{Sc}(\text{OTf})_3$, whilst removing the water produced by imine formation. The desired imine [2.1] was isolated in 67% yield after recrystallisation, Scheme 2.1.



Scheme 2.1

However, other reactions using this method were disappointing, with aniline and benzophenone the imine [2.2] was isolated in 41% yield. With acetophenone and aniline the ^1H NMR spectra of the crude material indicated only a 30% conversion of starting materials to the imine, which was not isolated.

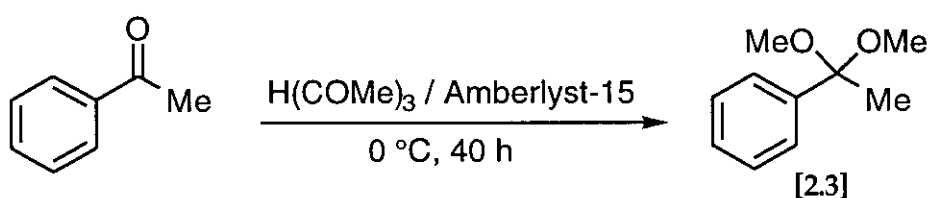
The above results show that as little as 5 mol% of $\text{Sc}(\text{OTf})_3$ can catalyse imine formation with aromatic ketones. Although, in comparison with the yields obtained using other Lewis acids the results are unsatisfactory. For example, titanium tetrachloride successfully catalysed the imine formation of several benzophenone derivatives at room temperature, with yields typically greater than 95%.¹¹⁶ This comparison suggested that an alternative strategy should be explored.

The preparation of imines from acetals and amines has been known since 1896, when Claisen reported using the dimethyl acetal of acetophenone with aniline.¹¹⁷ In 1935, Hoch produced a range of imines by heating several acetals with amines.¹¹⁸ He found that aromatic amines gave good yields (75-95%) whilst with aliphatic amines the yields were poorer (10-29%). This method required vigorous heating, typically 180-200 °C, in order to produce the imines and the yields varied greatly depending on the substrate employed. More recently aminopyridines were reacted with the dimethyl acetal of benzophenone which gave the corresponding imines in moderate yields (30-45%).¹¹⁹ Another group achieved significantly better yields (62-81%) by heating the diethyl acetals of cycloalkanes with 3-amino-2-chloropyridine with removal of the ethanol produced by distillation.¹²⁰

As we have seen $\text{Sc}(\text{OTf})_3$ successfully promotes reactions using acetals as the substrate. For example both Aldol reactions¹⁴ and acetal exchange reactions⁷² have been catalysed by $\text{Sc}(\text{OTf})_3$. In addition *N*-tosylimines have been prepared *in-situ* from *p*-toluenesulfonamide and the dimethyl acetals of aldehydes, and reacted under $\text{Sc}(\text{OTf})_3$ catalysis with alkynyl sulfides to give α,β -unsaturated thioimidates.⁹¹ However, it is questionable if the $\text{Sc}(\text{OTf})_3$ was involved in the imine formation as these imines have been reported previously without catalysis.¹²¹ These reports suggested that $\text{Sc}(\text{OTf})_3$ catalysed imine formation from acetals and amines should be possible. To test this proposal it was first necessary to prepare a range of acetals.

2.3 Acetal Formation

There are numerous procedures for the conversion of aldehydes and ketones into their corresponding acetals. Several methods use ortho esters in the presence of acidic catalysts such as sulfuric acid,¹²² *p*-toluenesulfonic acid,¹²³ Scandium(III) triflate⁷² and iron(III) chloride.¹²⁴ Initially the method developed by Patwardhan and Dev using Amberlyst-15, a sulfonic acid resin, to catalyse the reaction between acetophenone and trimethyl orthoformate was employed, **Scheme 2.2**.¹²⁵ The desired acetal **[2.3]** was obtained in 59% yield after distillation.

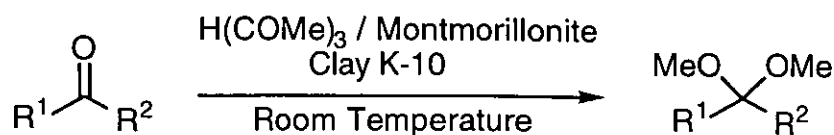


Scheme 2.2

With this method removal of the catalyst simply required filtration of the crude reaction mixture. However, long reaction times were necessary for unreactive ketones and distillation was needed to obtain pure product.

More recently trimethyl orthoformate adsorbed on commercially available acidic montmorillonite clay K-10 has been reported as a remarkably effective reagent for the conversion of carbonyl compounds into their acetals, **Scheme 2.3**.¹²⁶ The K-10/trimethyl orthoformate reagent proved superior to amberlyst-15 giving consistently higher yields in much shorter reaction times. For example, the reaction between acetophenone and trimethyl orthoformate using the K-10/trimethyl orthoformate reagent gave an 80% yield of the desired acetal **[2.3]** after 3 h. Using amberlyst-15 as the catalyst the reaction gave only 59% of **[2.3]** after 40 h.

This method was applied to a number of carbonyl compounds, whose results are summarised in **Table 2.1**. In each example filtration and removal of the solvent yielded products of high purity which required no further purification.



Scheme 2.3

Compound	R ¹	R ²	Reaction Time	Yield
[2.4]	C ₆ H ₅	H	1 h	82%
[2.3]	C ₆ H ₅	Me	3 h	80%
[2.5]	C ₆ H ₅	C ₆ H ₅	16 h	73%
[2.6]	-(CH ₂) ₅ -		3 h	93%

Table 2.1

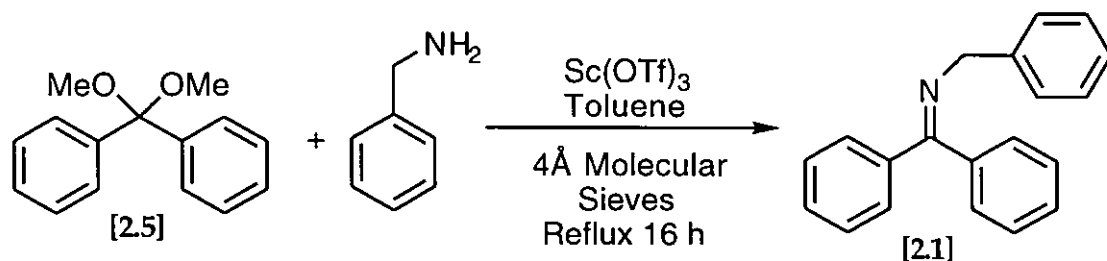
2.4 Imine Formation

The formation of imines from the reaction of acetals with amines requires the elimination of two equivalents of alcohol. In some procedures the reactions were refluxed through a fractionating column in order to remove, by distillation, the alcohol formed.¹²⁰ Removal of the alcohol shifts the equilibrium and so drives the reaction to completion. We reasoned that activated 4 Å molecular sieves should be sufficient to remove the methanol produced by reaction of dimethyl acetals with amines.

For the model reaction to test the suitability of Sc(OTf)₃ as a catalyst for imine formation, a challenging target was desirable. Therefore an acetal derived from an aromatic ketone, the dimethyl acetal of benzophenone [2.5], was chosen. Initially, benzylamine was refluxed with [2.5] in toluene using 5 mol% of Sc(OTf)₃ for 16 h. The reaction flask was fitted with a Dean-Stark trap containing activated 4 Å molecular sieves for the removal of the methanol produced by imine formation. Filtration followed by removal of the solvent gave, after recrystallisation, the desired imine product [2.1] in 88% yield, Scheme 2.4.

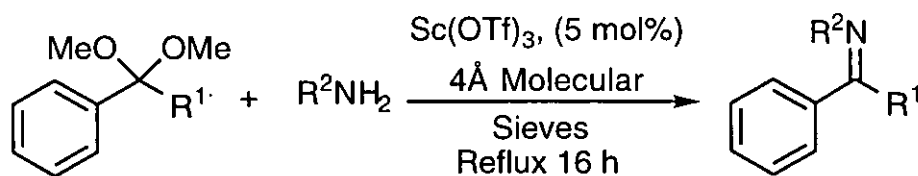
A control reaction was carried out in order to confirm that the Sc(OTf)₃ was required to catalyse the reaction. The reaction, Scheme 2.4, was repeated under identical conditions except that no Sc(OTf)₃ was used. The ¹H NMR

spectrum of the reaction mixture indicated that only unreacted starting materials were present, no imine was produced under these conditions.



Scheme 2.4

This procedure was successfully applied to a range of imines derived from aromatic acetals, see **Table 2.2**.



Scheme 2.5

R^1	Amine	Solvent	Product	Yield
H	Isopropylamine	Toluene	[2.7]	97%
H	Aniline	Toluene	[1.26]	92%
CH_3	Isopropylamine	Toluene	[2.8]	41%
CH_3	Aniline	Toluene	[2.9]	89%
Ph	Isopropylamine	Toluene	[2.10]	96%
Ph	Benzylamine	Toluene	[2.1]	88%
Ph	(R)- α -Methylbenzylamine	Toluene	[2.11]	10%*
Ph	(R)- α -Methylbenzylamine	Xylene	[2.11]	90%
Ph	4-Aminopyridine	Toluene	[2.12]	0%
Ph	4-Aminopyridine	Xylene	[2.12]	55%*
Ph	4-Aminopyridine	Xylene	[2.12]	76%+

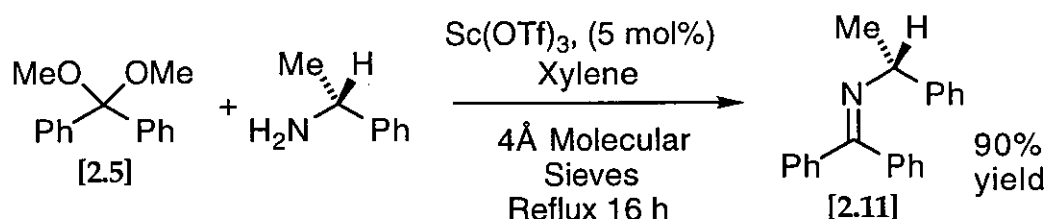
* The yield was estimated from the ^1H NMR.

+ This reaction was refluxed for 4 days.

Table 2.2

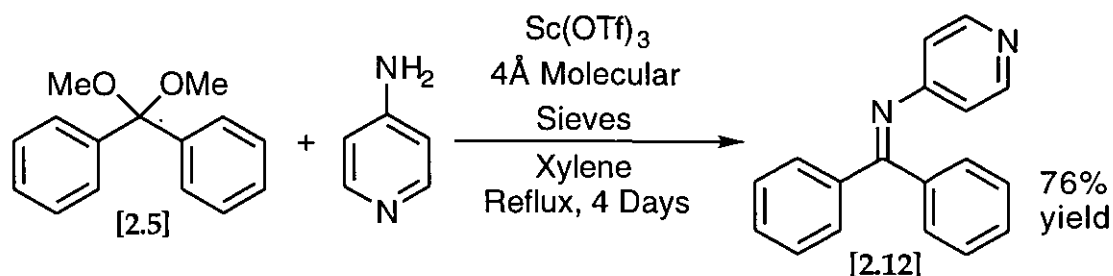
As can be seen from **Table 2.2** a variety of imines were produced in excellent yields by our procedure. Significantly $\text{Sc}(\text{OTf})_3$ acts as a true catalyst, with as little as 5 mol% promoting the reaction. By contrast imine formation promoted by titanium tetrachloride and thallium acetate required stoichiometric amounts to be used.¹¹⁴⁻¹¹⁶

Disappointingly the reaction of (R)- α -methylbenzylamine and the acetal of benzophenone **[2.5]** yielded only 10% of the desired imine **[2.11]** under our standard conditions. The lower reactivity of (R)- α -methylbenzylamine compared to benzylamine was presumably due to the increased steric bulk. However, it was observed that increasing the reaction temperature, by changing the solvent to xylene, produced the imine **[2.11]** in excellent yield, **Scheme 2.6**. Our procedure significantly improved on the literature preparations which report 45-60% yields of the imine **[2.11]** using titanium tetrachloride.^{127,128} The recrystallised product **[2.11]** had an optical rotation, $[\alpha]_D -19.2^\circ$, comparable to that previously reported for the (R) isomer.¹²⁷



Scheme 2.6

Desbène reported that heating 4-aminopyridine with the acetal **[2.5]** in a sealed tube at 200°C for 4 days produced a modest 32% yield of the imine **[2.12]**.¹¹⁹ Under our conditions the reaction failed to produce any imine **[2.12]**, only unreacted starting materials were recovered, **Table 2.2**. When xylene was used as the solvent our procedure gave a mixture of imine **[2.12]** and starting materials. The yield was estimated to be 55% by comparison of the ^1H NMR peaks for the pyridine ring of the imine with the acetal peak of the starting material. When the reaction time was the same as for the sealed tube experiment, 4 days, no unreacted starting materials were observed. After purification the imine **[2.12]** was isolated in 76% yield, more than double that previously reported, **Scheme 2.7**.



Scheme 2.7

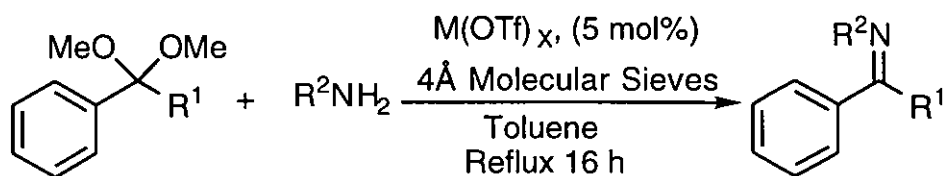
Of the imines prepared from aromatic acetals only the imine [2.8] derived from the acetal of acetophenone [2.3] and isopropylamine was isolated in a poor yield, Table 2.2. Analysis of the crude product indicated that impurities were present along with the desired imine product, no unreacted acetal remained. Distillation of the imine proved problematic and losses during distillation may help to explain the low yield obtained.

Although our procedure was generally very effective for imines derived from aromatic acetals, with aliphatic substrates problems were encountered. The reaction of cyclohexanone dimethyl acetal [2.6] with several amines was investigated. With each of isopropylamine, benzylamine and 3-amino-2-chloropyridine the acetal [2.6] produced a complex mixture of products, in which at best only a trace amount of the imine was present. Attempted purification by distillation failed to yield any pure imine. Whilst some unreacted amine remained in these reactions, the acetal appeared to have been largely consumed. It is possible that the acetals have formed the Aldol condensation products under the influence of the Sc(OTf)₃ catalysis.

For example, Couture observed that reaction of cyclohexanone and 3-amino-2-chloropyridine with Lewis acids gave poor yields of the imine contaminated with Aldol condensation products.¹²⁰ He reported that heating the aminopyridine with cyclohexanone diethyl acetal, without catalysis, whilst distilling off the ethanol gave the desired imine in good yield (based on the amount of the pyridine used).

2.5 Imine Formation With Other Metal Triflates

The ability of other metal triflates to catalyse the imine formation was also investigated, **Scheme 2.8**. The metal triflates were applied to reactions which had given poor results under our standard conditions and the results compared with those obtained using $\text{Sc}(\text{OTf})_3$, **Table 2.3**.



Scheme 2.8

R ¹	Amine	M(OTf) _x	Product	Yield
CH ₃	Isopropylamine	Sc(OTf) ₃	[2.8]	41%
CH ₃	Isopropylamine	Yb(OTf) ₃	[2.8]	54%
CH ₃	Isopropylamine	Cu(OTf) ₂	[2.8]	32%
Ph	(R)-α-Methylbenzylamine	Sc(OTf) ₃	[2.11]	10%*
Ph	(R)-α-Methylbenzylamine	Yb(OTf) ₃	[2.11]	15%*
Ph	(R)-α-Methylbenzylamine	Cu(OTf) ₂	[2.11]	<5%*
Ph	(R)-α-Methylbenzylamine	La(OTf) ₃	[2.11]	20%*
Ph	4-Aminopyridine	Sc(OTf) ₃	[2.12]	0%
Ph	4-Aminopyridine	Yb(OTf) ₃	[2.12]	10%*
Ph	4-Aminopyridine	Cu(OTf) ₂	[2.12]	0%

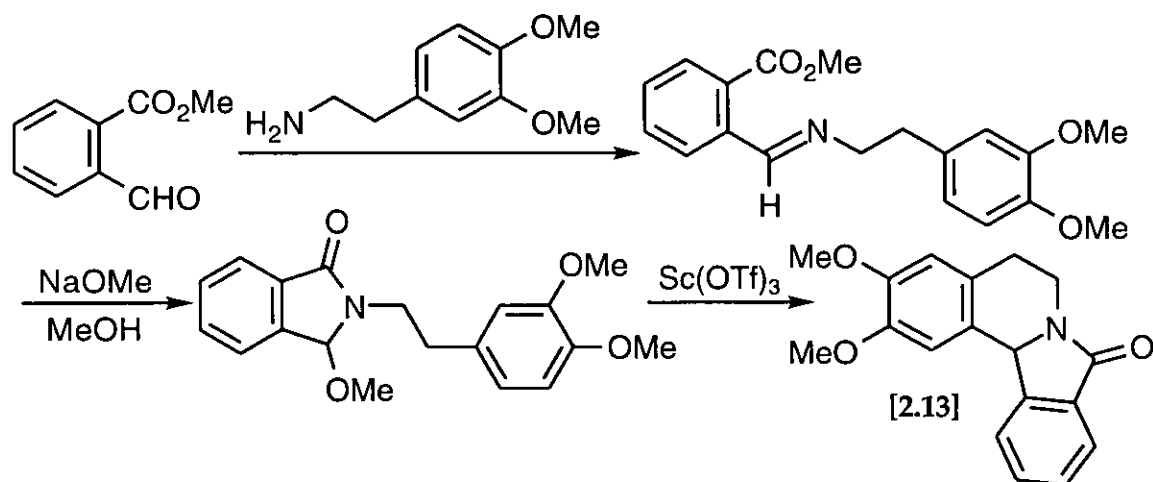
* The yield was estimated from the ¹H NMR.

Table 2.3

These results, **Table 2.3**, indicate that the catalytic activity of the metal triflates descends in the order $\text{La}(\text{OTf})_3 > \text{Yb}(\text{OTf})_3 > \text{Sc}(\text{OTf})_3 > \text{Cu}(\text{OTf})_2$, although the differences in the activities appear to be small. For example, the activities of $\text{La}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$ were not sufficient for a viable synthesis of imines [2.11] and [2.12] at refluxing toluene temperatures. The similar activity of $\text{Yb}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$ was demonstrated when the acetal [2.5] was refluxed with 4-aminopyridine for 4 days. The imine [2.12] was isolated in almost identical yield, 74%, using $\text{Yb}(\text{OTf})_3$, to that obtained with $\text{Sc}(\text{OTf})_3$, 76%.

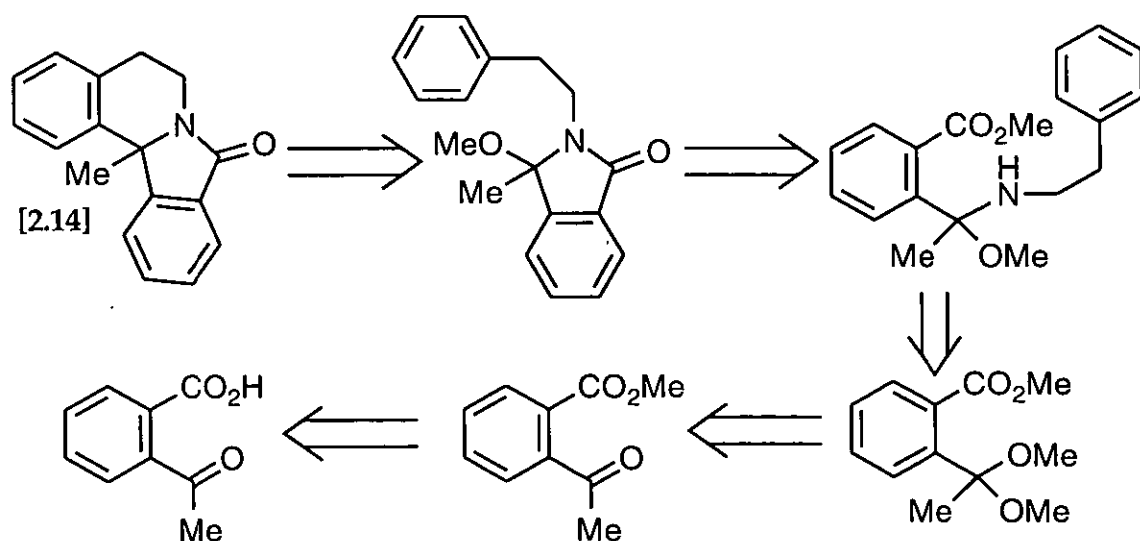
2.6 Applications to Isoquinolinone Synthesis

It was decided to test the utility of our imine methodology by applying it in a short synthesis. Our group recently published a synthesis of the nuevamine skeleton [2.13] *via* a $\text{Sc}(\text{OTf})_3$ catalysed Pictet-Spengler cyclisation, **Scheme 2.9**.^{129,34(a)}



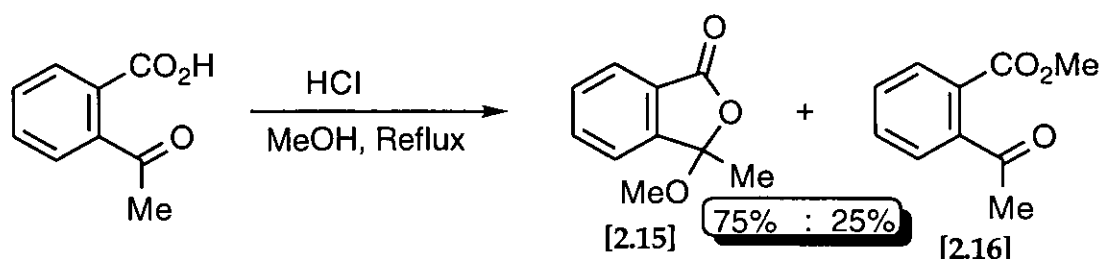
Scheme 2.9

It was considered that the synthesis of [2.14] an analogue of [2.13] would provide a more complex target for our methodology. The synthetic plan was envisaged as shown in the following retrosynthetic strategy, **Scheme 2.10**.



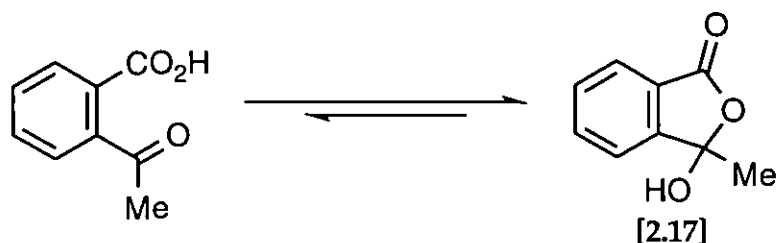
Scheme 2.10

This approach first required the preparation of methyl 2-acetylbenzoate [2.16]. Although the old literature suggested that the acid catalysed esterification of 2-acetylbenzoic acid gave the methyl ester,¹³⁰ more recent work showed that the major product was the pseudo ester [2.15]. The Fischer esterification of 2-acetyl benzoic acid using hydrogen chloride in methanol gave only 25% of the desired ester [2.16], **Scheme 2.11**.¹³¹ These authors did not separate the mixture of products, their analysis was based on ¹H NMR integration. We confirmed this result using sulfuric acid in methanol and isolated the two products [2.15] and [2.16] by flash chromatography in 65 and 29% yields respectively.



Scheme 2.11

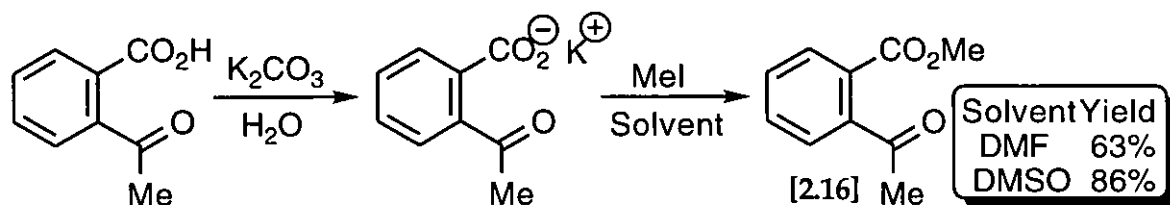
This result arises because 2-acetyl benzoic acid actually exists as an equilibrium between the acid and the lactone or pseudo acid [2.17]. The equilibrium lies in favour of the pseudo acid [2.17], **Scheme 2.12**.



Scheme 2.12

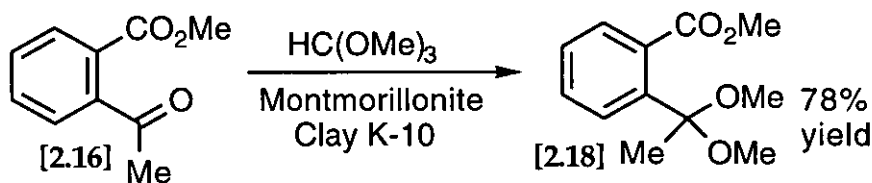
Several groups have used diazomethane with 2-acetyl benzoic acid to produce, as expected, the desired methyl 2-acetylbenzoate [2.16] in near quantitative yields.¹³² However, diazomethane can be troublesome to prepare and must be used with caution as it can cause explosions, which makes its use unattractive.

An alternative preparation of esters is *via* the alkylation of the carboxylic acid salt.^{131,133} Since the pKa of a carboxylic acid is lower than that of a pseudo acid the formation of a metal salt will ensure that the product is the carboxylate salt. Subsequent alkylation would then give the true ester rather than the pseudo ester. Treatment of 2-acetyl carboxylic acid with potassium carbonate in water smoothly gave the acid salt. After removal of the water the salt was reacted with methyl iodide in a dipolar aprotic solvent, **Scheme 2.13**. The best yield, 86%, was achieved using DMSO as the solvent.



Scheme 2.13

The methyl 2-acetylbenzoate [2.16] was converted into the dimethyl acetal [2.18] in good yield using the K-10/trimethyl orthoformate procedure described previously, **Scheme 2.14**.

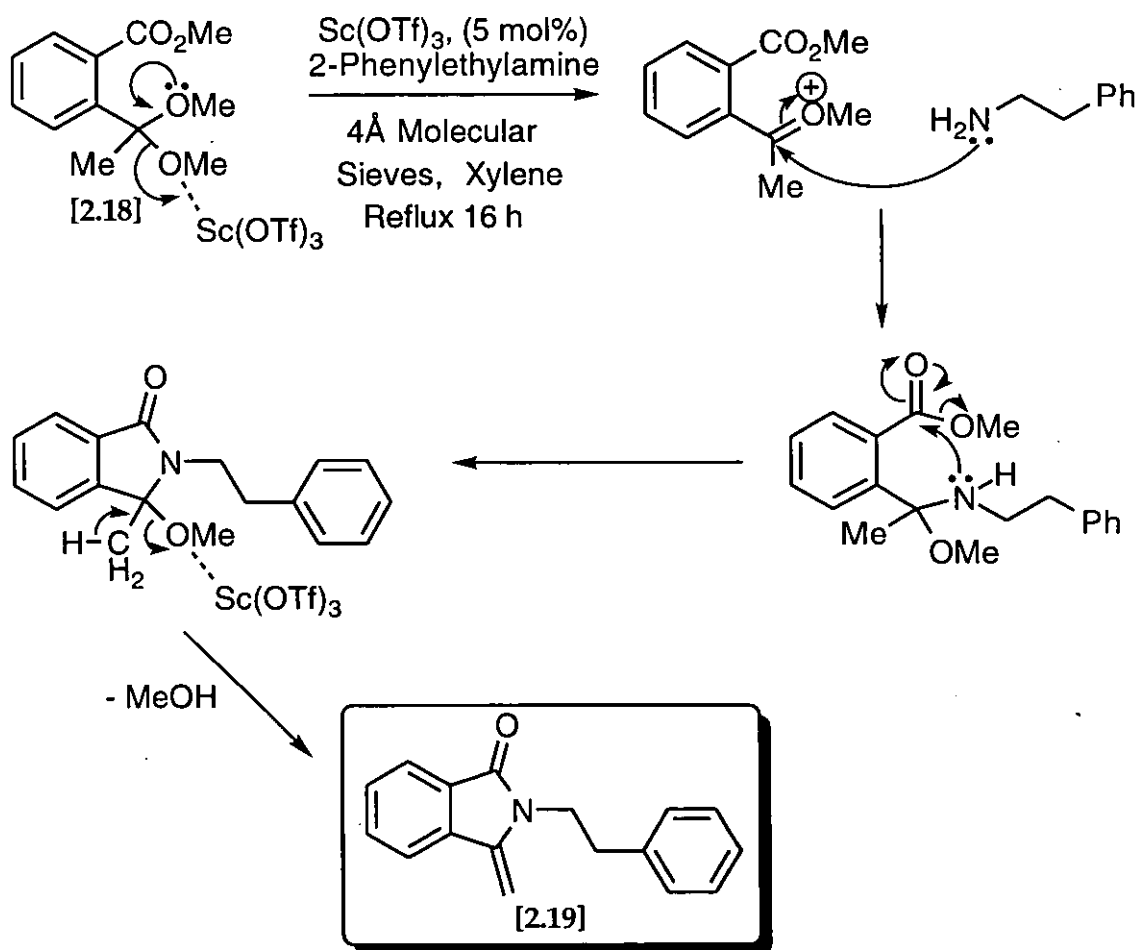


Scheme 2.14

The earlier cyclisation reactions based on 2-formylbenzoic acid had used titanium tetrachloride. Success using scandium triflate in the cyclisation reaction was only achieved when the aryl residue was 3,4-dimethoxyphenyl. It was therefore expected that reaction of the acetal [2.18] and 2-phenylethylamine would give the aminol ether when subjected to our standard procedure using toluene as the solvent.

However, no reaction occurred and unreacted starting materials were recovered. Repeating the reaction at a higher temperature, by changing the solvent to xylene, allowed a reaction to proceed. However, the methoxy signals that appeared between 3.90 and 3.00 ppm in the ¹H NMR spectrum of [2.18] were no longer present in the product, indicating that both the ester and

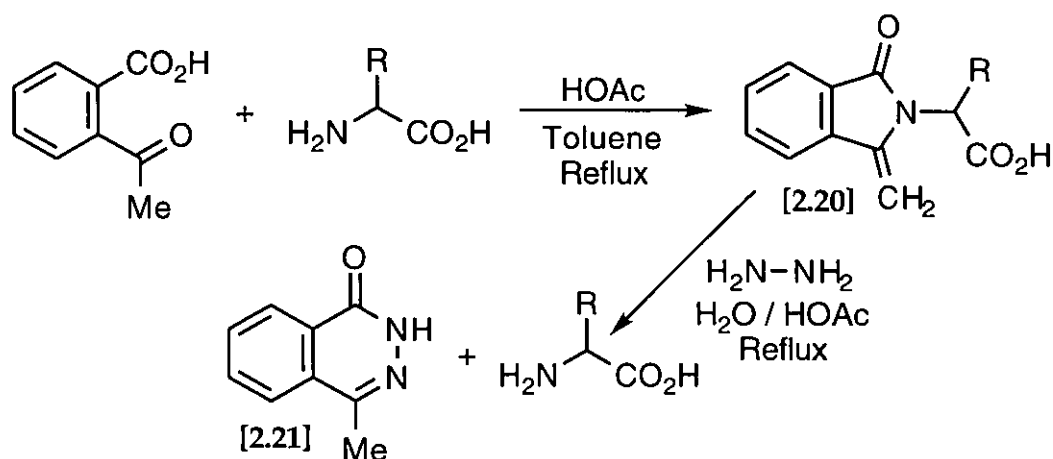
the acetal groups had reacted. The ^1H NMR spectrum also contained coupled protons at 4.82 and 4.00 ppm, and the ^{13}C NMR spectrum included a methylene signal at 88.6 ppm. This data showed that a terminal alkene was formed in the reaction. Measurement of the accurate mass confirmed the molecular formula as $\text{C}_{17}\text{H}_{15}\text{NO}$. Analysis of all the spectroscopic data allowed the structure to be assigned as the 3-methylene-isoindol-1-one [2.19] which was isolated after flash chromatography in 75% yield. The product [2.19] was evidently formed by an intra-molecular rearrangement which followed the initial attack of the amine, during the process three molecules of methanol were lost. A possible mechanism which explains the formation of this compound is shown, Scheme 2.15.



Scheme 2.15

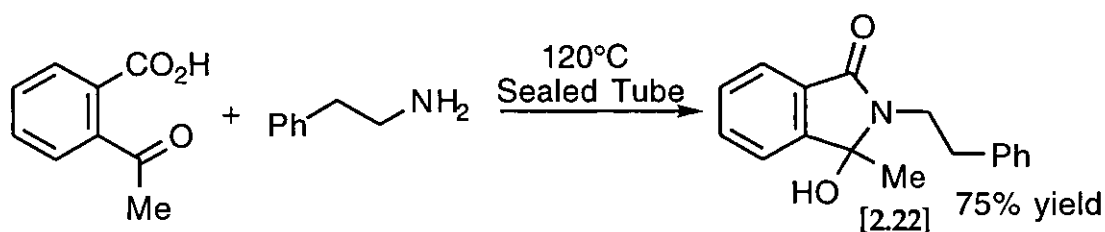
This result showed that the retrosynthetic analysis presented in Scheme 2.10 was appropriate to the isoindolone stage. The final cyclisation required a more nucleophilic aryl residue.

The analogous rearrangement has been reported for the reaction of 2-acetyl benzoic acid with amines in the presence of an acid.¹³⁴ The product [2.20] has been utilised as a protecting group for amino acids. Deprotection was effected by reaction with hydrazine which produces the free amino acid and 1-methyl-4-phthalazone [2.21], Scheme 2.16.



Scheme 2.16

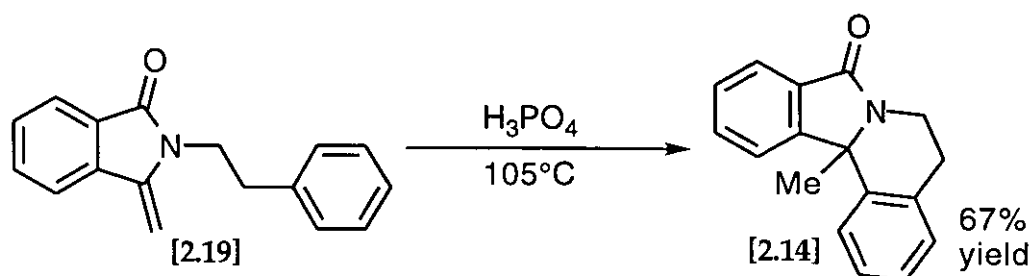
When 2-acetyl benzoic acid was heated with 2-phenylethylamine in the absence of any catalyst or solvent the 3-hydroxyisoindol-1-one [2.22] was produced, Scheme 2.17.¹³⁵



Scheme 2.17

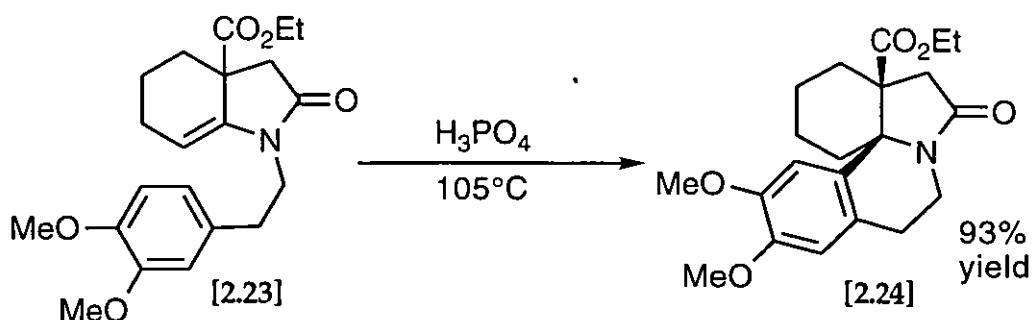
However, by contrast refluxing 2-acetylbenzoic acid with amines in *o*-dichlorobenzene, without catalysis, using a Dean-Stark trap to remove water resulted in the 3-methylene-isoindol-1-one derivatives being formed.¹³⁶

Heating [2.19] in ortho-phosphoric acid successfully produced the target cyclised isoquinolin-8-one product [2.14], Scheme 2.18.



Scheme 2.18

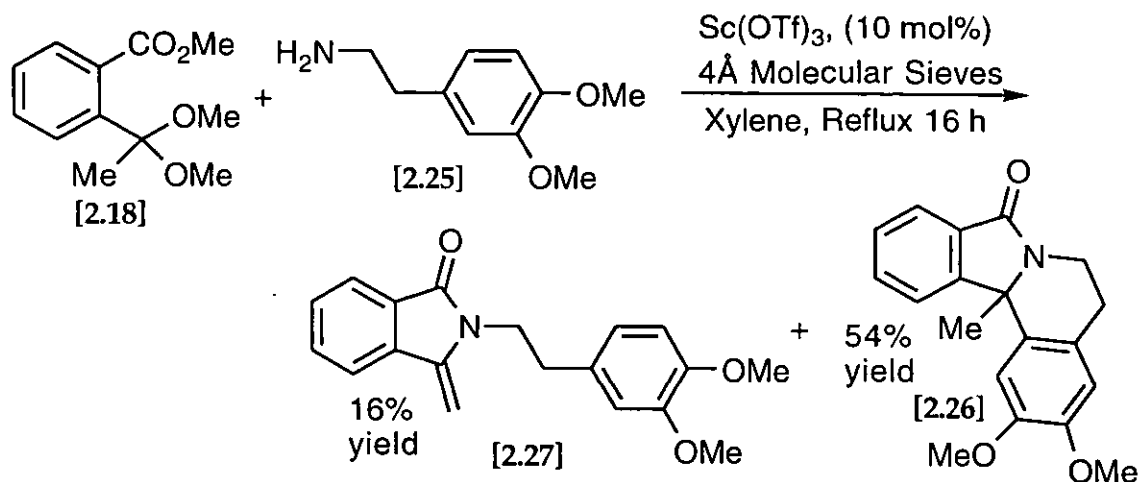
A similar acid catalysed cyclisation of tetrahydro-2-indolone [2.23] yielding the *cis*-fused erythrinanone [2.24], Scheme 2.19 has been reported.¹³⁷



Scheme 2.19

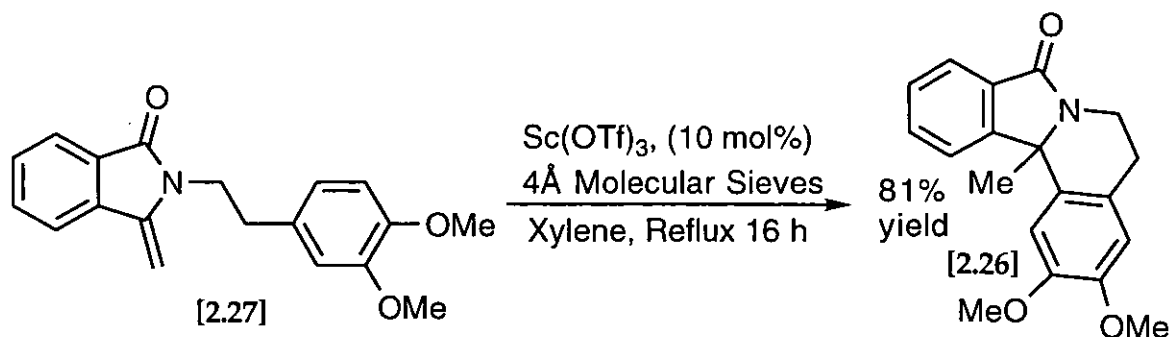
Scandium triflate proved unable to catalyse the cyclisation of [2.19] into [2.14]. However, as was shown in **Chapter One**, $\text{Sc}(\text{OTf})_3$ has catalysed tandem reactions, such as the one-pot acylation-Fries rearrangement. It was proposed that reacting an amine, containing a suitably nucleophilic aromatic ring, with the acetal [2.18] under $\text{Sc}(\text{OTf})_3$ catalysis would yield the cyclised product in one-pot.

Therefore the acetal [2.18] and 2-(3,4-dimethoxyphenyl)ethylamine [2.25] were refluxed in xylene with $\text{Sc}(\text{OTf})_3$ for 16 h. This produced a mixture of the cyclised product [2.26] and the 3-methylene-isoindol-1-one derivative [2.27], Scheme 2.20.



Scheme 2.20

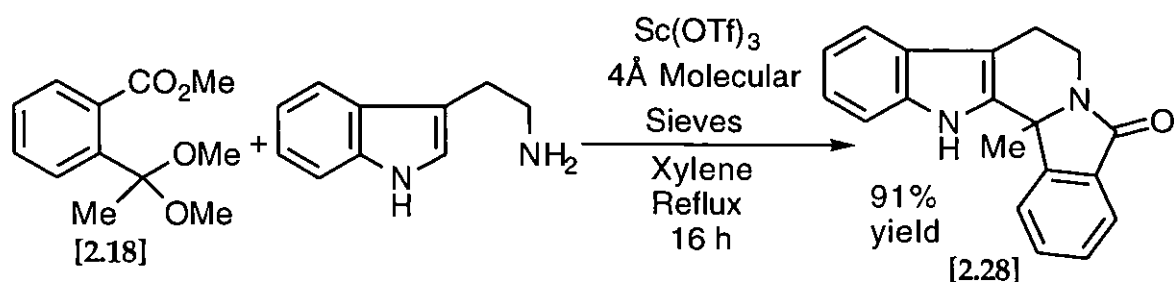
It was believed that the 3-methylene-isoindol-1-one derivative [2.27] was an intermediate in the synthesis of the cyclised product [2.26]. Further evidence supporting this proposal was obtained when [2.27] was refluxed in xylene under $\text{Sc}(\text{OTf})_3$ catalysis for 16 h, Scheme 2.21. The cyclised product [2.26] was isolated in 81% yield, some unreacted starting material [2.27] was also observed in the reaction mixture.



Scheme 2.21

2.7 Application to β -Carboline Synthesis

In order to extend this methodology to the synthesis of β -carboline derivatives, the acetal [2.18] was reacted with tryptamine under the conditions developed above. After chromatography the desired product [2.28] was isolated in 91% yield, Scheme 2.22.

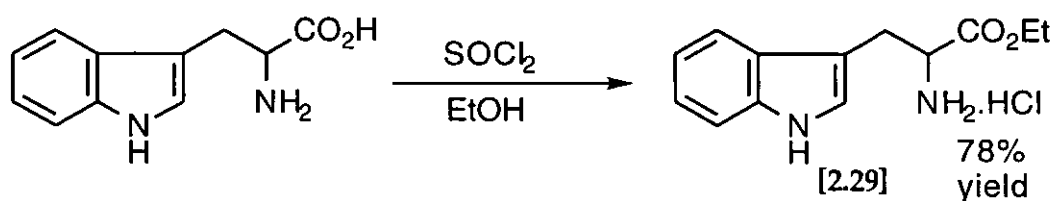


Scheme 2.22

The β -carboline derivative [2.28] has been reported previously by Nordstrom.¹³⁸ Direct reaction of 2-acetyl benzoic acid with tryptamine in refluxing xylene whilst removing water with a Dean-Stark trap produced [2.28] in 63% yield. By comparison our procedure gave a significantly better yield for the coupling step resulting in the desired product [2.28], although two extra synthetic steps were required to produce the acetal starting material [2.18].

The possibility of diastereoselectivity in the ring forming reaction was investigated next by using an amine containing a chiral center. Logically an ester of tryptophan was chosen because of its structural similarity to tryptamine and the ready availability of the parent acid.

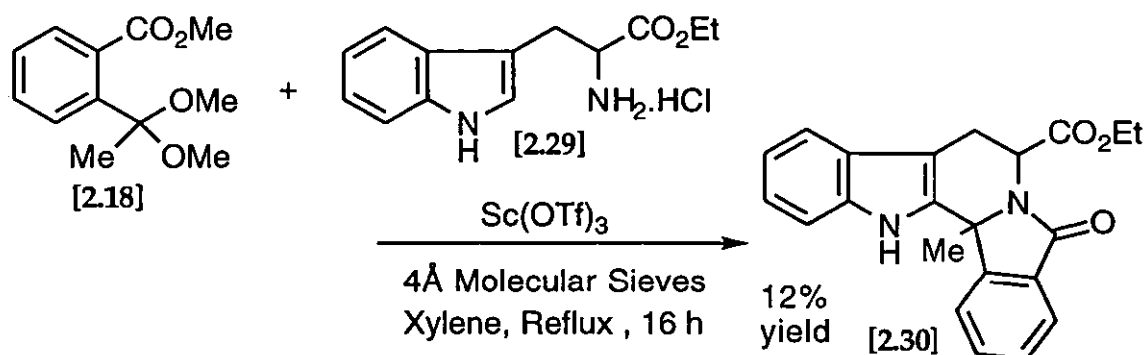
The hydrochloride salt of the ethyl ester [2.29] was prepared by reacting racemic D,L-tryptophan with thionyl chloride in ethanol, Scheme 2.23.



Scheme 2.23

The ethyl ester [2.29] was then reacted with the acetal [2.18] under our conditions producing the desired product [2.30] albeit in a poor 12% yield, Scheme 2.24. The main component recovered from the reaction mixture, accounting for 48% of the starting material, was methyl 2-acetylbenzoate [2.16]. Presumably this arose by hydrolysis of the acetal.

equilibrium between the free amine and its hydrochloride was not favourable towards the intended reaction.



Scheme 2.24

Only one diastereomer of the β -carboline product [2.30] was isolated from this reaction. Recrystallisation from deuteriochloroform produced a crystal suitable for X-ray crystallography. The crystal structure obtained, **Figure 2.1**, shows that both the ethyl ester and the methyl group are in axial positions and appear on the same face of the molecule.

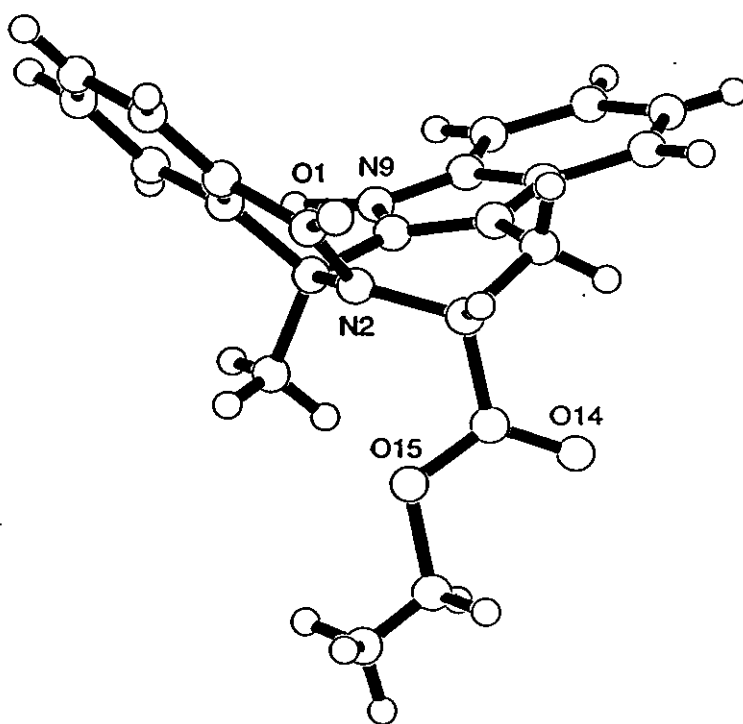
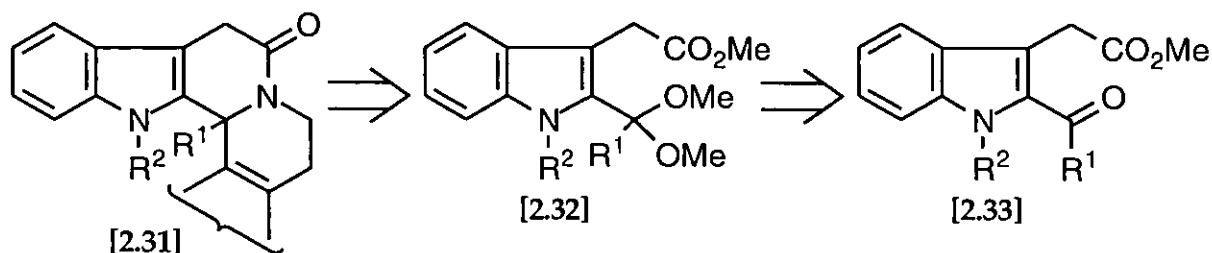


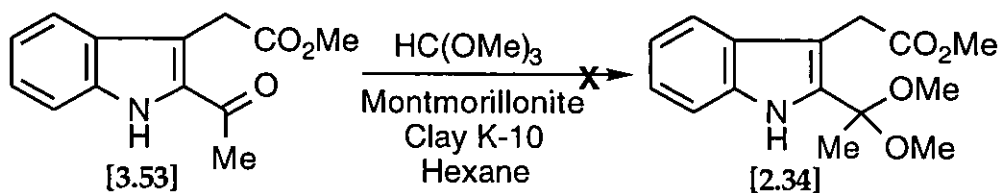
Figure 2.1

The problem associated with the poor yield should be limited by liberating the ethyl ester from its hydrochloride salt [2.29] with base prior to use. Reaction of the free ethyl ester with the acetal [2.18] under the same conditions yielded the desired product [2.30] in an improved 36% yield. Again only the diastereomer shown above was successfully isolated from the reaction mixture. The complicated nature of the crude product made it impossible to determine from the ^1H NMR if the diastereomer isolated was the only one formed by the reaction.



Scheme 2.25

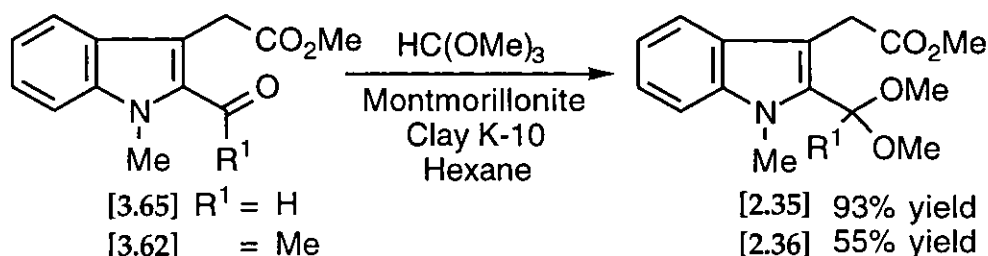
Each of the above reactions of the acetal [2.18] with suitable amines produced heterocycles in which both a 5- and a 6-membered ring were formed. It was envisaged that changing the acetal to an appropriate precursor would allow the methodology to be extended to the formation of two 6-membered rings. Products of the type [2.31] could be formed by reaction of the acetal [2.32] with either tryptamine or 2-phenylethylamine derivatives, Scheme 2.25.



Scheme 2.26

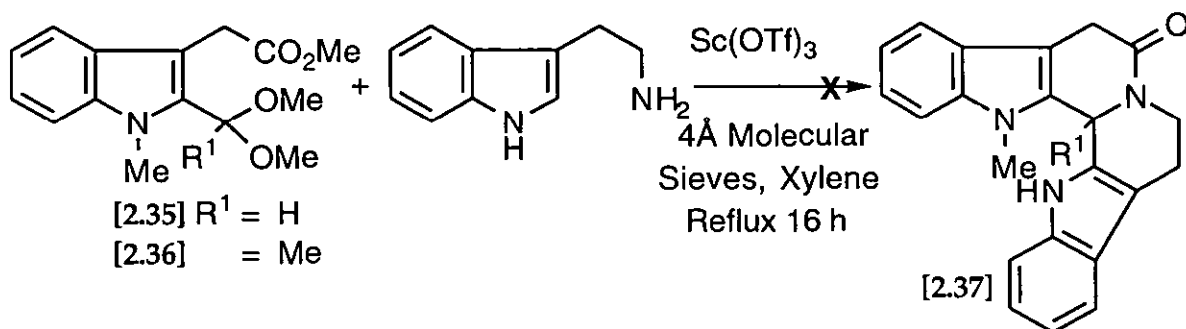
The acetal precursors [2.33] containing aldehyde or ketone functionality in the 2-position were prepared as described in **Chapter Three**. Initially the indole derivative [3.53] was reacted with the $\text{HC}(\text{OMe})_3$ /montmorillonite clay K-10 reagent in order to produce the acetal [2.34], Scheme 2.26. Surprisingly none of the desired product was observed, even after 24 h the starting material remained.

It was proposed that the unprotected indole nitrogen was causing the problem. To test this theory the indole derivatives, [3.65] and [3.62], in which the nitrogen was protected by a methyl group, were used in the acetal procedure. Both [3.65] and [3.62] were successfully converted into the corresponding acetals [2.35] and [2.36] in modest to excellent yields, **Scheme 2.27**.



Scheme 2.27

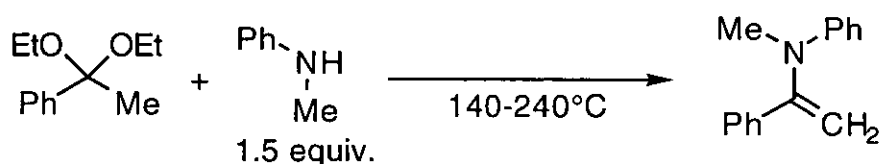
Tryptamine gave the highest yields and cleanest products when cyclised with the acetal [2.18]. It was therefore chosen as the ideal substrate for the trial reactions with the indole acetals [2.35] and [2.36]. However, the reactions of these acetals with tryptamine resulted in complex mixtures being formed. Column chromatography failed to yield any of the desired cyclised heterocycles [2.37], **Scheme 2.28**. When the acetal [2.36] was employed, analysis of the crude reaction mixture by 1H NMR showed no signals between 4.60 to 3.20 ppm, suggesting that the heterocycle [2.37] was not formed. In the related compound [2.28] the protons of the methylene group adjacent to the nitrogen appeared at 4.51 and 3.38 ppm in the 1H NMR. For the desired product [2.37] the corresponding methylene protons would be expected to appear in the same region.



Scheme 2.28

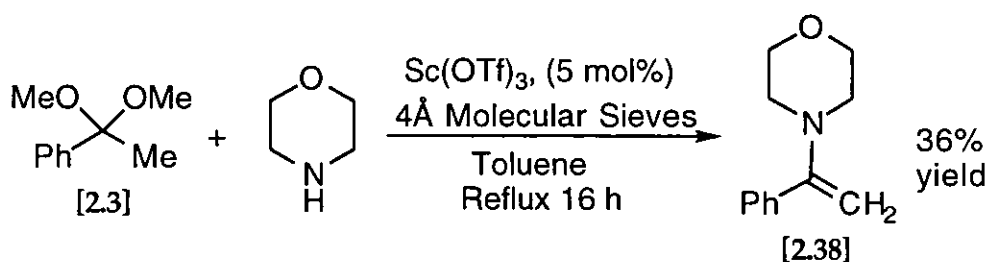
2.8 Enamine Formation

The preparation of enamines by the reaction of secondary amines with ketals has been known since 1935, but has received relatively little attention.^{139,140} Hoch reported that condensation of the diethyl acetals of ketones with secondary amines containing both an alkyl and an aromatic substituent produced enamines in moderate to good yields, 50-85%.¹³⁹ In addition to styrene derivatives, for example **Scheme 2.29**, some stilbene and cyclohexene derivatives were also prepared. More recently Fusco used *p*-toluenesulfonic acid to catalyse the reaction of morpholine with ethyl acetals.¹⁴⁰



Scheme 2.29

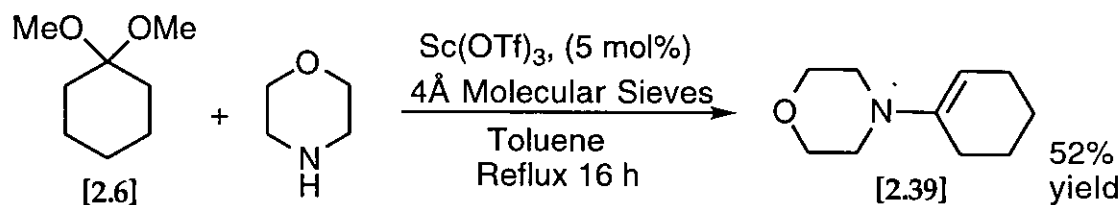
These reports prompted the application of our methodology to the synthesis of enamines. The dimethyl acetal of acetophenone [2.3] was reacted with morpholine producing the enamine [2.38], **Scheme 2.30**. However, the yield of [2.38] was moderate and its purification by distillation was problematic.



Scheme 2.30

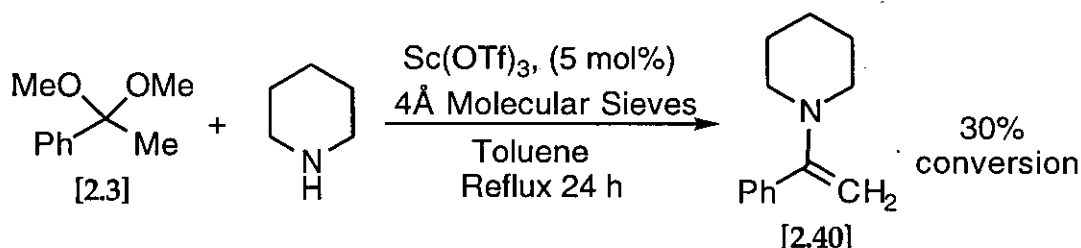
Morpholine was also employed in a reaction with cyclohexanone dimethyl acetal [2.6], **Scheme 2.31**. Analysis of the crude reaction mixture indicated a mixture containing mainly the enamine [2.39], along with impurities and a small amount of unreacted starting materials even after

refluxing for 16 h. Distillation was troublesome and the enamine was isolated in a modest 52% yield.



Scheme 2.31

Changing the secondary amine to piperidine gave disappointing results. With the acetal [2.3] it was estimated that 30% of the starting materials had been converted to the enamine [2.40] after refluxing for 24 h, **Scheme 2.32**. This estimate was determined by comparison of the integrals of the aromatics with the integrals of the terminal methylene of [2.40] in the ^1H NMR of the crude reaction mixture. Analysis showed that the majority of the acetal [2.40] had been consumed and that significant amounts of unidentified impurities were present.



Scheme 2.32

When piperidine was reacted with cyclohexanone dimethyl acetal [2.6] no enamine was produced. The reaction mixture contained mainly unreacted starting materials. These disappointing results and the difficulties encountered in obtaining pure products from the reaction mixtures led to work in this area being discontinued.

2.9 Summary

A diverse range of acetals were prepared in high yields using the trimethyl orthoformate/montmorillonite clay K-10 reagent developed by Taylor and Chiang.¹²⁶

The reaction of these acetals with amines to produce imines was shown to be efficiently promoted by a catalytic amount of $\text{Sc}(\text{OTf})_3$. The procedure proved particularly effective with the acetal of benzophenone [2.5].

Several nitrogen-containing heterocycles including 3-methylene-isindol-1-one derivatives and β -carboline derivatives were successfully prepared when the acetal [2.18] was utilised in this procedure.

The methodology was also applied to the synthesis of enamines by using secondary amines.

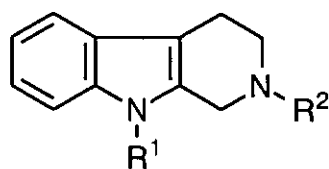
Chapter 3

Synthesis of Tetrahydro- β -Carboline Derivatives

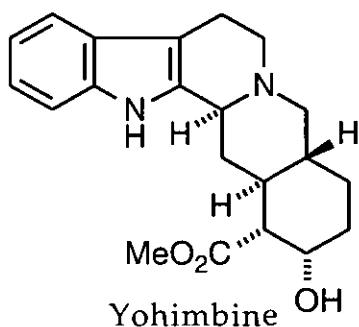
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3.1 Introduction

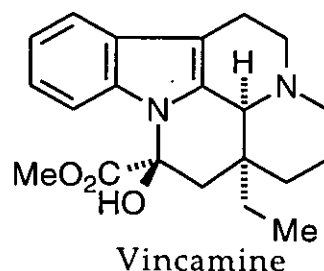
A wide range of alkaloids incorporate the tricyclic tetrahydro- β -carboline skeleton [3.1].¹⁴¹ For example the natural products yohimbine, vincamine and (-) akagerine all contain the subunit [3.1]. For this reason there has been considerable interest in the synthesis of tetrahydro- β -carbolines.



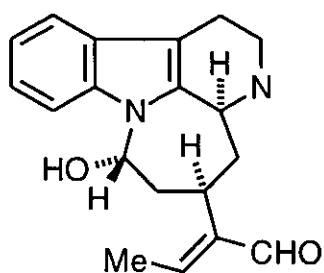
[3.1]



Yohimbine

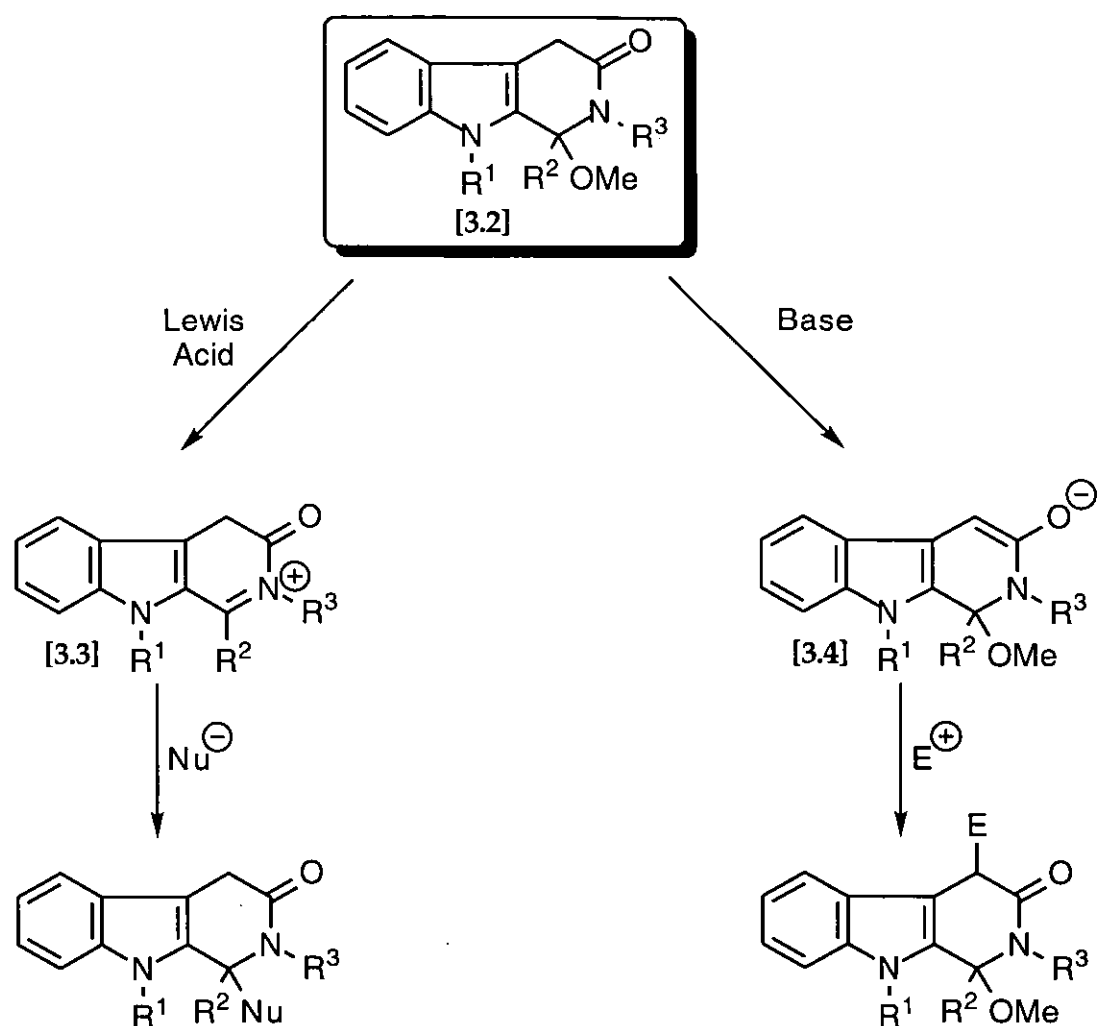


Vincamine



(-) Akagerine

A new approach to these compounds was envisaged through the synthesis of the β -carboline template compound [3.2]. This key target compound [3.2] provides considerable scope for functionalisation. The range of reactions applicable to this template should make it an ideal precursor to many β -carboline natural products and their analogues.

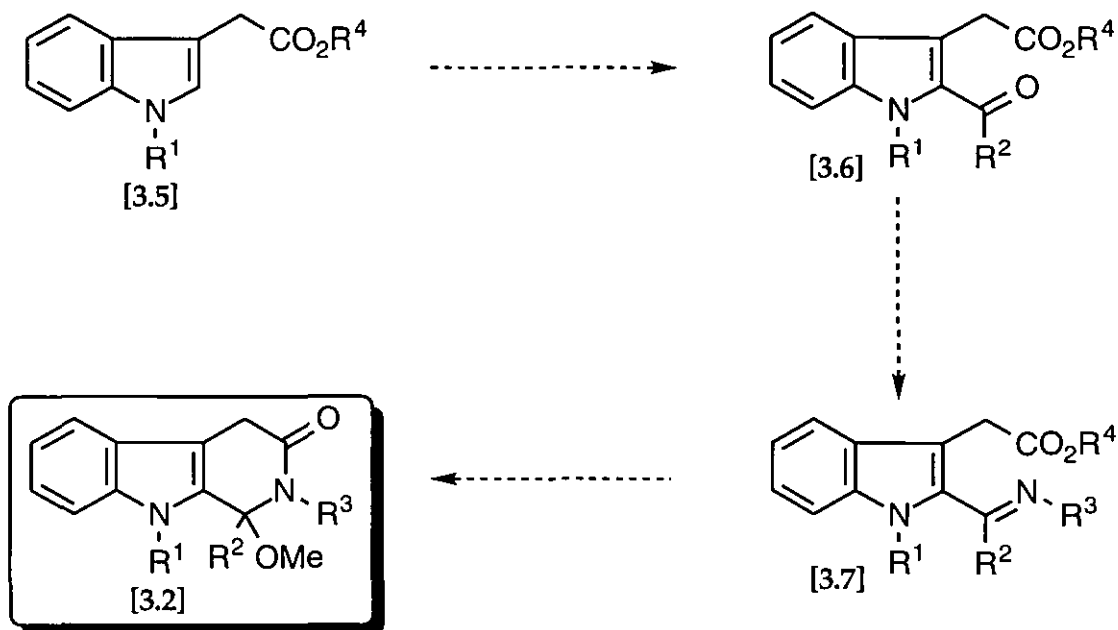


Scheme 3.1

For example addition of a suitable Lewis acid to [3.2] would promote the formation of the iminium salt [3.3]. This could then be attacked by a range of nucleophiles, **Scheme 3.1**, resulting in overall nucleophilic substitution. Alternatively, reaction of [3.2] with an appropriate base would generate the enolate species [3.4], which could then be substituted with a wide variety of electrophiles. It was anticipated that a chiral R^3 group would exert some stereocontrol over these substitution reactions, allowing the possibility for the stereoselective synthesis of a large number of β -carboline analogues.

3.2 Proposed Strategy

The following synthetic plan, **Scheme 3.2**, was proposed for the preparation of the key template compound [3.2].

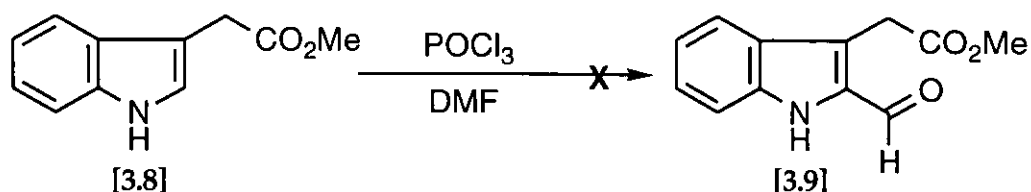


Scheme 3.2

Formylation or Friedel-Crafts acylation of [3.5] would provide [3.6] as the corresponding aldehyde (where $R^2 = \text{H}$) or ketone (where $R^2 = \text{alkyl}$) derivatives respectively. Reaction with a primary amine would produce the imine [3.7] which should rearrange using sodium methoxide to the cyclised target compound [3.2]. Use of a chiral amine would enable the introduction of a chiral auxiliary at R^3 .

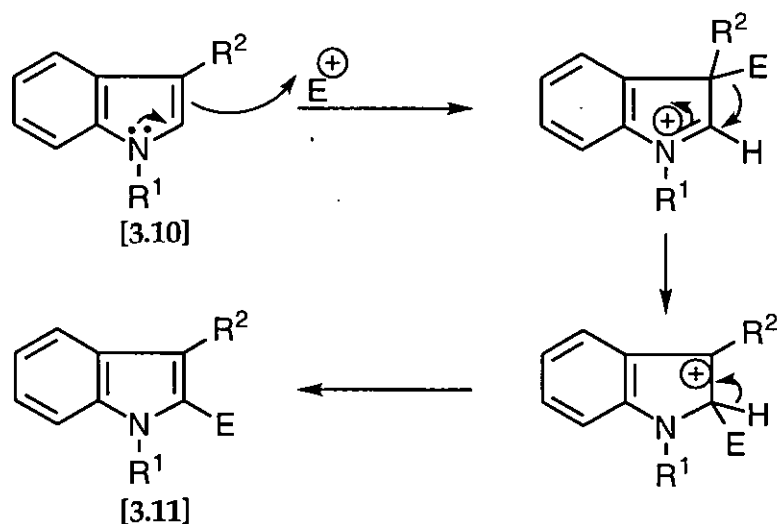
3.3 Attempted Formylation

Commercial indole-3-acetic acid smoothly underwent Fischer esterification using sulfuric acid in methanol to give the methyl ester [3.8], in 88% yield. Initially formylation of [3.8] was attempted under standard Vilsmeier-Haack conditions using phosphorus oxychloride and DMF, **Scheme 3.3**.¹⁴² The reaction failed to produce any of the aldehyde product [3.9], a mixture of unidentified side products were obtained together with unreacted ester [3.8].



Scheme 3.3

Formylation of indole compounds in the C-2 position is difficult because the preferred site for electrophilic substitution reactions on indole compounds is at the C-3 position. Indeed many electrophilic substitution reactions at C-2 using a blocked C-3 indole [3.10] actually involve initial attack at the C-3 position followed by rearrangement to give the C-2 substituted product [3.11], Scheme 3.4.¹⁴³

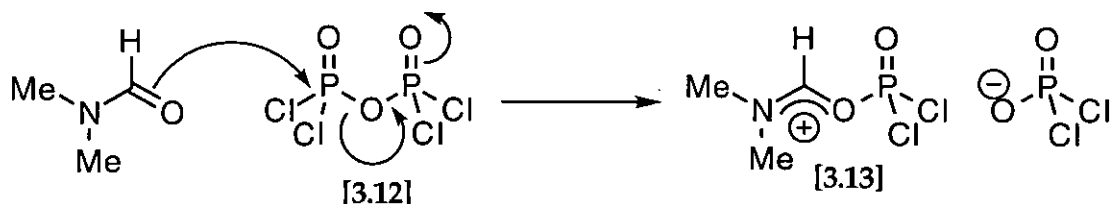


Scheme 3.4

Heaney reported that the formylating agent [3.13], formed from pyrophosphoryl chloride [3.12] and DMF, Scheme 3.5, is more electrophilic and therefore a more powerful formylating agent than the adduct formed by phosphorus oxychloride and DMF.¹⁴⁴ For example, the reaction of anisole with DMF/pyrophosphoryl chloride [3.13] gave 4-methoxybenzaldehyde in 71% yield whereas with DMF/phosphorus oxychloride the yield was only 34%.

However, the DMF/pyrophosphoryl chloride reagent [3.13] failed to convert methyl 2-(1*H*-3-indolyl)acetate [3.8] into the desired aldehyde

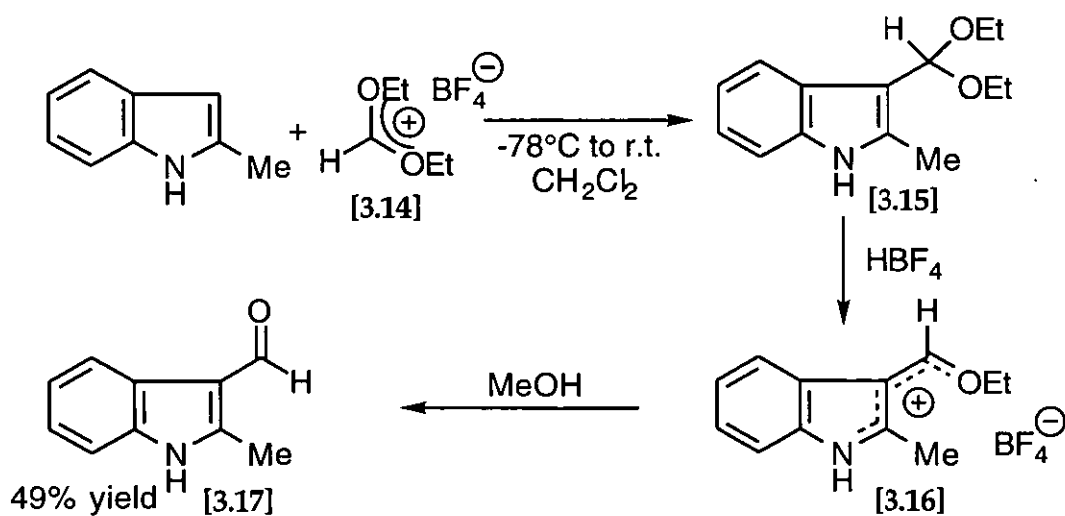
compound [3.9]. A mixture of unreacted starting material and unidentified product was again observed.



Scheme 3.5

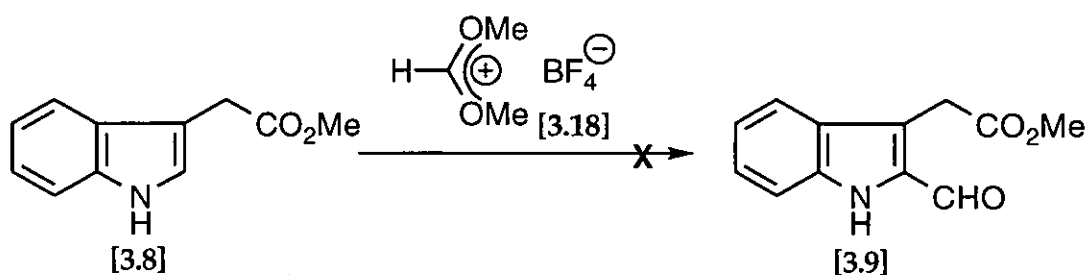
We next considered using dialkoxycarbenium tetrafluoroborates to formylate [3.8]. Dialkoxycarbenium tetrafluoroborates were first prepared by Meerwein from the reaction of ortho esters with Lewis acids such as BF_3 ,¹⁴⁵ they have also been formed with the Brønsted acid HBF_4 .¹⁴⁶ Pindur has utilised these oxo-stabilized carbenium ions as acylation reagents with several heterocyclic compounds.^{146, 147}

For example, diethoxycarbenium tetrafluoroborate [3.14] prepared by the reaction of HBF_4 -etherate with triethyl orthoformate, reacted with 2-methylindole at low temperature, Scheme 3.6.^{147(a)} The initially formed indolylacetal [3.15] spontaneously split to form the resonance stabilised 3-indolyloethoxycarbenium ion [3.16]. On addition of a nucleophilic solvent, such as methanol, dealkylation occurred to yield the aldehyde derivative [3.17].



Scheme 3.6

Dimethoxycarbenium tetrafluoroborate [3.18] was prepared from trimethyl orthoformate and BF_3 -etherate using the procedure developed by Heaney.¹⁴⁸ Attempted formylation of [3.8] using [3.18] failed to give the desired aldehyde [3.9], Scheme 3.7. At low temperature no reaction occurred and starting material was recovered. At higher temperatures, above 0°C , the reaction gave a complex mixture, in which none of the aldehyde [3.9] was observed. The reactions of indoles with [3.14] have been known to result in the formation of complex products. For example, 4-methoxyindole was regiospecifically functionalised at the 3-position by triethyl orthoformate to yield a tris(indolyl)methane.¹⁴⁶

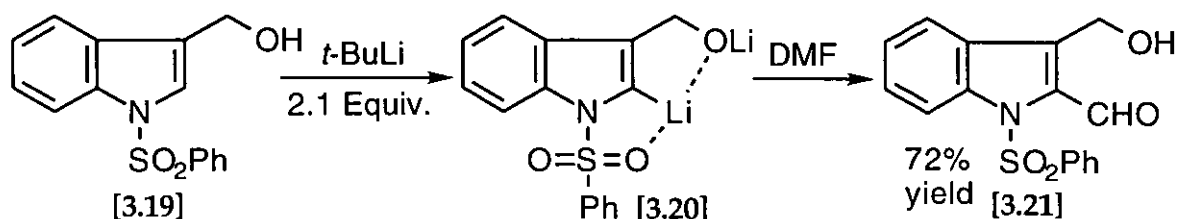


Scheme 3.7

The difficulty of direct formylation at the 2-position of [3.8] was confirmed by Shah.¹⁴⁹ He reported that formylation with either the Vilsmeier reagent or α,α -dichloromethyl methyl ether were unsuccessful.

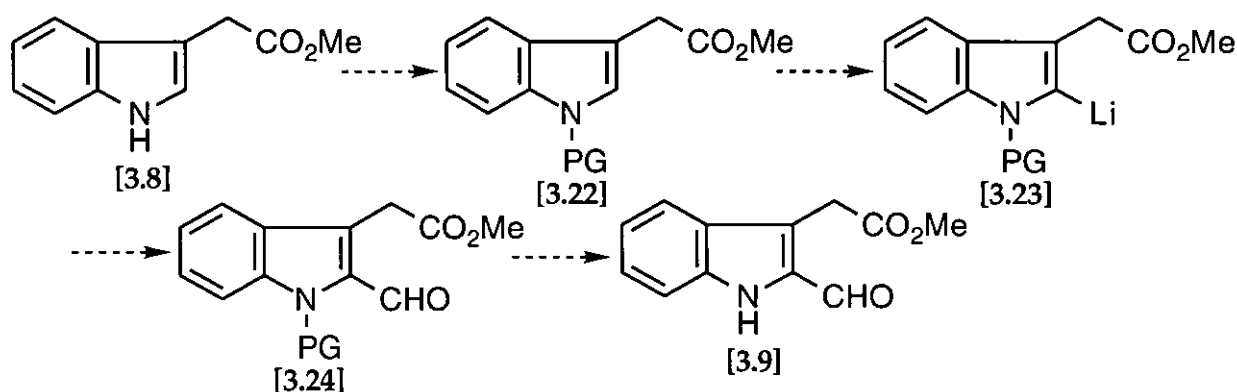
3.4 Attempted *ortho*-Lithiation

Another method of effecting nucleophilic substitution in the C-2 position of indoles is *via* directed *ortho*-metalation.¹⁵⁰ Certain protected indoles, such as the *N*-methyl,¹⁵¹ *N*-2-trimethylsilylethoxymethyl,¹⁵² and *N*-benzenesulfonylindole,¹⁵³ can be selectively lithiated at the C-2 position and subsequently reacted with a range of electrophiles. The appropriate protecting groups coordinate to the lithiating species and so direct attack into the adjacent position of the ring. For example, the *N*-benzenesulfonyl protected indole [3.19] was regioselectively dilithiated with *tert*-butyllithium,¹⁵⁶ presumably to give the species [3.20] with the lithium coordinated to both the alkoxide¹⁵⁴ and the sulfonyl groups,¹⁵⁵ Scheme 3.8. Treatment of [3.20] with DMF gave the aldehyde [3.21] in good yield.



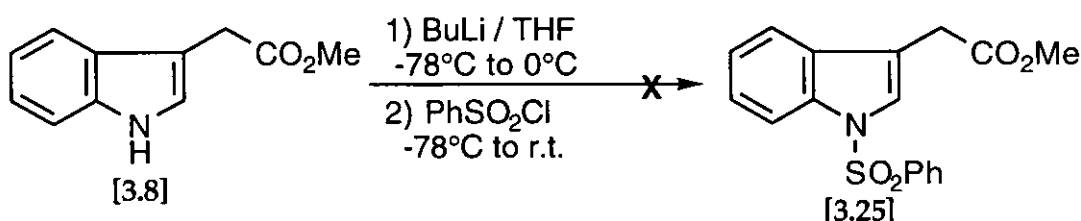
Scheme 3.8

The synthetic strategy for the desired indole compound [3.9] was as shown, **Scheme 3.9**. Protection of [3.8] with a group PG, which directs *ortho*-lithiation, would give [3.22]. Lithiation of [3.22] followed by reaction with DMF should provide the protected aldehyde [3.24], which on deprotection would yield the desired indole [3.9]. A requirement for the successful application of protecting groups is that both their preparation and removal should be high yielding without effecting other functionality present in the substrate.¹⁵⁷



Scheme 3.9

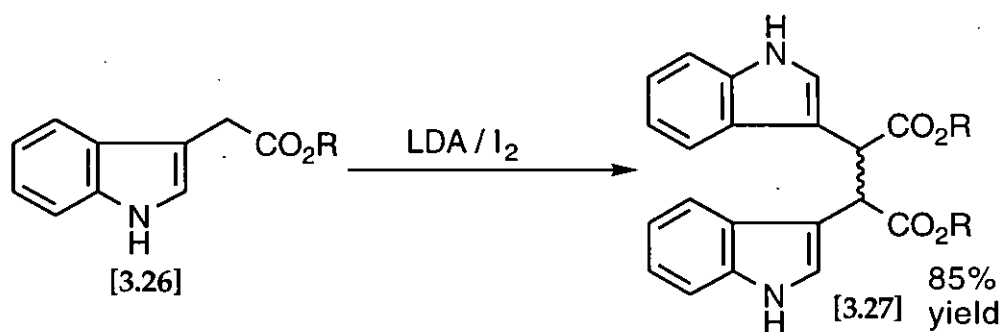
The initial target molecule was the 1-phenylsulfonyl protected ester [3.25]. The indole ester [3.8] was reacted with butyllithium and phenylsulfonyl chloride using the procedure of Gribble, **Scheme 3.10**.¹⁵⁸ This reaction resulted in a complex mixture from which it proved impossible to isolate any of the desired *N*-protected indole [3.25].



Scheme 3.10

Protection of [3.8] with the methoxymethyl (MOM) group was also attempted. A mild base, potassium carbonate, was employed to deprotonate the indole nitrogen, followed by reaction with chloromethyl methyl ether ($\text{ClCH}_2\text{OCH}_3$). Unfortunately this reaction gave a complex mixture and failed to produce the desired protected indole.

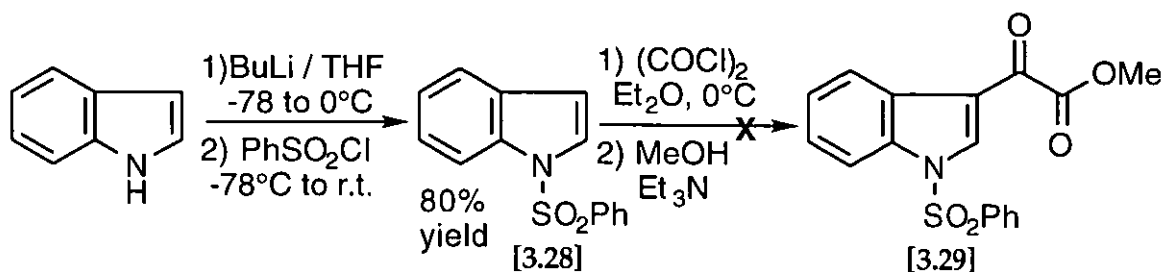
The problem of producing the *N*-protected analogues of [3.8] is presumably due to the acidity of the methylene protons. The methylene group at the 3-position of indole-3-acetic acid derivatives is adjacent to both carboxyl functionality and the indole ring. This makes the protons acidic because the anion resulting from their reaction with base is extensively stabilised by conjugation. Several groups have exploited the acidity of these protons.^{159,160} Bergman reported that the reaction of an ester of indole-3-acetic acid [3.26] with two equivalents of lithium diisopropylamine LDA and iodine produced the product [3.27] where two indole molecules were coupled *via* the methylene bridge, **Scheme 3.11**.¹⁶⁰



Scheme 3.11

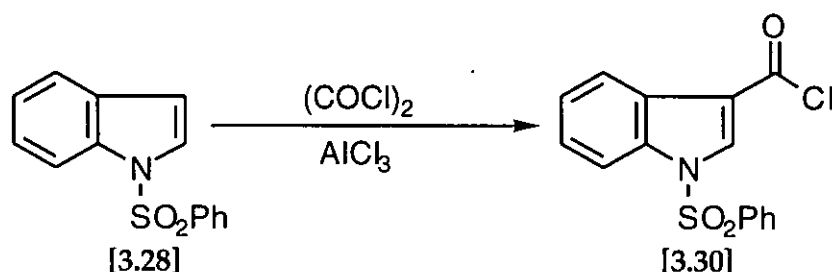
An alternative route to the lithiation precursor [3.25] was proposed. This involved initial protection of indole, followed by introduction of the methyl 3-acetate functionality by a two-step process of glyoxylation and subsequent selective reduction to provide [3.25].

Protection of indole with phenylsulfonyl chloride proceeded smoothly to give [3.28] in 80% yield, **Scheme 3.12**. Addition of oxalyl chloride followed by reaction with methanol, in the presence of triethylamine to quench the hydrochloric acid produced, should have provided the methyl glyoxylate derivative [3.29]. However, the reaction failed and unreacted [3.28] was recovered, presumably because the electron withdrawing phenylsulfonyl group decreased the nucleophilicity of the indole.



Scheme 3.12

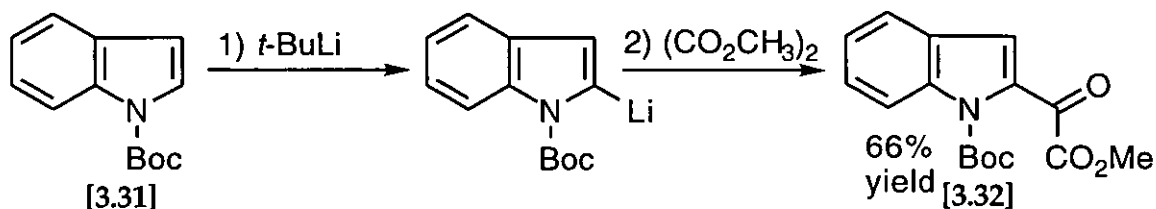
The decreased reactivity of [3.28] was demonstrated by Gribble's report that [3.28] failed to react with ethyl chloroformate.¹⁶¹ It was also found that use of a Lewis acid, AlCl_3 , in the addition of oxalyl chloride to [3.28] unexpectedly proceeded with decarbonylation to give the acid chloride [3.30] rather than the anticipated 3-glyoxalyl chloride derivative, Scheme 3.13.



Scheme 3.13.

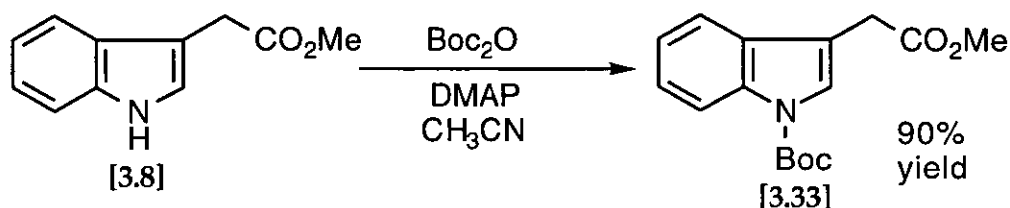
The difficulties encountered suggested that further research on this route would be unprofitable.

The *tert*-butoxycarbonyl (Boc) group has also been successfully used as a directing group for *ortho*-lithiation.¹⁶² For example, lithiation of Boc protected indole [3.31] with *tert*-butyllithium followed by addition of dimethyl oxalate produced the methyl 2-glyoxylate derivative [3.32], Scheme 3.14.



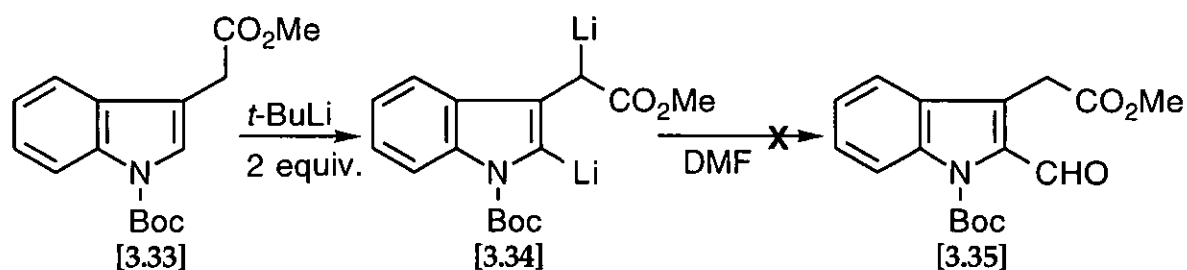
Scheme 3.14

The authors prepared the *N*-protected indole [3.31] by the reaction of sodium hydride and *tert*-butoxycarbonyl azide $[\text{N}_3\text{CO}_2\text{C}(\text{CH}_3)_3]$.¹⁶³ Obviously this method is unsuitable for [3.8] because of the problems caused by the methylene protons. However, Boc protection can also be achieved using *di-tert*-butyl-dicarbonate and 4-dimethylaminopyridine (DMAP) in acetonitrile. Under these conditions [3.33] was successfully prepared in high yield, **Scheme 3.15**.



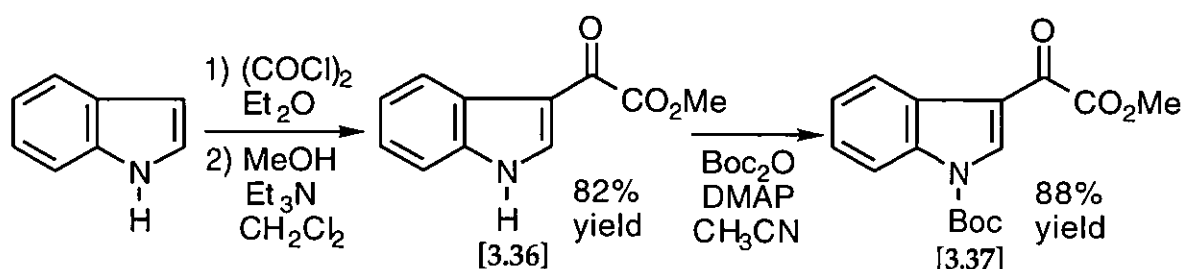
Scheme 3.15

It was reasoned that initial lithiation of [3.33] would remove one of the methylene protons and that a second molecule of *tert*-butyllithium would be required to lithiate the α -position giving the dilithiated species [3.34]. Subsequent addition of DMF should produce the aldehyde [3.35]. Unfortunately none of the desired aldehyde was observed after reaction with [3.33] under these conditions. The reaction mixture gave a complex mixture from which the only recognisable isolated material was unreacted starting material [3.33], **Scheme 3.16**.



Scheme 3.16

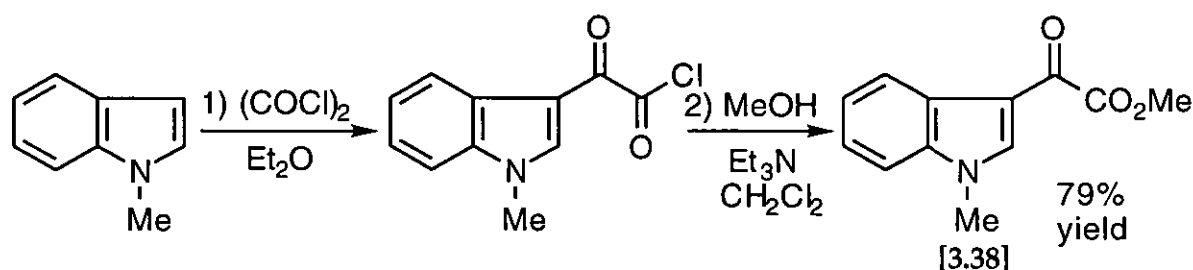
It was envisaged that lithiation of an analogue of [3.33] without a methylene group would limit the possible side products. To achieve this a methyl 3-glyoxylate derivative [3.37] was prepared by addition of oxalyl chloride followed by methanol and triethylamine to indole and then protection of the indole nitrogen with a Boc group, **Scheme 3.17**.



Scheme 3.17

Lithiation of this substrate [3.37] was attempted using a slight excess of *tert*-butyllithium, followed by reaction with DMF. Again a complex mixture resulted, from which some unreacted starting material was the only recognisable product recovered.

It was proposed that replacing the methyl 3-acetate functionality with an analogue containing a directing group instead of the methylene protons would enable *ortho*-lithiation without unwanted side products. In order to obtain the desired product it is necessary to use a directing group which is removable after the reaction is completed. As a first step 1-methylindole was converted to the glyoxylate derivative [3.38], Scheme 3.18.

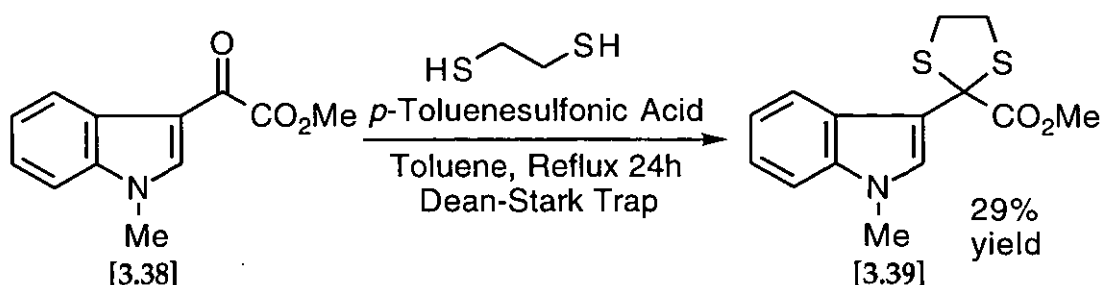


Scheme 3.18

It was envisaged that conversion of the glyoxylate [3.38] into the dithiolane [3.39] would provide a directing group for lithiation. After lithiation and introduction of an aldehyde group in the 2-position the dithiolane [3.39] could be reductively cleaved by Raney nickel to produce the desired methyl 3-acetate functionality.

Refluxing [3.38] and 1,2-ethane dithiol with a catalytic amount of *para*-toluenesulfonic acid whilst azeotropically removing the water with a Dean-

Stark trap gave the dithiolane [3.39], Scheme 3.19.¹⁶⁴ However the product [3.39] was isolated in only a poor 29% yield.



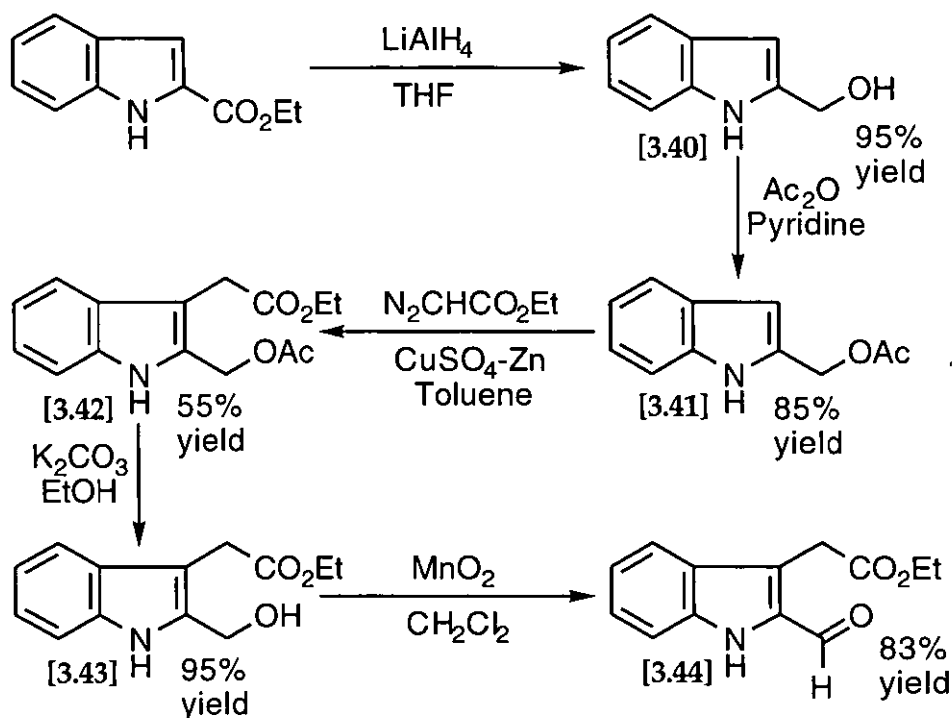
Scheme 3.19

An alternative procedure for preparing thioketals such as [3.39] is to react [3.38] and the dithiol with boron trifluoride etherate in acetic acid.¹⁶⁵ Under these conditions the thioketal [3.39] was again obtained but only in a disappointing 31% yield. The absence of a high yielding procedure for the formation of [3.39] made this approach impractical.

The continued problems encountered in developing a synthesis based on the introduction of a formyl group *via ortho*-lithiation indicated that an alternative approach was required.

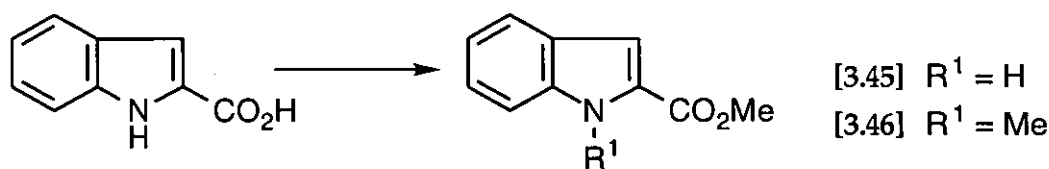
3.5 Oxidation Strategy

The indole compound [3.44], containing both 2-formyl and ethyl 3-acetate groups has been prepared by the following multi-stage procedure, Scheme 3.20.¹⁶⁶ Ethyl 2-indolecarboxylate was reduced to the alcohol [3.40] which was then protected as the acetate [3.41] by reaction with acetic anhydride. The key step was decomposition of ethyl diazoacetate with [3.41] to introduce the ethyl 3-acetate functionality. The reaction, catalysed by a copper reagent formed from copper sulfate and zinc metal, gave the product [3.42] in a modest 55% yield. Selective hydrolysis of the acetate gave the unmasked alcohol [3.43] which was oxidised to the aldehyde [3.44] using manganese dioxide, Scheme 3.20.



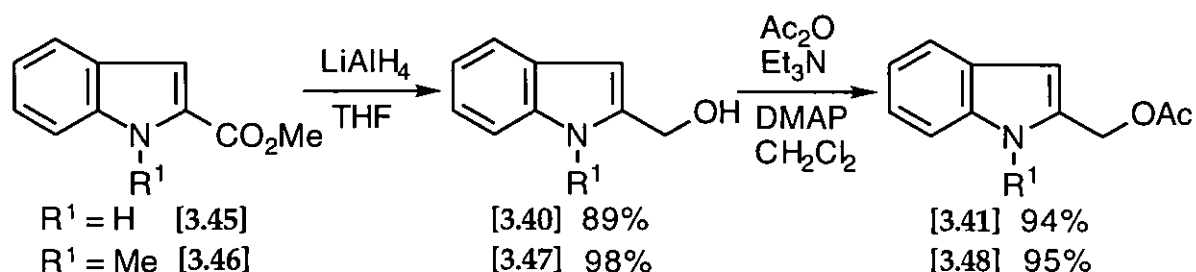
Scheme 3.20

Both the unprotected and the methyl protected indole esters were prepared from indole-2-carboxylic acid, Scheme 3.21. Fischer esterification with sulfuric acid in methanol provided the methyl ester [3.45] in 91% yield. The dimethylated compound [3.46] was prepared according to the procedure of Heaney and Ley.¹⁶⁷ Deprotonation of the indole-2-carboxylic acid with potassium hydroxide in DMSO followed by reaction with methyl iodide gave [3.46] in 96% yield.



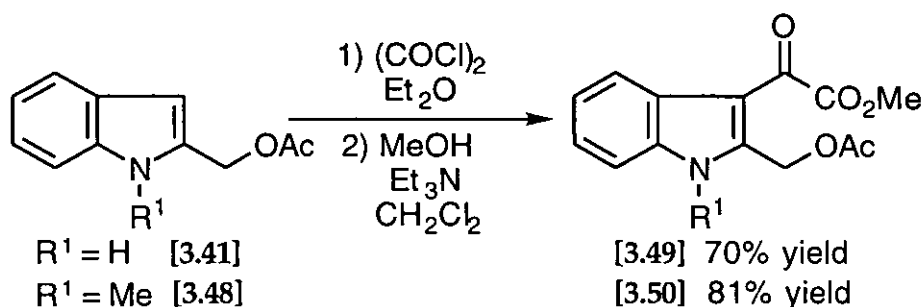
Scheme 3.21

These indole esters [3.45] and [3.46] were reduced with lithium aluminium hydride to give the corresponding alcohols [3.40] and [3.47] which were protected as the acetates [3.41] and [3.48], Scheme 3.22. Protection was effected using acetic anhydride in the presence of triethylamine and DMAP. All these reactions proceeded in excellent yields.



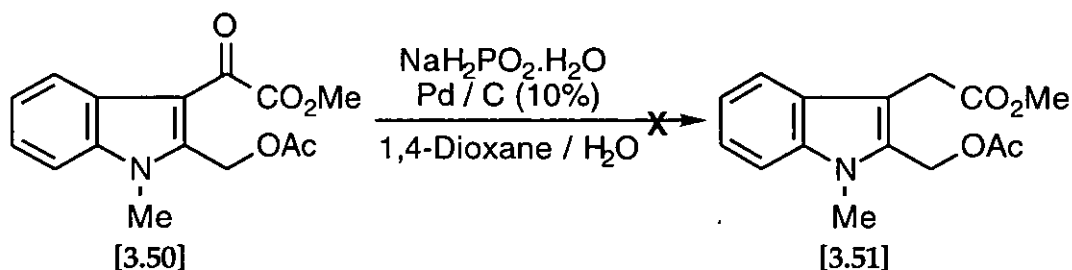
Scheme 3.22

It was proposed that the modest yield for the introduction of the 3-acetate functionality could be improved by utilising the two-step glyoxylation-hydrogenolysis procedure instead of the reaction with ethyl diazoacetate. Glyoxylation of [3.41] and [3.48] was carried out as described previously, Scheme 3.17, producing the methyl 3-glyoxylate derivatives [3.49] and [3.50] in good yields, Scheme 3.23.



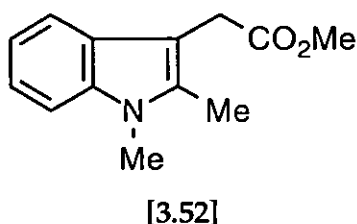
Scheme 3.23

Palladium on charcoal combined with sodium hypophosphite has proved a convenient method for hydrogen transfer hydrogenation for a range of functional groups.¹⁶⁸ In 1989 Demopoulos reported its application to the hydrogenolysis of indole and pyrrole glyoxylates.¹⁶⁹ However when this procedure was applied to [3.50] the desired product [3.51] was not formed, Scheme 3.24.



Scheme 3.24

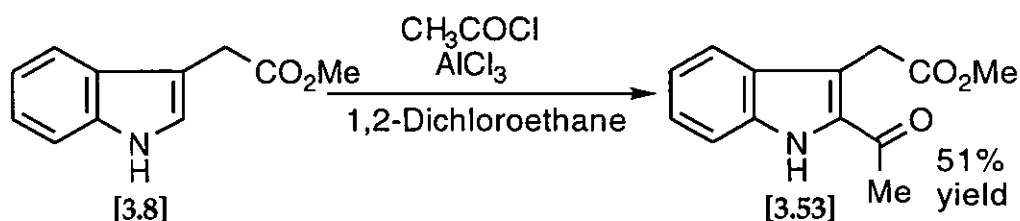
Analysis of the reaction mixture indicated that the main product, isolated in 83% yield, was [3.52]. It was formed by hydrogenolysis of the glyoxylate and loss of acetic acid from the 2-position. The formation of [3.52] was unexpected as Demopoulos' stated that the presence of a glyoxylate group is essential.¹⁶⁹ Both carboxylic acid and acetyl substituents are normally stable to the reaction conditions even on prolonged exposure. Due to this unexpected reduction and time constraints, work in this area was halted.



3.6 Ketone Targets

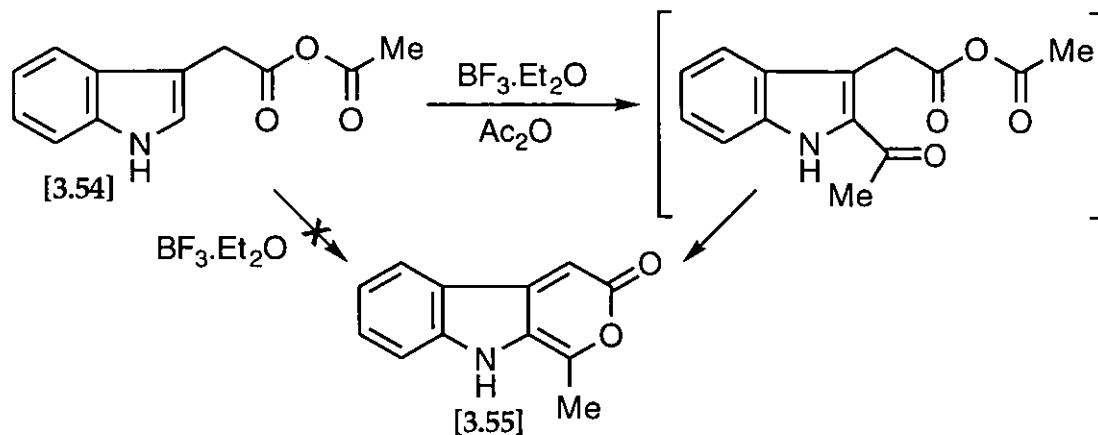
The difficulties encountered substituting indole-3-acetate derivatives with a 2-formyl group led to the consideration of the corresponding 2-acetyl compounds.

The Friedel-Crafts acylation of [3.8] provided the desired 2-acetyl substituted indole [3.53] in 51% yield, Scheme 3.25.



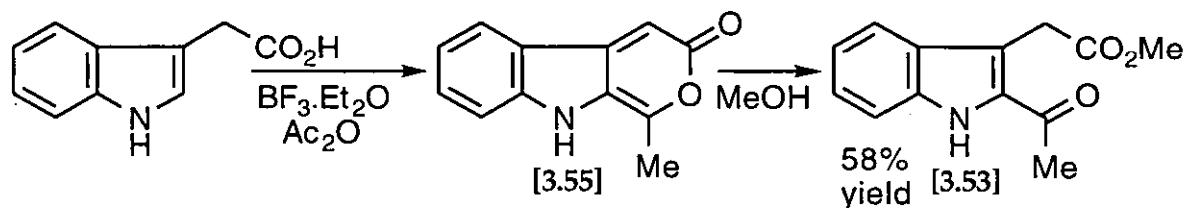
An alternative method of preparing [3.53] is *via* the ring opening of the pyrano[3,4-*b*]indol-3-one [3.55] with methanol. Plieninger discovered in 1964 that treatment of indole-3-acetic acid with acetic anhydride in the presence of boron trifluoride etherate gave the pyrano[3,4-*b*]indol-3-one [3.55].¹⁷⁰ Pindur determined that the reaction proceeded by initial formation of the mixed anhydride [3.54] followed by intermolecular reaction with a second molecule of acetic anhydride to introduced the 2-acyl substituent.¹⁷¹ By contrast treatment of [3.54] with boron trifluoride etherate in the absence of acetic

anhydride failed to give any of the pyrano[3,4-*b*]indol-3-one [3.55], Scheme 3.26.



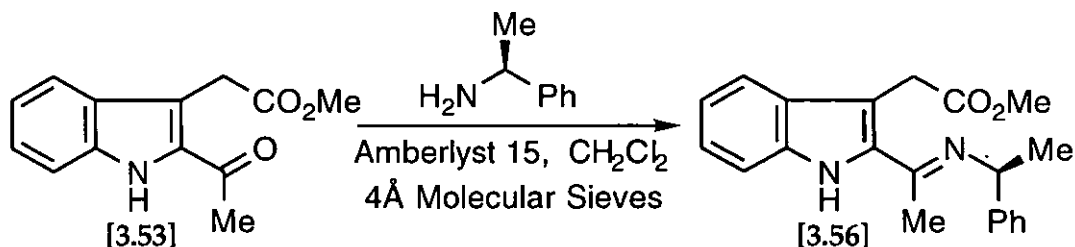
Scheme 3.26

Treating indole-3-acetic acid with boron trifluoride etherate and acetic anhydride gave [3.55] which opened on stirring with methanol to give after chromatography [3.53] in 58% overall yield, Scheme 3.27.



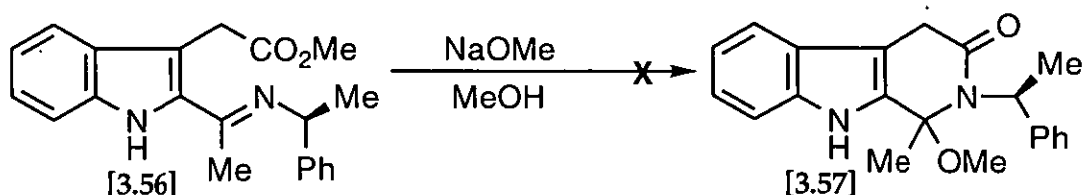
Scheme 3.27

Refluxing [3.53] with an excess of S-(1)-phenylethylamine in the presence of amberlyst 15 produced the imine [3.56] in 90% yield, Scheme 3.28. The water formed as a by-product of imine formation was removed by activated 4Å molecular sieves.



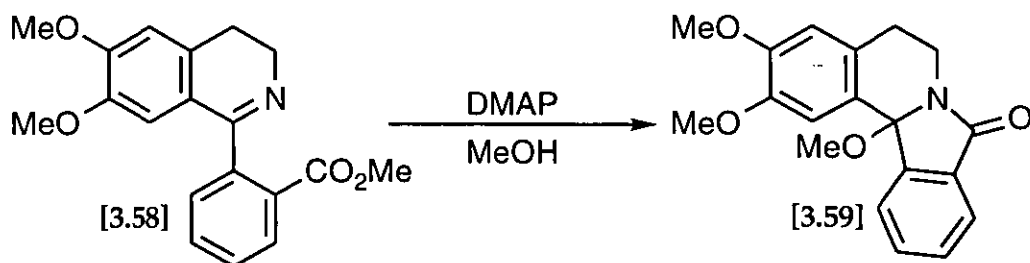
Scheme 3.28

As was shown in **Chapter Two**, imines of this type can be cyclised by reaction with sodium methoxide. When these conditions were applied to [3.56] none of the cyclised product [3.57] was observed, **Scheme 3.29**. After aqueous work-up the main isolated product was the 2-acetyl indole derivative [3.53]. Presumably [3.53] was formed by unreacted imine [3.56] cleaving under the conditions of the work-up. A small amount of unidentifiable material was also formed during this reaction.



Scheme 3.29

Related isoquinolines have been cyclised by refluxing the isoquinoline in methanol with a catalytic quantity of DMAP. For example the isoquinoline derivative [3.58] rearranged quantitatively under these conditions to the acyl aminol ether [3.59], **Scheme 3.30**.¹⁷²

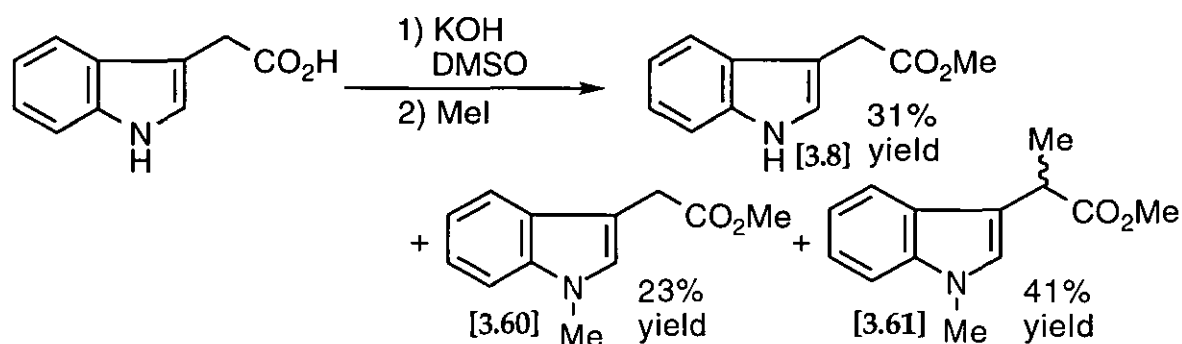


Scheme 3.30

The imine [3.56] was refluxed with DMAP in methanol in order to carry out the rearrangement to [3.57]. Again the reaction failed to produce [3.57], with [3.53] being the main isolated product. It was not possible to identify any of the other products.

The failure to produce the product [3.57] using either of the procedures was disappointing. In order to gain further insight into this rearrangement it was decided to prepare the corresponding *N*-methyl analogue.

Methylation of indole-3-acetic acid with methyl iodide using the Heaney-Ley procedure gave a mixture of products, **Scheme 3.31**.¹⁶⁷ The mono- [3.8], bi- [3.60], and tri-alkylated [3.61] products were all formed in the reaction. Only 23% of the desired *N*-methyl ester [3.60] was isolated from the reaction mixture. In addition, purification of the compound was problematic with separation of [3.60] from [3.61] by chromatography proving to be particularly troublesome.



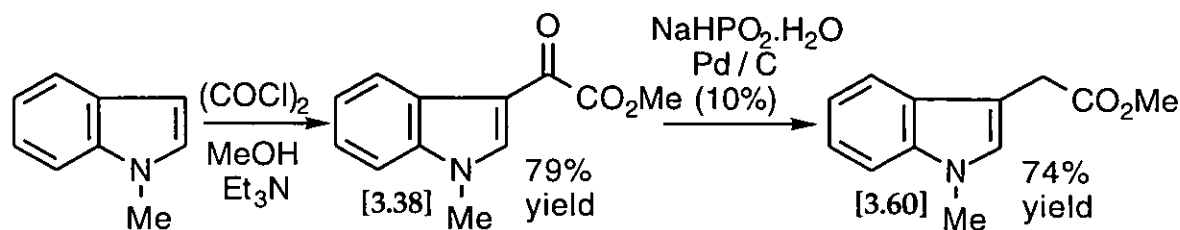
Scheme 3.31

An improved synthesis was obviously required in order to make [3.60] more accessible. It was reasoned that the production of a trianion was very unlikely. Therefore the tri-alkylated species [3.61] must be formed by deprotonation of either the mono- [3.8] or di-alkylated species [3.60] after addition of the methyl iodide. Removal of the base before addition of the methyl iodide should remove the possibility of forming [3.61].

A modified procedure was developed where treatment of indole-3-acetic acid with potassium hydroxide for several hours gave the dipotassium salt as a green solution. This salt was filtered under nitrogen to remove the potassium hydroxide before addition of methyl iodide. This modified process gave the desired *N*-methyl ester [3.60] in a much improved 63% yield. Some of the tri-alkylated species [3.61] was still produced, 17% yield, presumable because of potassium hydroxide dissolved in the DMSO.

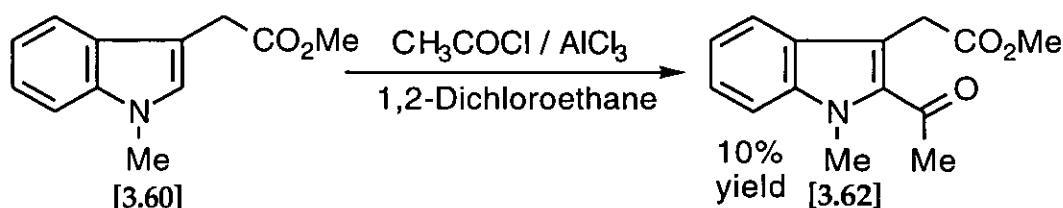
This procedure still required a difficult separation by chromatography. Bloxham described the formation of [3.60] by a two-step route of glyoxylation followed by reduction of *N*-methyl indole.¹⁷³ In our hands this procedure gave the desired product [3.60] in 58% overall yield for the two steps, **Scheme 3.32**. This approach gave a slightly lower yield of [3.60] and required an extra

step but it avoided the difficult purification of the modified Heaney-Ley procedure.



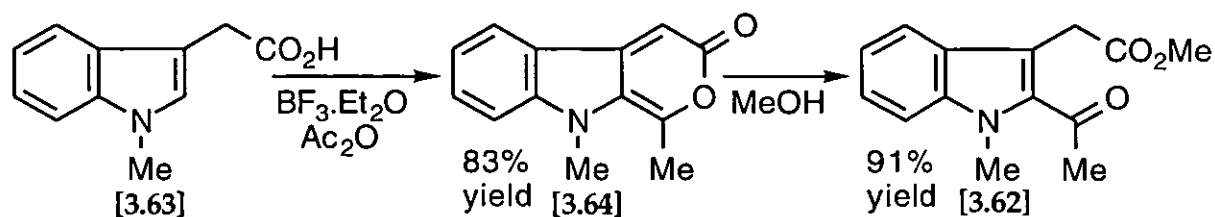
Scheme 3.32

Friedel-Crafts acylation of [3.60] with acetyl chloride and aluminium chloride proved to be disappointing, providing only a 10% yield of the 2-acetyl indole derivative [3.62], Scheme 3.33.



Scheme 3.33

Another route was obviously required so formation of [3.62] *via* the pyranone was investigated. Hydrolysis of [3.60] proceeded smoothly using lithium hydroxide in THF/water to give the *N*-methyl indole-3-acetic acid [3.63] in 87% yield. Reaction of [3.63] with acetic anhydride in the presence of boron trifluoride etherate using the procedure of Plieninger gave the pyrano[3,4-*b*]indol-3-one [3.64].¹⁷⁰ Stirring with methanol provided the desired 2-acetyl substituted product [3.62] in 66% overall yield, Scheme 3.34.

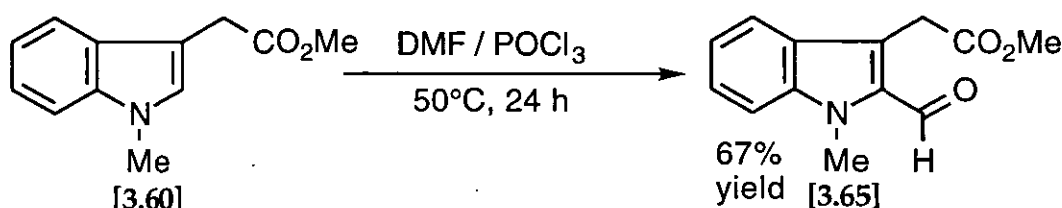


Scheme 3.34

Surprisingly imine formation proved problematic. When [3.62] was refluxed with S-(1)-phenylethylamine and amberlyst 15 using the same procedure as for the imine [3.56], **Scheme 3.28**, the reaction failed to produce the imine in good yield. Small amounts of the imine were formed but the reaction mixture largely consisted of unreacted starting material [3.62] even after refluxing for 48 h.

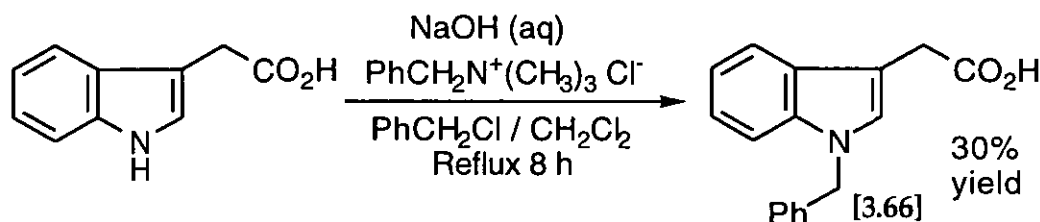
3.7 Formylation of *N*-Protected Derivatives

The *N*-methylation of indole derivatives increases the nucleophilicity of the indole 2-position. It was speculated that the nucleophilicity of methyl *N*-methylindole-3-acetate [3.60] would be sufficient for successful Vilsmeier-Haack formylation. Under standard conditions, DMF and phosphorus oxychloride, the 2-formylation was achieved in good yield, **Scheme 3.35**.¹⁴² Replacing phosphorus oxychloride with pyrophosphoryl chloride gave no improvement and the product [3.65] was formed in a comparable yield, 65%.



Scheme 3.35

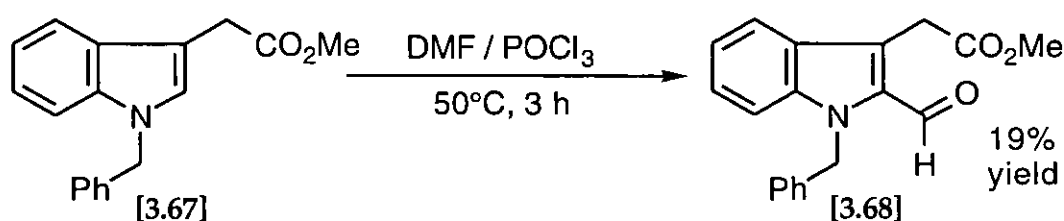
It was proposed that the *N*-benzyl protected analogue of [3.60] would be nucleophilic enough to allow formylation, with the advantage of allowing deprotection of the indole nitrogen at a later stage. The *N*-benzyl indole-3-acetic acid [3.66] was prepared using aqueous sodium hydroxide solution and benzyl chloride in dichloromethane with the phase transfer catalyst benzyl trimethylammonium chloride, **Scheme 3.36**.¹⁷⁴



Scheme 3.36

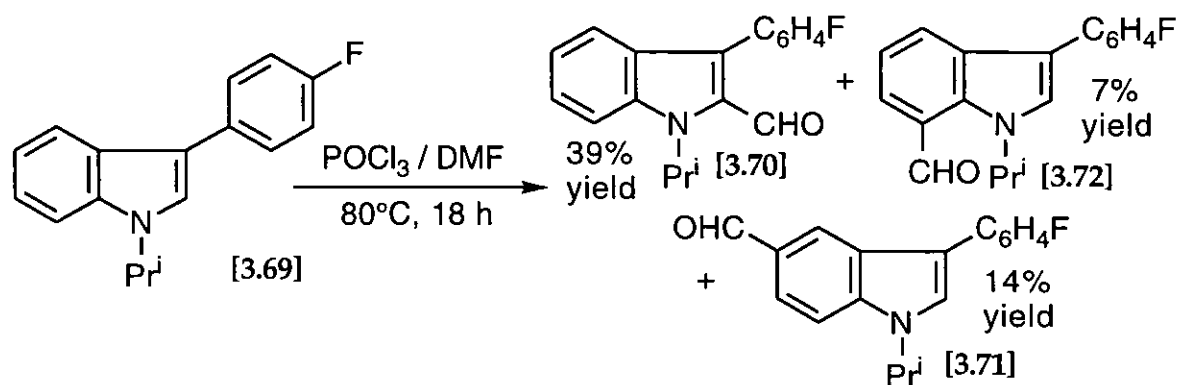
The disappointing yield of this reaction prompted the investigation of other methods of preparation. An alternative procedure using an excess of sodium hydride to deprotonate the indole-3-acetic acid in DMF was utilised.¹⁷⁵ Reaction of the anion with benzyl bromide provided, following acidic work-up, the desired protected indole [3.66] in excellent yield, 90%.

Fischer esterification of [3.66] proceeded smoothly with sulfuric acid in methanol to give [3.67] in 97% yield. Formylation of [3.67] using the Vilsmeier reagent, pre-formed from DMF and phosphorus oxychloride, gave a mixture of products. The desired 2-formylated derivative [3.68] was isolated in only 19% yield, **Scheme 3.37**.



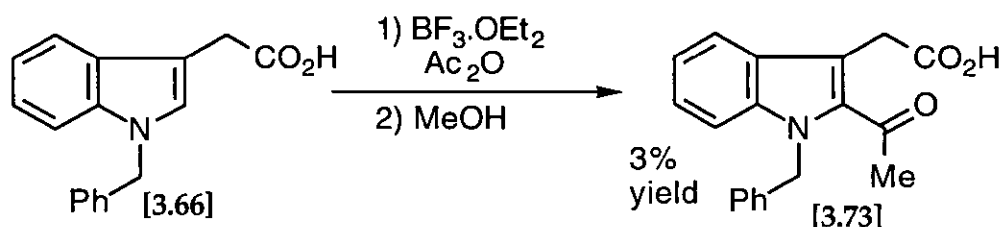
Scheme 3.37

Analysis of the ¹H NMR of the crude reaction mixture showed that other formylated compounds were present, presumably the 5- or 7-formylated regioisomers, although their isolation proved problematic. Evidence to support this proposal was disclosed by Walkup, who found that the 1,3-substituted indole [3.69] gave a mixture of the 2- [3.70], 5- [3.71] and 7-formylated [3.72] products when subjected to Vilsmeier-Haack conditions, **Scheme 3.38**.¹⁷⁶ With the *N*-methyl protected analogue of [3.69] the 2-formylated indole was the sole product. The authors concluded that the lower regioselectivity with [3.69] was due to the increased steric requirements.



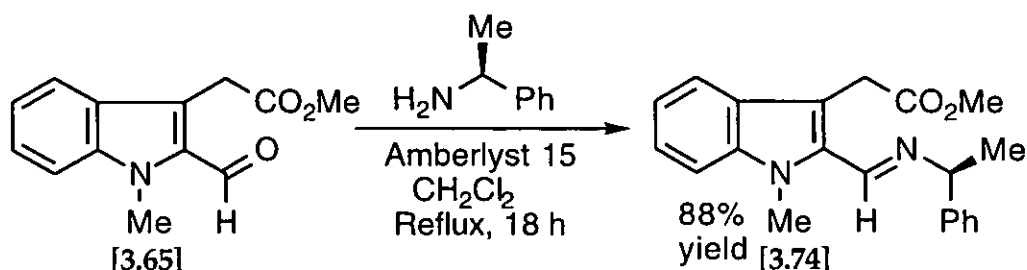
Scheme 3.38

The difficulty of carrying out reactions at the 2-position of the *N*-benzyl derivatives was also illustrated by the preparation of the 2-acetyl derivative of **[3.67]** *via* the pyranone. Initial pyranone formation from **[3.66]** was problematic so the crude product was stirred in methanol and purified as the 2-acetyl product **[3.73]**, **Scheme 3.39**. After chromatography, **[3.73]** was isolated in a mere 3%, indicating the steric problems of substitution in the 2-position of these substrates.



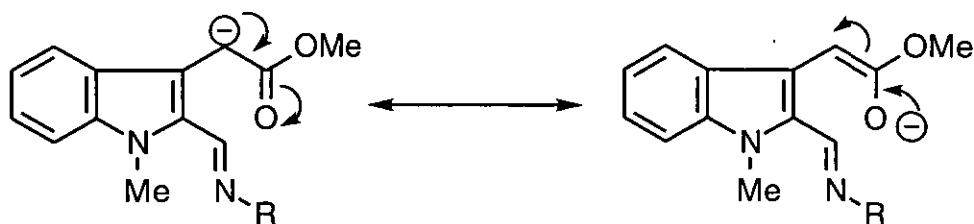
Scheme 3.39

Reaction of **[3.65]** and *S*-(1)-phenylethylamine with amberlyst 15 produced the imine **[3.74]** in good yield, **Scheme 3.40**. Filtration of the amberlyst 15 and removal of the solvent was sufficient to give imine **[3.74]** of high purity.



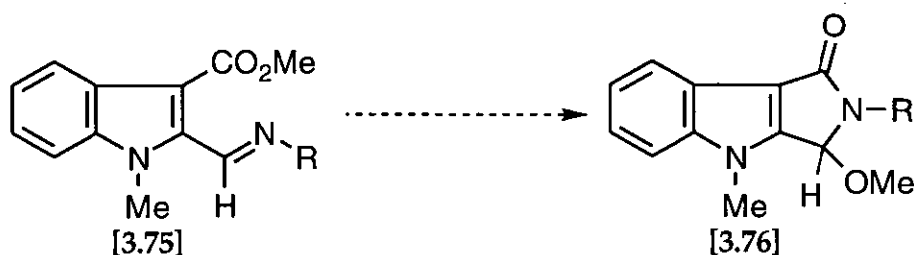
Scheme 3.40

Attempted rearrangement of [3.74] with either sodium in methanol or refluxing with DMAP in methanol both failed to give the cyclised product. It was postulated that the sodium methoxide produced in the reaction deprotonated the acidic methylene bridge of [3.74] to give the stabilised anion, **Scheme 3.41**. On work-up this anion is re-protonated to give unreacted starting material [3.74].



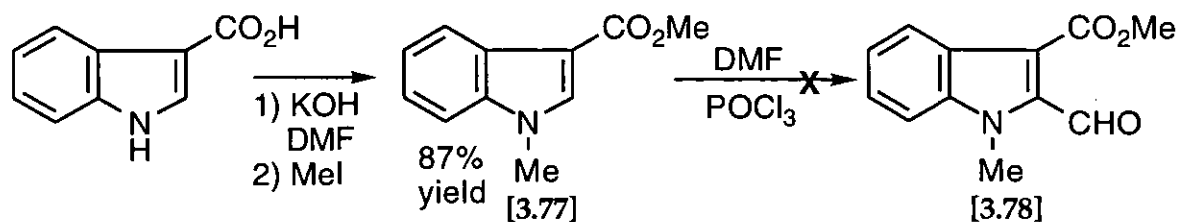
Scheme 3.41

In order to test this proposal it was decided to prepare an imine of the type [3.75] which does not contain the acidic methylene protons of [3.74]. Successful cyclisation would give the 5-membered ring product [3.76], **Scheme 3.42**.



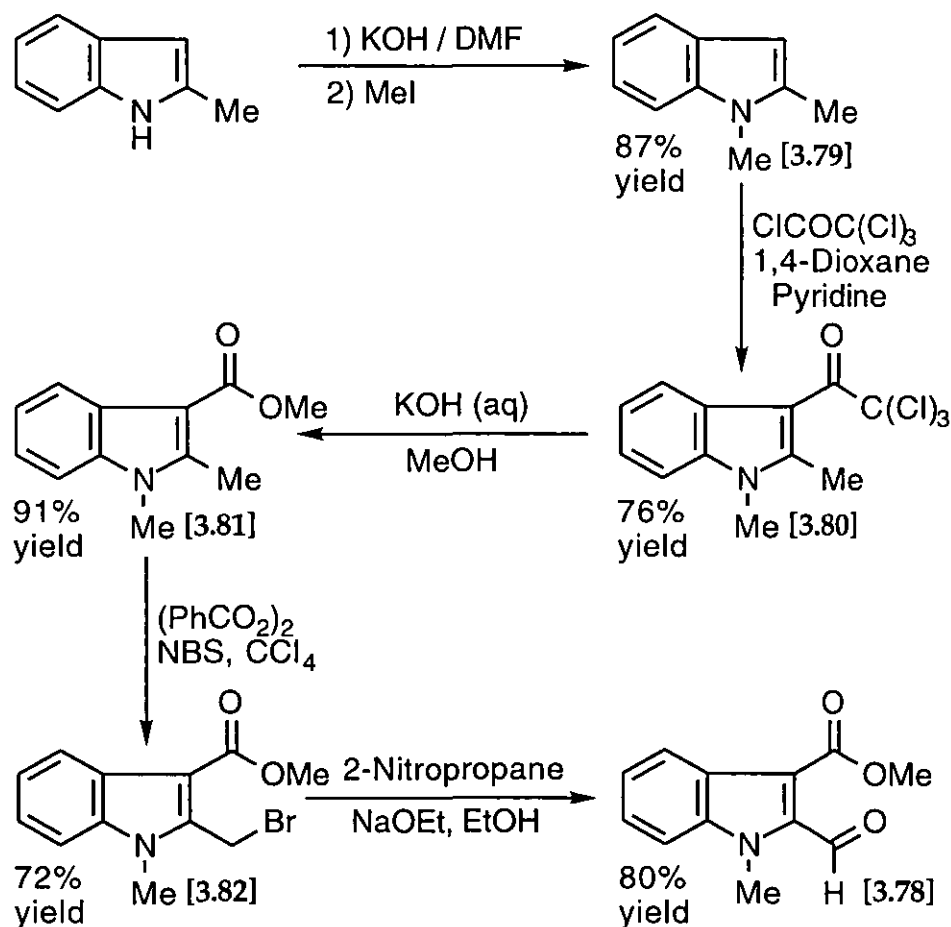
Scheme 3.42

Methyl 1-methyl-3-indolecarboxylate [3.77] was prepared by methylation of the parent acid. However Vilsmeier-Haack formylation failed because the electron withdrawing 3-carboxylate group reduces the nucleophilicity of the indole, **Scheme 3.43**.



Scheme 3.43

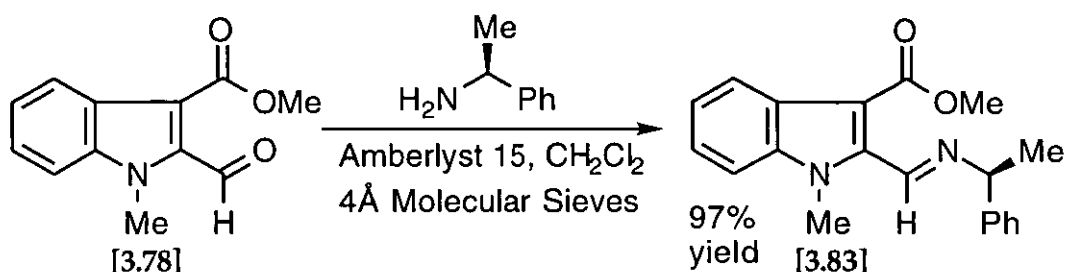
The aldehyde [3.78] was synthesised as previously reported by Jones, Scheme 3.44.¹⁷⁷



Scheme 3.44

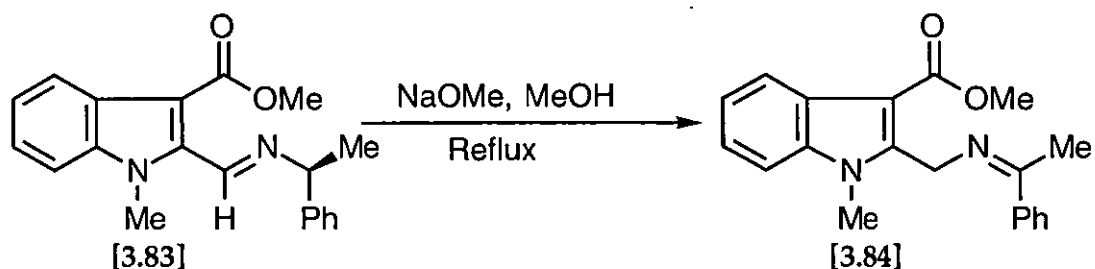
Methylation *via* the Heaney-Ley procedure converted the 2-methyl indole into the 1,2-dimethylindole [3.79], Scheme 3.44. Acylation with trichloroacetyl chloride gave the trichloro ketone [3.80], which underwent a haloform-type reaction with potassium hydroxide in methanol to give the methyl ester [3.81]. Radical bromination with *N*-bromosuccinimide (NBS) is highly regioselective for the benzylic position adjacent to an aromatic ring providing the benzylic bromide derivative [3.82].¹⁷⁸ The benzylic bromide was converted into an aldehyde using the method developed by Hass.¹⁷⁹ Reaction of 2-nitropropane with sodium ethoxide followed by refluxing with [3.82] gave the aldehyde [3.78].

The imine [3.83] was prepared in excellent yield by refluxing the aldehyde [3.78] with S-(1)-phenylethylamine in the presence of a catalytic amount of amberlyst 15, **Scheme 3.45**.



Scheme 3.45

Rearrangement of [3.83] catalysed by sodium methoxide failed to give any reaction after stirring at room temperature for 24 h. Refluxing in methanol did enable a reaction to occur, however the desired cyclised product of the type [3.76] was not isolated. Recrystallisation gave a product whose ^1H NMR contained aromatic signals but lacked the distinctive doublet of the methyl group of the 2-phenylethyl substituent and any signal for the methine proton. The ^1H NMR contained singlets at 5.39 ppm, corresponding to a methylene group, and at 2.47 ppm, from a methyl group. On the basis of this data the rearranged imine [3.84] was proposed as the product formed by this reaction **Scheme 3.46**.



Scheme 3.46

3.8 Summary

The reactions of indole-3-acetic acid derivatives proved to be very problematic. The high acidity of the methylene protons of these substrates made base activated reactions very difficult to carry out cleanly. In addition a fine balance of factors made the reactivity of various related substrates difficult to predict. For example, methyl indole-3-acetate was not sufficiently nucleophilic to undergo formylation, whereas the *N*-methyl analogue gave the 2-formyl product in good yield. However on using the *N*-benzyl analogue the 2-formyl product was obtained in only poor yield because of the increased steric hindrance of the substrate.

The failure of all the imine derivatives to cyclise was very disappointing and questions the validity of the initial proposal. In particular the failure of [3.83] which contained no acidic protons was difficult to understand and suggests that the lack of reactivity of these imines to the cyclisation procedure may be more complex than we have suspected.

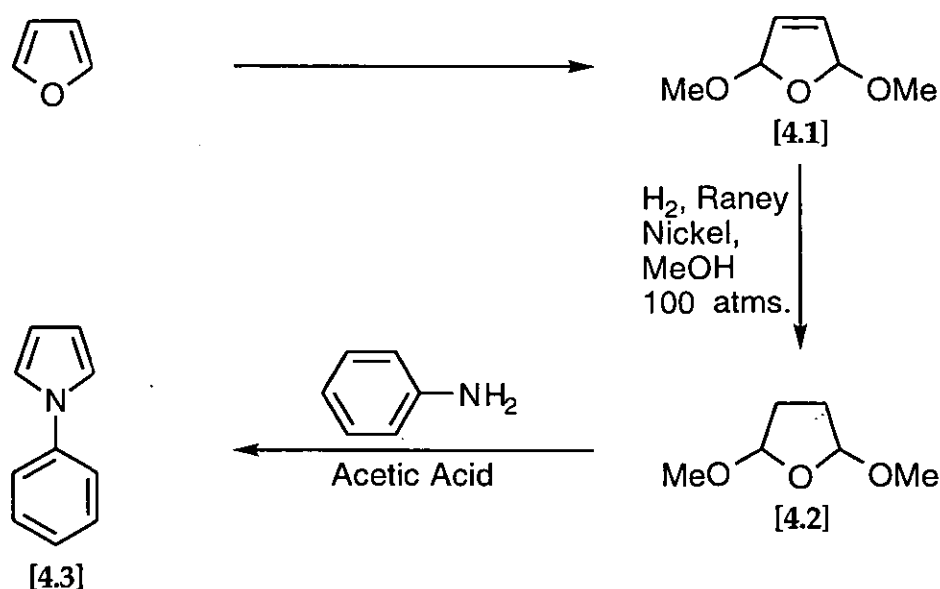
Chapter 4

The Modified Clauson-Kaas Pyrrole Synthesis

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4.1 Introduction

In 1952 Clauson-Kaas reported a general method for the production of pyrroles from furans *via* a three step procedure.^{180,181} For example, furan was electrolytically methoxylated to give the 2,5-dimethoxy-2,5-dihydrofuran [4.1], **Scheme 4.1**. Catalytic hydrogenation of [4.1] using Raney Nickel resulted in the 2,5-dimethoxytetrahydrofuran [4.2], which when reacted with aniline in refluxing acetic acid gave 1-phenylpyrrole [4.3] in 59% overall yield for the three steps.



Scheme 4.1

The key step in this procedure is the reaction of 2,5-dimethoxytetrahydrofuran [4.2] with primary amines in acetic acid. In addition to aniline, alkylamines such as methyl- and ethylamine have been converted to the corresponding pyrroles. When the optically active amine, (R)-(+)- α -methylbenzylamine, was used the desired pyrrole product was obtained without any loss in optical activity.¹⁸²

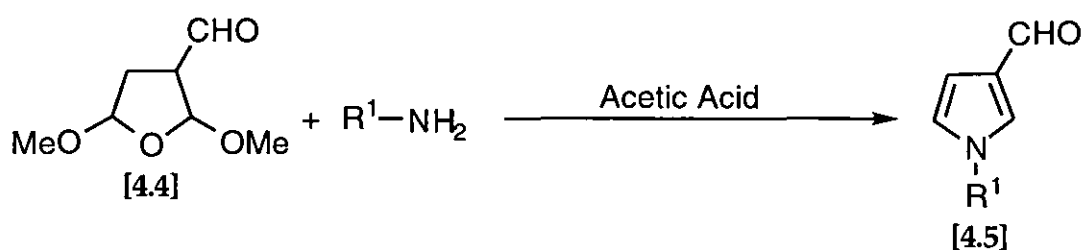
The general utility of this procedure has been demonstrated by its success with other substrates. With 1-arylsulfonamides the 1-arylsulfonylpyrroles were formed in moderate to excellent yields, 42-91%, depending on the substrate employed.¹⁸³ The reaction also converted *N,N*-dimethylhydrazine into *N*-(*N,N*-dimethylamino)pyrrole.¹⁸⁴ This product was then *ortho*-lithiated and reacted with suitable electrophiles such as

aldehydes. When ammonia was used in this reaction the desired unprotected pyrroles were produced.

One of the main problems associated with this reaction is that the product yields are very substrate dependant. For example, the reaction with *n*-butylamine gave only 28% yield of the pyrrole while benzylamine was reported to give none of the desired pyrrole.¹⁸⁰

Clauson-Kaas also found that use of substituted 2,5-dimethoxy-tetrahydrofuran derivatives resulting in pyrroles containing the substituent in the corresponding position of the pyrrole. Clauson-Kaas prepared pyrroles using tetrahydrofuran derivatives containing alkyl groups in either the 2- or the 3-positions and also with 2-(acetamidomethyl) tetrahydrofuran.¹⁸⁰ Kiely reported the formation of methyl 1-arylpyrrole-2-carboxylates by reaction of arylamines with methyl tetrahydro-2,5-dimethoxy-2-furancarboxylate.¹⁸⁵

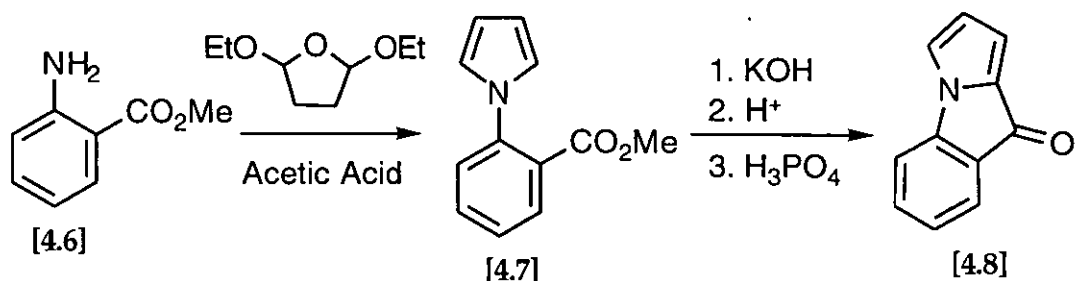
Therefore careful selection of the tetrahydrofuran derivative should allow the synthesis of pyrroles containing substituents in less favoured positions. This was demonstrated by the preparation of pyrrole-3-carboxaldehydes which normally require a multi-stage synthesis unless the 2- and 5-positions are blocked.¹⁸⁶ Wasley showed that alkylamines, arylamines and 1-arylsulfonamides reacted with 2,5-dimethoxy-3-formyl-tetrahydrofuran [4.4] under Clauson-Kaas conditions to give the 1-substituted pyrrole-3-carboxaldehydes [4.5], Scheme 4.2.¹⁸⁷



Scheme 4.2

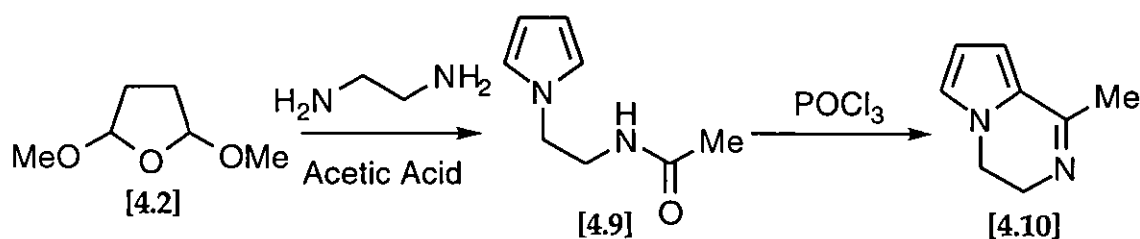
The Clauson-Kaas reaction has also been used as an important step in the formation of a number of novel pyrrole containing heterocycles.¹⁸⁸⁻¹⁹² Careful choice of the amine and the 2,5-dimethoxytetrahydrofuran derivative provides pyrroles with the necessary substituents for further elaboration. Josey reported the formation of 1-(2-methoxycarbonylphenyl)-pyrrole [4.7]

which was converted into the free acid and cyclised via a Friedel-Crafts acylation to the 9-keto-9*H*-pyrrolo[1,2-*a*]indole [4.8], **Scheme 4.3**.¹⁸⁸



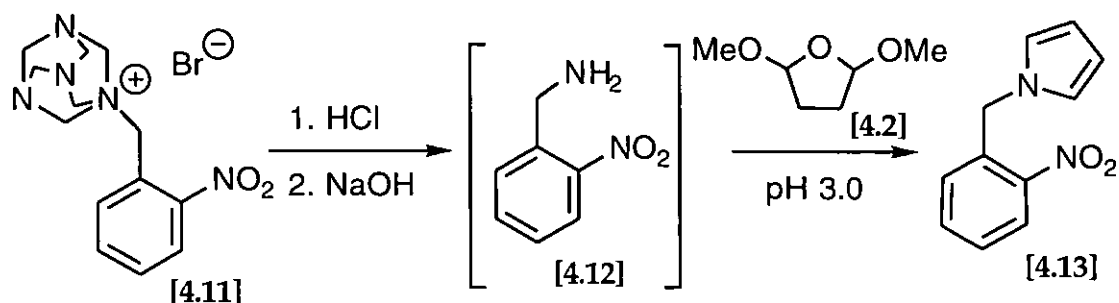
Scheme 4.3

Jirkovsky reported an efficient synthesis of 1,2,3,4-tetrahydro-pyrrolo[1,2-*a*] pyrazine derivatives *via* initial pyrrole formation.¹⁸⁹ Reaction of 1,2-ethanediamine with [4.2] in acetic acid/dioxan gave the pyrrole amide [4.9]. Cyclisation with phosphorus oxychloride gave the bicyclic 3,4-dihydro-pyrrolo[1,2-*a*]pyrazine [4.10], **Scheme 4.4**. Several related compounds were prepared from [4.9] and [4.10], for example, treating the amide [4.9] with base gave the free amine which underwent condensation with aromatic aldehydes yielding 1,2,3,4-tetrahydro-pyrrolo[1,2-*a*] pyrazine derivatives.



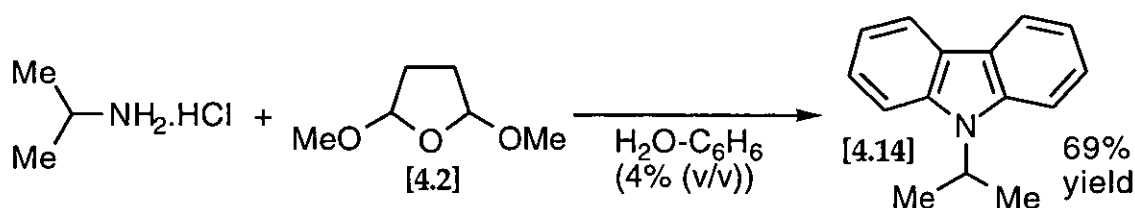
Scheme 4.4

More recently *o*-nitrobenzylpyrrole [4.13] was synthesised from *o*-nitrobenzylamine [4.12] prepared *in-situ* from the hexamethylene tetramine salt [4.11], **Scheme 4.5**.¹⁹⁰ Elaboration of [4.13] led to the potential anti-depressant drug aptazapine.



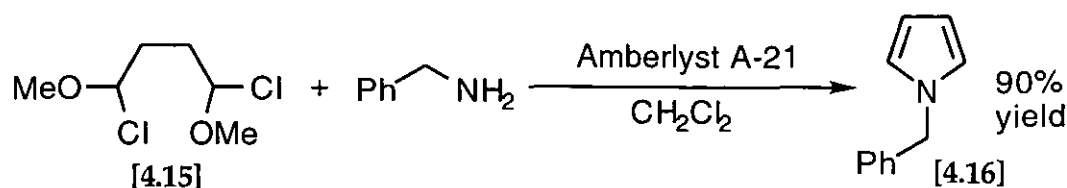
Scheme 4.5

Kashima observed that use of a water-benzene solvent system in the reaction of alkylamine hydrochlorides with 2,5-dimethoxytetrahydrofuran [4.2] gave *N*-substituted carbazoles in moderate to good yields.¹⁹³ The authors suggested that the initially formed pyrrole reacted with further molecules of [4.2] under these conditions to give the *N*-substituted indole and then the observed carbazole product.¹⁹⁴ For example, isopropylamine hydrochloride gave the carbazole [4.14], Scheme 4.6.



Scheme 4.6

In 1983 Chan reported a modification to the Clauson-Kaas reaction.¹⁹⁵ Stirring an excess of trimethylchlorosilane with 2,5 dimethoxytetrahydrofuran [4.2] for 48 h produced 1,4-dichloro-1,4-dimethoxybutane [4.15], a more reactive functional equivalent of [4.2].¹⁹⁶ When [4.15] was reacted with primary amines in the presence of the weakly basic ion-exchange resin, Amberlyst A-21, the pyrroles were formed in excellent yields. For example, benzylamine produced 1-benzylpyrrole [4.16] in 90% yield,¹⁹⁵ by comparison under the original Clauson-Kaas conditions no pyrrole was produced, Scheme 4.7.¹⁸⁰ The use of Amberlyst A-21 was found to be crucial, when other reagents, such as tertiary amines, were used as the neutralising agent the reaction was rather less successful. By using a more polar solvent, dimethyl sulfoxide, it was possible to convert amino acids directly to the pyrrole derivative.

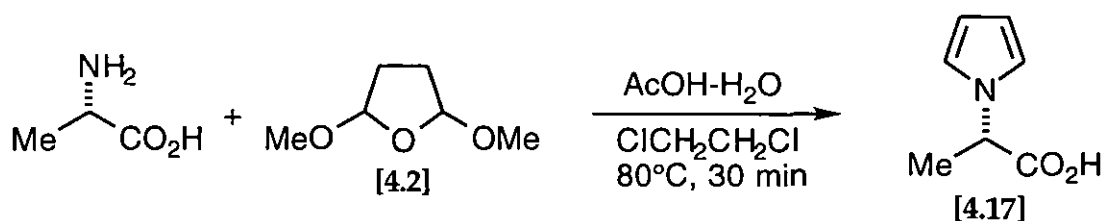


Scheme 4.7

However, attempts by our group to utilise this procedure proved less effective. El Gihani reported problems in isolating [4.15] and the best yield, 77%, required a reaction time of ten days.¹⁹⁷ Reaction of [4.15] with 3,5-dimethoxy-benzylamine using Chan's procedure provided the corresponding pyrrole in only 17% yield.

Jefford investigated the Clauson-Kaas reaction of enantiomerically pure primary amines possessing an epimerizable centre, such as α -amino acids and their ester hydrochlorides.¹⁹⁸ It was found that heating at 80°C for 30 min gave only modest yields of the 1-substituted pyrroles and that partial racemization (72-88% ee) had occurred. When the reactions were repeated in the presence of sodium acetate, added to buffer the acetic acid, the enantioselectivity improved to 82-94% e.e. but the yields remained modest.

These results indicate that the acid is required for the condensation but its continued presence causes racemization and is detrimental to the reaction. So removal of the pyrrole product from the strongly acidic medium as it forms is desirable to prevent racemization. Therefore, the condensation was carried out in a strongly stirred two phase system of warm aqueous acetic acid and 1,2-dichloroethane. This provided essentially enantiomerically pure (>99% e.e.) pyrrole products in good yields. For example, L-alanine gave the corresponding pyrrole product [4.17] in 73% yield and >99% e.e., Scheme 4.8.



Scheme 4.8

With the ester hydrochlorides a water-1,2-dichloroethane system was used as the acid contained in the solid is sufficient to catalyse the reaction. β -Amino alcohols were also efficiently converted to their pyrrole derivatives with complete retention of configuration under the same reaction conditions.¹⁹⁸ This is a real improvement on the previous method which required a four-fold excess of the amine in order to achieve an adequate yield of the pyrrole.

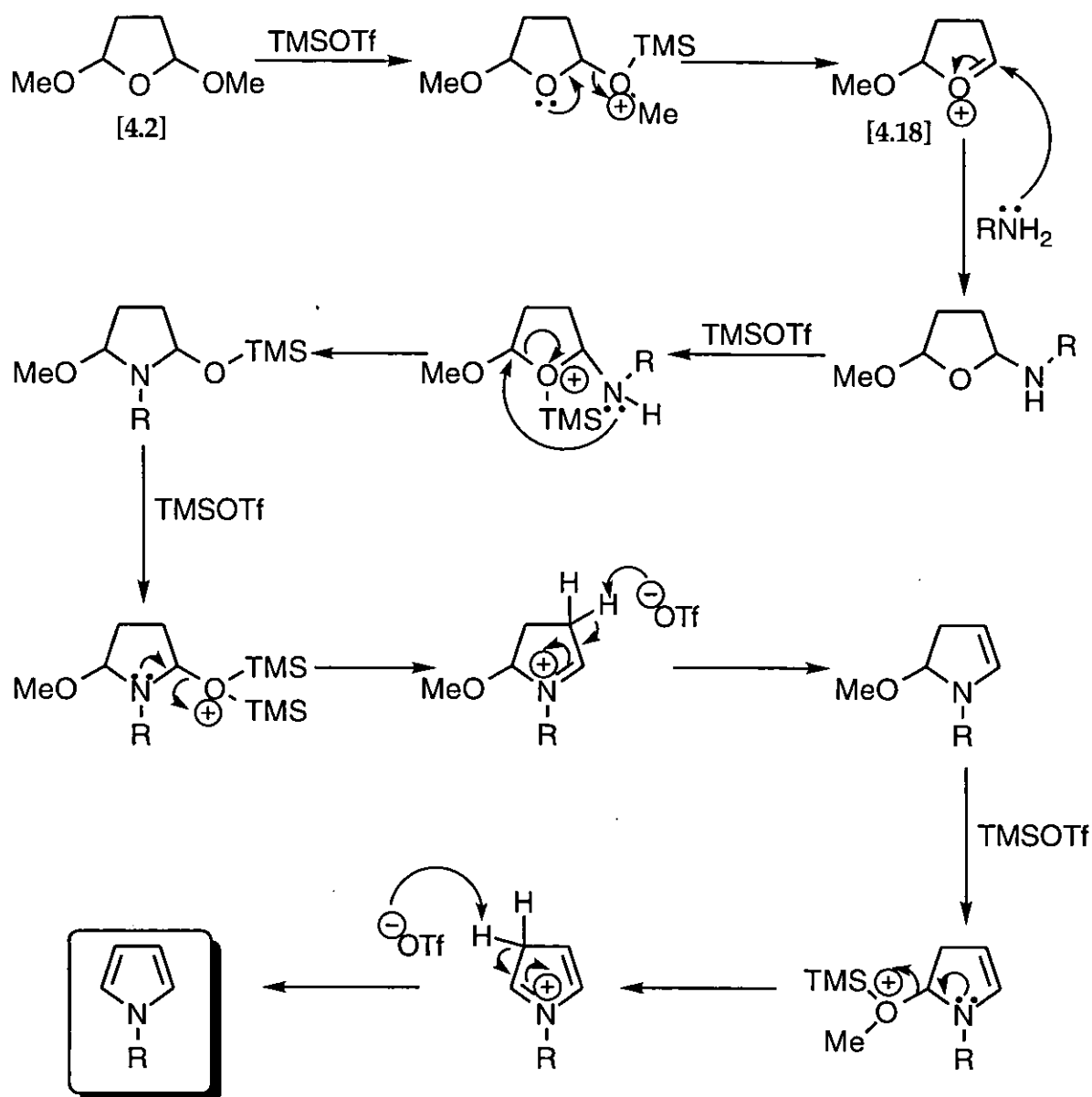
4.2 Proposed Methodology

As section 4.1 has shown the Clauson-Kaas procedure is an important method of preparing pyrrole-based products. Unfortunately the reaction suffers from some drawbacks which restrict its application. The reaction is very substrate dependant, giving variable yields and with some common substrates, for example *n*-butylamine and benzylamine, little or no pyrrole product was obtained.¹⁸⁰ Also the presence of acetic acid as the solvent can cause some problems, such as racemisation of acid sensitive substrates.¹⁹⁸

These difficulties prompted the investigation of new reagents in a modified procedure. The possibility of replacing the acetic acid used in the reaction with a more reactive and oxophilic Lewis acid such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) was considered. The strong electron withdrawing effect of the trifluoromethanesulfonyl group makes the covalent Si-O bond of TMSOTf highly polarised. This leads the electron deficient Si atom to interact strongly with the heteroatoms of substrates, most notably oxygen.¹⁹⁹

The TMSOTf activates a methoxy group of [4.2] whose loss provides the reactive oxonium cation [4.18] which undergoes attack by the primary amine, **Scheme 4.9**. Further activation by TMSOTf should lead to pyrrole in an analogous fashion to the reaction using acetic acid.

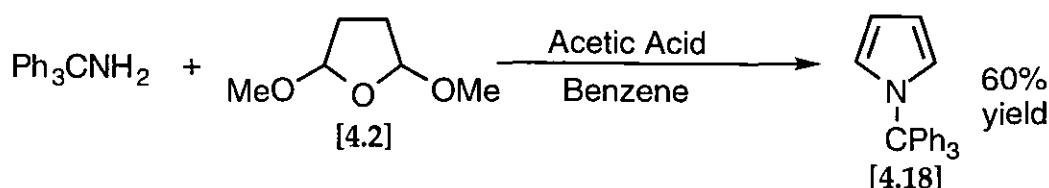
A potential problem of the proposed method is that 4 equivalents of TMSOTf are required for the reaction to go to completion, **Scheme 4.9**. The expense and the difficulty of handling large quantities of TMSOTf make this undesirable. In addition 4 equivalents of trifluoromethanesulfonic acid (TfOH), a strong acid which can be detrimental to reactions of TMSOTf, would be produced as a by-product of the reaction.²⁰⁰



Scheme 4.9

4.3 The Trimethylsilyl Triflate Catalyzed Clauson-Kaas Reaction

Trityl pyrrole **[4.18]** was chosen as the model substrate for the pyrrole methodology because it forms a crystalline solid which it was hoped would simplify purification. An authentic sample of trityl pyrrole **[4.18]** was prepared using the modified Clauson-Kaas procedure described by Chadwick, **Scheme 4.10**.²⁰¹ The authors used benzene as a co-solvent to reduce the amount of acetic acid required and so minimise polymerisation side reactions. The solvent system also had the advantage that trityl pyrrole **[4.18]** crystallised on cooling allowing the pyrrole to be collected by filtration.

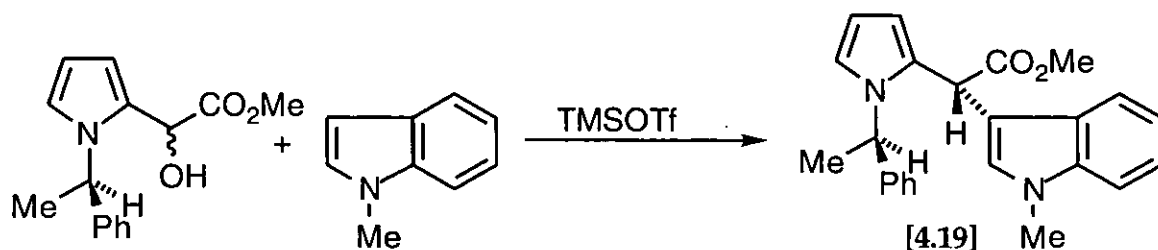


Scheme 4.10

The preparation of trityl pyrrole [4.18] using TMSOTf was initially attempted by adding four equivalents of TMSOTf to tritylamine and 2,5-dimethoxytetrahydrofuran [4.2] in benzene at low temperature, below -30°C . The reaction mixture was then stirred for 5 h whilst maintaining the temperature at 0°C . After aqueous work-up the ^1H NMR of the crude material showed that none of the desired trityl pyrrole [4.18] had been formed. The crude material appeared to be a mixture of unreacted tritylamine and some unidentified side product, no unreacted [4.2] remained. The lack of even a trace amount of pyrrole [4.18] was very disappointing.

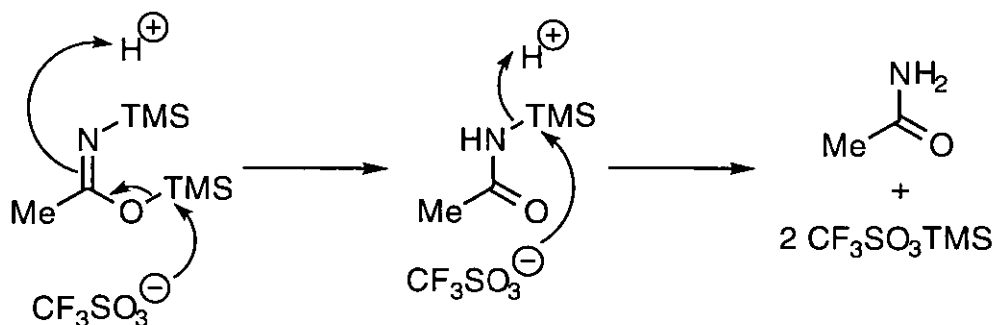
It was reasoned that the large concentration of TMSOTf, and the TfOH produced from it, was providing too harsh conditions for the pyrrole formation. The reaction was attempted using only one equivalent of TMSOTf, in order to see if reducing the concentration of TMSOTf would enable some product to be formed. However, stirring at 0°C , room temperature and heating to 80°C all failed to give any pyrrole [4.18].

It was still suspected that TfOH was causing the reaction to fail. Heaney reported that the Friedel-Crafts reaction, Scheme 4.11 failed when TMSOTf contaminated with TfOH was used.²⁰⁰ However, when purified TMSOTf was used the reaction gave the product [4.19] in high yield and diastereoselectivity.



Scheme 4.11

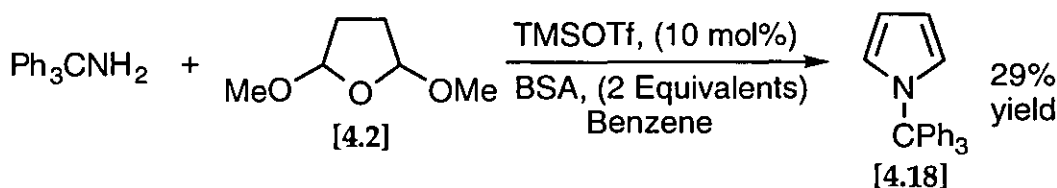
Heaney also showed that treatment of the contaminated TMSOTf with *N,O*-bis(trimethylsilyl)acetamide (BSA) was sufficient to enable it to catalyse the reaction **Scheme 4.11**. The use of BSA as a proton scavenger is known,²⁰² BSA when reacted with TfOH produces two equivalents of TMSOTf and one of acetamide, **Scheme 4.12**



Scheme 4.12

It is known that the reaction of TfOH with BSA fails to produce TMSOTf in quantitative yields.²⁰³ However, Heaney demonstrated that the reaction of TfOH and BSA could be utilised for *in-situ* generation of TMSOTf for catalytic reactions.²⁰⁰ The yields obtained were comparable to those produced by commercially available TMSOTf.

It was anticipated that addition of BSA would remove the TfOH and allow the pyrrole formation to proceed. Also because BSA re-cycles the TfOH to produce TMSOTf it should be possible to use a catalytic amount of TMSOTf. So substantially reducing the amount of TfOH that is present at any time in the reaction mixture. Refluxing trityl amine and [4.2] with TMSOTf (10 mol%) and BSA in benzene for 16 h provided after purification a 29% yield of trityl pyrrole [4.18], **Scheme 4.13**.



Scheme 4.13

Reactions using TMSOTf are commonly carried out in chlorinated solvents. It was therefore decided to carry out the reaction replacing benzene with 1,2-dichloroethane which has a comparable boiling point to benzene. Repeating the reaction, **Scheme 4.13**, in refluxing 1,2-dichloroethane for 16 h gave a slightly improved 32% yield of trityl pyrrole [4.18]. This reaction was repeated across a range of reaction times in order to determine the effect of reaction time, **Table 4.1**.

Reaction Time/h	Yield
2	30%
4	34%
6	35%
16	32%
24	38%

Table 4.1

Increasing the reaction time had little effect on the isolated yields of trityl pyrrole [4.18], **Table 4.1**. This was surprising because examination of the ^1H NMR of the crude product showed that unreacted starting materials remained if the reaction was refluxed for less than 6 h. However, when the reaction time was increased to 16 h no unreacted 2,5-dimethoxytetrahydrofuran [4.2] was observed in the ^1H NMR but there was no significant improvement in the yield of pyrrole [4.18].

Next the effect of changing solvent and the reaction temperature was investigated for trityl pyrrole [4.18], **Table 4.2**.

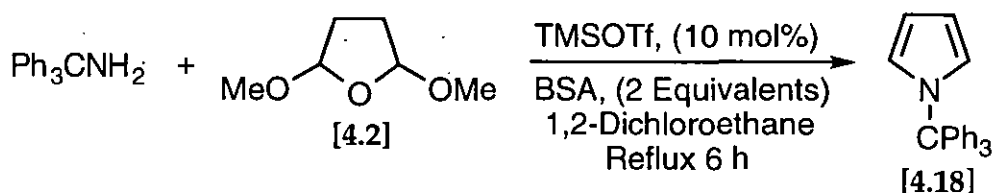
Solvent	Temperature/°C	Reaction Time/h	Yield
1,2-dichloroethane	rt	24	12%
1,2-dichloroethane	rt	48	14%
dichloromethane	40	6	21%
cyclohexanone	81	6	30%
benzene	80	16	29%
1,2-dichloroethane	84	6	35%

Table 4.2

The reaction temperature appears to have some effect on the yield, **Table 4.2**. For example at room temperature the reaction is poor providing only 14% of trityl pyrrole after 48 h, increasing the temperature to 40°C and then to 80°C gave some improvements to the yield. However, the yields from these reactions were still not comparable to those achieved using the classical Clauson-Kaas procedure.

The polarity of the solvent appears to have little effect on the outcome of the reaction. Changing from 1,2-dichloroethane to much less polar solvents such as benzene or cyclohexanone, which have comparable boiling points, gave similar yields. One difference with cyclohexane was that on cooling some of the product crystallised and could be isolated simply by filtration. When trityl amine, [4.2], TMSOTf and BSA were refluxed in cyclohexane for 24 h a slightly better yield of 37% was achieved.

The reaction, **Scheme 4.14**, was also carried out using different ratios of tritylamine and 2,5-dimethoxytetrahydrofuran [4.2], **Table 4.3**. The yields quoted are based on one equivalent (3.0 mmol in each reaction) of starting material.



Scheme 4.14

Tritylamine (equiv.)	2,5-Dimethoxytetra hydrofuran [4.2] (equiv.)	Yield
1	2	28%
1	1.25	34%
1	1	35%
1.25	1	33%
2	1	31%

Table 4.3

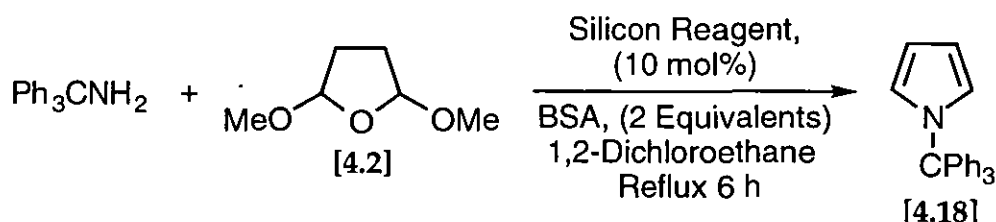
These results, **Table 4.3**, indicate that using an excess of either trityl amine or **[4.2]** has no significant effect on the yield of trityl pyrrole **[4.18]**. The

yields obtained were found to be consistent across the range of tritylamine to [4.2] ratios which were investigated.

It was suggested that a further reduction in the amount of TMSOTf, so reducing the amount of TfOH acid present at any time, would improve the yield. Therefore the reaction was attempted using TMSOTf (2 mol%), unfortunately only a 28% yield of trityl pyrrole [4.18] was isolated.

4.4 Alternative Catalysts

It was proposed that using other silicon reagents which produce less reactive by-products than TfOH might prove more efficient in catalysing pyrrole formation. Therefore several related silicon reagents were used in the general procedure, Scheme 4.15



Scheme 4.15

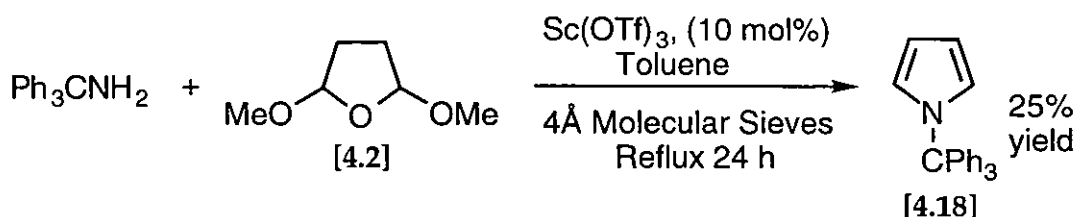
Silicon Reagent	Yield
$\text{CH}_3\text{CO}_2\text{Si}(\text{CH}_3)_3$	0%
$\text{CF}_3\text{CO}_2\text{Si}(\text{CH}_3)_3$	18%
$\text{CH}_3\text{SO}_3\text{Si}(\text{CH}_3)_3$	0%
$\text{ClSi}(\text{CH}_3)_3$	9%

Table 4.4

These reagents proved to be rather less successful than TMSOTf at catalysing the pyrrole formation, Table 4.4. Both trimethylsilyl acetate and trimethylsilyl sulfonate failed to produce any trityl pyrrole [4.18] under these reaction conditions. With both trimethylsilyl trifluoroacetate and trimethylsilyl chloride a very modest yield of [4.18] was isolated.

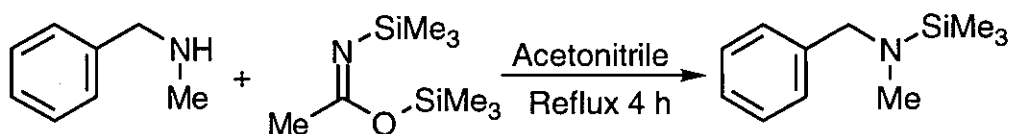
2,5-Dimethoxytetrahydrofuran [4.2] can be viewed as a double acetal compound. It was proposed that reaction of [4.2] with tritylamine catalysed by $\text{Sc}(\text{OTf})_3$ in an analogous manner to the imine procedure developed in

Chapter Two would give the desired pyrrole [4.18]. Refluxing for 24 h gave [4.18] in modest yield, Scheme 4.16. Unreacted tritylamine was still present but all the 2,5-dimethoxy-tetrahydrofuran [4.2] had been consumed.



Scheme 4.16

Amines are known to be converted to their corresponding trimethylsilyl derivatives by reaction with BSA.²⁰⁴ For example, Djerassi reported the preparation of the TMS derivative of *N*-methyl benzylamine by refluxing the amine with BSA in acetonitrile, Scheme 4.17.



Scheme 4.17

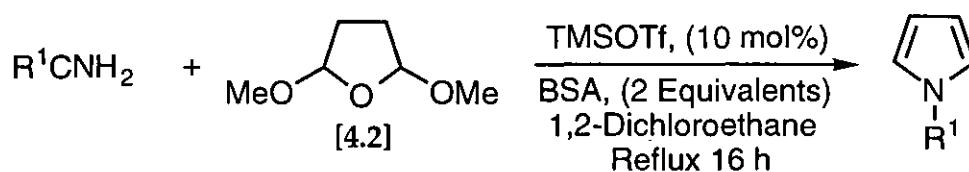
It was proposed that this competing silylation of the amine might be reducing its reactivity in the pyrrole formation. Therefore the reaction was repeated in the presence of 0.2 equivalents of BSA with the slow addition of a further 1.8 equivalents of BSA to the refluxing solution over 16 h. Unfortunately use of these conditions led to a very poor 8% yield of the desired trityl pyrrole [4.18]. This result was ascribed to there being a higher concentration of TfOH in this case because of the lower amount of BSA present initially. The reaction was repeated under the same conditions except that only 0.1 mol% of TMSOTf was used. This reaction gave an improved but still disappointing yield of trityl pyrrole [4.18] of 16%. These results suggest that the silylation of the amine is not the problem limiting the yield of the pyrrole.

One of the main obstacles to the optimisation of the trityl pyrrole [4.18] reaction was the difficulty in determining what alternative products were formed. Apart from pyrrole [4.18] and some starting material the other products were unrecognisable. In some of the TMSOTf catalysed reactions,

several peaks were observed in the ^1H NMR between 5.7-6.7 p.p.m. in addition to those due to the pyrrole [4.18]. It was speculated that these peaks corresponded to trimethylsilyl substituted pyrroles. Simchen has reported the substitution of *N*-alkylpyrroles with TMS groups using TMSOTf and triethylamine.²⁰⁵ Unfortunately purification of these products proved impossible.

4.5 Alternative Target Pyrroles

One of the problems of the Clauson-Kaas reaction is that it is very substrate dependant. An investigation of the TMSOTf catalysed procedure with a range of substrates was therefore desirable. So several amines were refluxed with TMSOTf/BSA in 1,2-dichloroethane, Scheme 4.18, and the results are collected in Table 4.5.



Scheme 4.18

Amine	Reaction Time/h	Product	Yield
<i>p</i> -toluenesulfonamide	4	[4.20]	19%
aniline	16	[4.3]	20%
4-nitroaniline	24	[4.22]	14%
benzylamine	16	[4.16]	0%
<i>t</i> -butylamine	16	[4.23]	0%

Table 4.5

Whilst the reactions with *p*-toluenesulfonamide, aniline and 4-nitroaniline all produced the corresponding pyrroles the yields were modest, Table 4.5. Wasley, for example, has reported that reaction of *p*-toluenesulfonamide with [4.2] using standard Clauson-Kaas conditions, refluxing in acetic acid, gave the pyrrole in 74% yield.¹⁸³ The failure to form 1-benzylpyrrole was not too surprising bearing in mind the failure of benzylamine to react using the standard Clauson-Kaas procedure.¹⁸⁰ The disappointing results with these substrates along with the continued difficulties encountered in attempting to optimise the trityl pyrrole reaction led to this work being discontinued.

4.6 Summary

It has been shown that both the TMSOTf/BSA and $\text{Sc}(\text{OTf})_3$ reagent systems can catalyse modified Clauson-Kaas pyrrole reactions. Unfortunately the yields proved to be relatively poor and attempts to develop a practical synthetic procedure failed.

This failure suggests that the chemistry of these reactions is considerably more complicated than was first anticipated. It is probable that a greater understanding of the different reactions taking place is required before significant improvement in the yields can be achieved.

Chapter 5

Experimental

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5.1. General Experimental Points

Solvents were purified before use as follows. Dichloromethane was distilled from phosphorus pentoxide. Diethyl ether and ethyl acetate were distilled from calcium chloride. Toluene was distilled from sodium wire. Anhydrous tetrahydrofuran was purchased from Aldrich, if necessary it was distilled from sodium-benzophenone ketyl immediately prior to use. 'Light petroleum' refers to the fraction of petroleum ether boiling between 40-60°C, and was distilled from calcium chloride. Methanol was distilled from magnesium methoxide. Commercially available compounds were generally used without further purification.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash column chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60; Samples were applied as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using either a Nicolet FT-205 or a Perkin Elmer Paragon 100 spectrometer, with internal calibration. ^1H and ^{13}C NMR spectra were recorded on using either a Bruker AC-250 or Ac-400 instrument in deuteriochloroform or deuteriodimethyl sulfoxide as solvent. NMR chemical shifts are quoted in ppm relative to tetramethylsilane as the internal standard. Coupling constants are quoted in Hertz. Spectroscopic data is annotated with the following abbreviations; s - singlet; d - doublet; t - triplet; q - quartet; sept. - septet; m - multiplet. High and low resolution mass spectra were recorded on a Kratos MS80 instrument with an ionising potential of 70 eV. Melting points were determined on Leica Galen III. Optical rotations were measured using an Optical Activity Ltd. polarimeter, with a 10 cm cell and chloroform as the solvent at 20°C. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser.

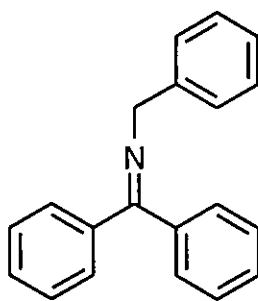
All reactions were carried out under an atmosphere of dry nitrogen or argon, using oven- or flame-dried glassware, unless obviously unnecessary.

5.2 Experimental for Chapter 2

General Method for Imine Formation

Metal triflate catalyst (0.125 mmol, 5 mol%) was added to a solution of acetal (2.5 mmol) and amine (2.5 mmol) in toluene (30 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure to yield the crude imine.

N-Benzyl-*N*-diphenylmethyleamine



[21]

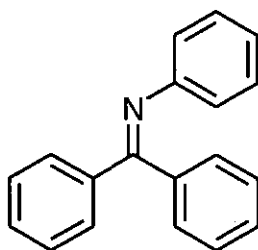
Method A : From the Ketone

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), benzophenone (0.456 g, 2.5 mmol) and benzylamine (0.268 g, 2.5 mmol, 0.27 ml) in toluene (30 ml) were reacted as in the general method. Recrystallisation from light petroleum/diethyl ether yielded the *title compound* (0.453 g, 67%) as a brown solid, m.p. 55-57°C (Lit.,²⁰⁶ 58-59°C); ν_{\max} (Nujol) 3060, 1624, 1287, 696 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.83-7.80 (1H, m, Ar-H), 7.71-7.67 (2H, m, Ar-H), 7.47-7.19 (12H, m, Ar-H), 4.60 (2H, s, CH_2).

Method B : From the Acetal.

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-[dimethoxy(phenyl)methyl] benzene [2.5] (0.570 g, 2.5 mmol) and benzylamine (0.268 g, 2.5 mmol, 0.27 ml) were reacted as in the general method. Recrystallisation from ethanol yielded the *title compound* (0.595 g, 88%) as a colourless crystals, m.p. 58-60°C (Lit.,²⁰⁶ 58-59°C). Identical by ^1H NMR and IR with the same compound prepared from the ketone.

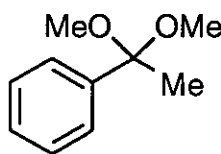
N-Diphenylmethylene-N-phenylamine



[22]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), benzophenone (0.456 g, 2.5 mmol) and aniline (0.233 g, 2.5 mmol, 0.22 ml) in toluene (30 ml) were reacted as in the general method. Recrystallisation from light petroleum/ethanol yielded the *title compound* (0.263 g, 41%) as a yellow solid, m.p. 114-117°C (Lit.,²⁰⁷ 116-117°C); ν_{\max} (Nujol) 1600, 1277, 1175 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.82-7.78 (4H, m, Ar-H), 7.62-7.44 (6H, m, Ar-H), 7.28-7.11 (4H, m, Ar-H), 6.76-6.47 (1H, m, Ar-H)

1-(1,1-Dimethoxyethyl)benzene



[23]

Method A

Acetophenone (5.00 g, 41.6 mmol, 4.85 ml) and Amberlyst-15 (0.25 g) were added to trimethyl orthoformate (22.08 g, 208.0 mmol, 22.8 ml) at 0°C and the mixture was stirred at 0°C for 48 h. The Amberlyst-15 resin was filtered off and washed with dichloromethane, the solvent and excess trimethyl orthoformate were removed under reduced pressure. Kugelrohr distillation under reduced pressure yielded the *title compound* (4.08 g, 59%) as a yellow oil, b.p. 44-46°C/1.5 mmHg (Lit.,²⁰⁸ 95-98°C/12 mmHg) (Found: M^+ , 166.0984. $\text{C}_{13}\text{H}_{11}\text{N}$ requires M , 166.0994); ν_{\max} (Neat) 2944, 2830, 1448, 1091 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.51-7.46 (2H, m, Ar-H), 7.38-7.25 (3H, m, Ar-H), 3.19 (6H, s, OCH_3), 1.54 (3H, s, CH_3); δ_{C} (62.9 MHz; CDCl_3) 142.8, 128.0 (ArCH), 127.4 (ArCH), 126.2

(ArCH), 101.6, 48.9 (OCH₃), 26.0 (CH₃); *m/z* (EI) 165 (M⁺, 3%), 151 (14), 135 (55), 105 (24), 77 (26), 51 (14), 43 (37), 19 (11), 18 (100), 17 (29).

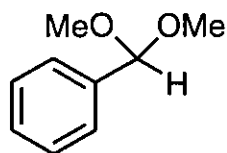
Standard Method for Acetal Formation¹²⁶

Trimethyl orthoformate (15 ml) was added to montmorillonite clay K-10 (10 g) and stirred at room temperature for 30 min. The suspension was filtered and the resultant wet filter cake was transferred into a dry flask. The carbonyl compound (5 g) and hexane (30 ml) were added and the suspension was stirred at room temperature until T.L.C. analysis indicated complete conversion. The clay was removed by filtration and washed with hexane. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (50 ml) and water (50 ml). The organic layer was dried (MgSO₄) and the solvent removed under reduced pressure yielding the acetal compound.

Method B

Trimethyl orthoformate (15 ml, 14.52 g, 0.137 mole), montmorillonite clay K-10 (10 g) and acetophenone (5 g, 0.042 mole) gave after stirring for 3 h the *title compound* (5.504 g, 80%) as an orange oil. Identical by ¹H NMR and IR with the same compound prepared using Method A.

1-(Dimethoxymethyl)benzene

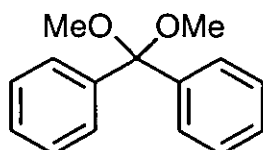


[24]

Trimethyl orthoformate (15 ml, 14.52 g, 0.137 mole), montmorillonite clay K-10 (10 g) and benzaldehyde (5 g, 0.047 mole) gave after stirring for 1 h the *title compound* (6.365 g, 82%) as a colourless oil (Found: M⁺, 152.0836. C₉H₁₂O₂ requires M, 152.0837); ν_{\max} (Neat) 2938, 2830, 1453, 1105 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.47-7.44 (2H, m, Ar-H), 7.41-7.33 (3H, m, Ar-H), 5.40 (1H, s, ArCH), 3.34 (6H, s, OCH₃); δ_{C} (62.9 MHz; CDCl₃) 138.2, 128.4 (ArCH), 128.2 (ArCH), 126.8 (ArCH), 103.1 (CH), 52.6 (OCH₃); *m/z* (EI) 152 (M⁺, 2%), 137 (18), 136 (33), 120

(13), 121 (100), 106 (19), 105 (76), 91 (12), 78 (21), 77 (71), 51 (35), 50 (16), 29 (11), 18 (16).

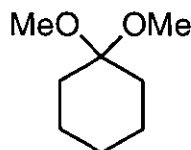
1-[Dimethoxy(phenyl)methyl]benzene



[2.5]

Trimethyl orthoformate (30 ml, 29.04 g, 0.274 mole), montmorillonite clay K-10 (20 g) and benzophenone (10 g, 0.055 mole) in hexane (60 ml) gave after stirring for 16 h the *title compound* (9.183 g, 73%) as colourless crystals, m.p. 104-106°C (Lit.,²⁰⁹ 106.5 °C); ν_{\max} (KBr Disc) 2936, 2828, 1450, 1093 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.52-7.49 (4H, m, Ar-H), 7.32-7.18 (6H, m, Ar-H), 3.13 (6H, s, OCH_3); δ_{C} (62.9 MHz; CDCl_3) 142.4, 130.0, 127.9 (ArCH), 127.4 (ArCH), 126.9 (ArCH), 49.2 (OCH_3); m/z (EI) 228 (M^+ , 5%), 198 (42), 197 (100), 165 (24), 152 (25), 151 (77), 106 (12), 105 (82), 91 (40), 78 (11), 77 (86), 59 (20), 51 (27).

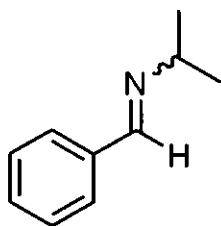
1,1-Dimethoxycyclohexane



[2.6]

Trimethyl orthoformate (15 ml, 14.52 g, 0.137 mole), montmorillonite clay K-10 (10 g) and cyclohexanone (5 g, 0.051 mole) gave after stirring for 3 h the *title compound* (6.813 g, 93%) as a colourless oil; ν_{\max} (Neat) 2939, 2829, 1449, 1105 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 3.18 (6H, s, OCH_3), 1.66-1.61 (4H, m, $\text{C}(2)\text{H}_2\text{-C}(6)\text{H}_2$), 1.55-1.40 (6H, m, $\text{C}(3)\text{H}_2\text{-C}(4)\text{H}_2\text{-C}(5)\text{H}_2$); δ_{C} (62.9 MHz; CDCl_3) 99.9, 47.2 (OCH_3), 32.6 (CH_2), 25.5 (CH_2), 22.7 (CH_2); m/z (EI) 144 (M^+ , 8%), 113 (76), 102 (11), 101 (100), 88 (14), 81 (47), 79 (12), 58 (11), 55 (28), 55 (28), 45 (20), 43 (17), 41 (15).

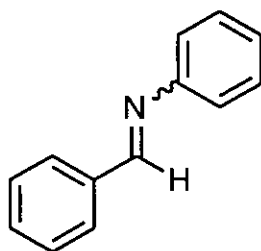
N-Isopropyl-N-(1-phenylmethyldene)amine



[2.7]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(dimethoxymethyl) benzene [2.4] (0.381 g, 2.5 mmol) and isopropylamine (0.148 g, 2.5 mmol, 0.21 ml) were reacted as in the general method. Kugelrohr distillation yielded the *title compound* (0.358 g, 97%) as a colourless oil, b.p. 95°C/10.0 mmHg (Lit.,²¹⁰ 85°C/12 mmHg); ν_{\max} (Neat) 2968, 2837, 1647, 1451 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.32 (1H, s, CH=N), 7.72-7.73 (2H, m, Ar-H), 7.42-7.40 (3H, m, Ar-H), 3.56 (1H, sept., J 6.5 Hz, NCH), 1.29 (6H, d, J 6.5 Hz, CH_3).

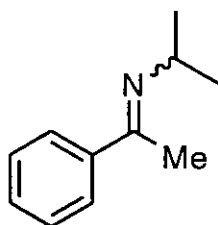
N-Phenyl-N-(1-phenylmethyldene)amine



[1.26]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(dimethoxymethyl) benzene [2.4] (0.381 g, 2.5 mmol) and aniline (0.349 g, 3.75 mmol, 0.34 ml) were reacted as in the general method. Recrystallisation from hexane yielded the *title compound* (0.419 g, 92%) as pale brown crystals, m.p. 49-51°C (Lit.,²¹¹ 48-49°C) (Found: M^+ , 181.0890. $\text{C}_{13}\text{H}_{11}\text{N}$ requires M, 181.0891); ν_{\max} (KBr Disc) 3059, 2889, 1626, 1590, 1450 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.45 (1H, s, CH=N), 7.93-7.88 (2H, m, Ar-H), 7.50-7.46 (3H, m, Ar-H), 7.42-7.36 (2H, m, Ar-H), 7.25-7.19 (3H, m, Ar-H); δ_{C} (62.9 MHz; CDCl_3) 160.4 (N=CH), 152.0, 136.2, 131.4 (ArCH), 129.2 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 126.0 (ArCH), 120.9 (ArCH); m/z (EI) 181 (M^+ , 100%), 180 (81), 104 (16), 78 (22), 77 (80), 57 (35), 51 (35), 50 (12), 39 (10).

N-Isopropyl-N-(1-phenylethylidene)amine



[2.8]

Method A : Using Sc(OTf)₃

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and isopropylamine (0.148 g, 2.5 mmol, 0.21 ml) were reacted as in the general method. Kugelrohr distillation yielded the *title compound* (0.167 g, 41%) as a colourless oil, b.p. 80-84°C/0.1 mmHg (Lit.,²¹⁰ 70°C/0.06 mmHg); ν_{max} (Neat) 2967, 1633, 1494 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.78-7.74 (2H, m, Ar-H), 7.41-7.36 (3H, m, Ar-H), 3.85 (1H, sept., J 6.3 Hz, CH), 2.27 (3H, s, CH_3) 1.24 (6H, d, J 6.3 Hz, CH_3).

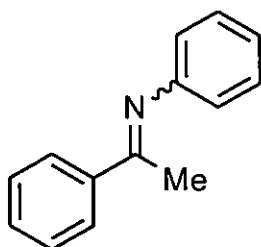
Method B : Using Yb(OTf)₃

Ytterbium triflate (0.080 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and isopropylamine (0.148 g, 2.5 mmol, 0.21 ml) were reacted as in the general method. Kugelrohr distillation yielded the *title compound* (0.217 g, 54%) as a colourless oil, b.p. 118-125°C/0.5 mmHg (Lit.,²¹⁰ 70°C/0.06 mmHg). Identical by ^1H NMR and IR with the same compound prepared using Method A.

Method C : Using Cu(OTf)₂

Copper triflate (0.045 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and isopropylamine (0.148 g, 2.5 mmol, 0.21 ml) were reacted as in the general method. Kugelrohr distillation yielded the *title compound* (0.129 g, 32%) as a colourless oil, b.p. 138-145°C/2.0 mmHg (Lit.,²¹⁰ 70°C/0.06 mmHg). Identical by ^1H NMR and IR with the same compound prepared using Method A.

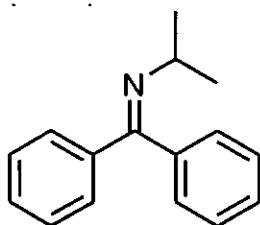
N-Phenyl-N-(1-phenylethylidene)amine



[2.9]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and aniline (0.233 g, 2.5 mmol, 0.22 ml) were reacted as in the general method to yield the *title compound* (0.437 g, 89%) as a brown oil b.p. 165-170°C/0.2 mmHg (Lit.,²¹⁰ 82°C/0.001 mmHg); ν_{\max} (Neat) 3031, 1601, 1499 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.96-7.93 (2H, m, Ar-H), 7.48-7.40 (3H, m, Ar-H), 7.40-7.33 (2H, m, Ar-H), 7.17-7.08 (1H, m, Ar-H), 6.64-6.60 (2H, m, Ar-H), 2.26 (3H, s, CH_3).

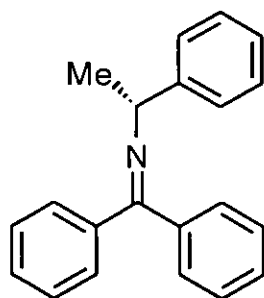
N-Diphenylmethylene-N-isopropylamine



[2.10]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-[dimethoxy(phenyl)methyl] benzene [2.5] (0.570 g, 2.5 mmol) and isopropylamine (0.148 g, 2.5 mmol, 0.21 ml) were reacted as in the general method to yield the *title compound* (0.564 g, 96%) as a light brown solid, m.p. 43-44°C (Lit.,¹¹⁶ 43-44°C); ν_{\max} (Nujol) 1663, 1624 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.60-7.57 (2H, m, Ar-H), 7.51-7.42 (3H, m, Ar-H), 7.35-7.25 (3H, m, Ar-H), 7.17-7.13 (2H, m, Ar-H), 3.56 (1H, sept., J 6.0 Hz, NCH), 1.76 (6H, d, J 6.0 Hz, CH_3); δ_{C} (62.9 MHz; CDCl_3) 165.2, 140.2, 137.4, 132.4 (ArCH), 130.0 (ArCH), 129.6 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 52.9 (CH), 23.9 (CH_3).

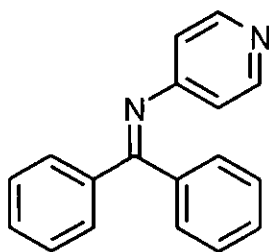
N-Diphenylmethylene-N-[(1R)-1-phenylethyl]amine



[2.11]

Scandium triflate (0.123 g, 0.25 mmol, 5 mol%), 1-[dimethoxy(phenyl)methyl] benzene [2.5] (1.141 g, 5.00 mmol) and R-(1)-phenylethylamine (0.606 g, 5.00 mmol, 0.64 ml) in xylene (50 ml) were reacted as in the general method. Recrystallisation from light petroleum/diethyl ether yielded the *title compound* (1.286 g, 90%) as a colourless crystals, m.p. 68-70°C (Lit.,¹²⁸ 69-70°C) (Found: M^+ , 285.1519. $C_{21}H_{19}N$ requires M , 285.1517); $[\alpha]_D$ -19.2° (c 0.25 in C_6H_6); ν_{max} (KBr Disc) 2966, 2885, 1624, 1444 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.68-7.64 (2H, m, Ar-H), 7.45-7.17 (11H, m, Ar-H), 7.14-7.11 (2H, m, Ar-H), 4.54 (1H, q, J 6.4 Hz, CH), 1.47 (3H, d, J 6.4 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 165.8, 145.6, 140.0, 136.8, 129.8 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 127.6 (ArCH), 126.6 (ArCH), 126.5 (ArCH), 61.3 (CH), 25.0 (CH_3); m/z (EI) 285 (M^+ , 82%), 284 (34), 270 (35), 182 (36), 180 (23), 167 (21), 166 (15), 165 (32), 152 (14), 106 (12), 105 (100), 104 (26), 103 (43), 79 (19), 78 (36), 77 (85), 76 (18), 51 (42), 50 (21), 39 (11).

N-Diphenylmethylene-N-(4-pyridyl)amine



[2.12]

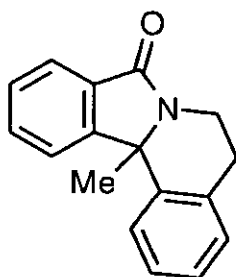
Method A : Using Sc(OTf)₃

Scandium triflate (0.123 g, 0.25 mmol, 5 mol%), 1-[dimethoxy(phenyl)methyl] benzene [2.5] (1.141 g, 5.00 mmol) and 4-aminopyridine (0.471 g, 5.00 mmol) in xylene (50 ml) were reacted as in the general method for 4 days. Purification by column chromatography (diethyl ether) and recrystallisation from light petroleum/ethyl acetate yielded the *title compound* (0.986 g, 76%) as a pale yellow crystals, m.p. 90-91°C (Lit.,¹¹⁹ 90°C) (Found: M⁺, 258.1160. C₁₈H₁₄N₂ requires M, 258.1157); ν_{\max} (KBr Disc) 3056, 1628, 1587 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 8.32 (2H, m, Ar-H), 7.42-7.33 (10H, m, Ar-H), 6.63 (2H, m, Ar-H); δ_{C} (100.0 MHz; CDCl₃) 169.0, 158.0, 150.1 (ArCH), 149.8 (ArCH), 129.8, 129.1, 128.2 (ArCH), 128.0 (ArCH), 115.5 (ArCH); m/z (EI) 258 (M⁺, 100%), 257 (31), 182 (10), 181 (78), 165 (54), 78 (43), 51 (28), 18 (17).

Method B : Using Yb(OTf)₃

Ytterbium triflate (0.155 g, 0.25 mmol, 5 mol%), 1-[dimethoxy(phenyl)methyl] benzene [2.5] (1.141 g, 5.00 mmol) and 4-aminopyridine (0.471 g, 5.00 mmol) in xylene (50 ml) were reacted as in the general method for 4 days. Purification by column chromatography (diethyl ether) and recrystallisation from light petroleum/ethyl acetate yielded the *title compound* (0.958 g, 74%) as a pale yellow crystals, m.p. 89-91°C (Lit.,¹¹⁹ 90°C). Identical by ¹H NMR and IR with the same compound prepared using Method A.

12b-Methyl-5,6,8,12b-tetrahydroisoindolo[1,2-a]isoquinolin-8-one

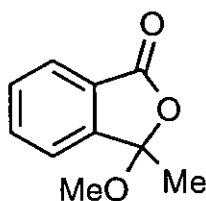


[2.14]

2,3-Dihydro-3-methylene-2-phenylethylisoindol-1-one [2.19] (0.150 g, 0.6 mmol) and ortho-phosphoric acid (85% aqueous solution, 2 ml) were heated with stirring to 105°C for 30 min. The solution was allowed to cool and water

(20 ml) was added, the mixture was then extracted with diethyl ether (3 x 25 ml). The combined organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.101 g, 67%) as a pale yellow solid, m.p. 162-164°C (Found: M⁺, 249.1155. C₁₇H₁₅NO requires M, 249.1154); ν_{\max} (KBr Disc) 2975, 1678, 1388 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.86 (2H, m, Ar-H), 7.72 (1H, dd, J 7.5, 1.2 Hz, Ar-H), 7.60 (1H, dt, J 7.5, 1.2 Hz, Ar-H), 7.45 (1H, dt, J 7.5, 0.8 Hz, Ar-H), 7.26-7.12 (3H, m, Ar-H), 4.63 (1H, ddd, J 13.2, 6.4, 1.5 Hz, NCH H), 3.39 (1H, ddd, J 13.2, 11.8, 4.4 Hz, NCHH), 3.17-3.03 (1H, ddd, 16.2, 11.8, 6.4 Hz, ArCH H), 2.82 (1H, ddd, J 16.2, 4.4, 1.5 Hz, ArCHH), 1.83 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 167.4, 150.8, 139.1, 133.4, 131.8 (ArCH), 131.2, 129.7 (ArCH), 128.3 (ArCH), 127.0 (ArCH), 126.5 (ArCH), 126.0 (ArCH), 123.7 (ArCH), 122.4 (ArCH), 63.8, 34.9 (NCH₂), 29.6 (CH₂), 29.1 (CH₃); *m/z* (EI) 249 (M⁺, 5%), 235 (44), 234 (100), 233 (10), 232 (13), 219 (5), 204 (8), 178 (8), 130 (5), 103 (5), 102 (7), 77 (6).

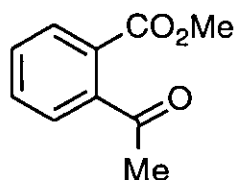
3-Methoxy-3-methyl-1,3-dihydro-1-isobenzofuranone



[215]

To a solution of 2-acetyl benzoic acid (0.500 g, 3.0 mmol) in methanol (30 ml) was added sulfuric acid (10 M, 5 drops). After refluxing for 15 h the solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.351 g, 65%) as a pale yellow oil; ν_{\max} (Neat) 2998, 2938, 1765, 1285, 1186, 1020 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.91 (1H, d, J 7.2 Hz, Ar-H), 7.74 (1H, t, J 7.2 Hz, Ar-H), 7.61 (1H, t, J 7.2 Hz, Ar-H), 7.52 (1H, d, J 7.2 Hz, Ar-H), 3.07 (3H, s, OCH₃), 1.84 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 168.1, 147.7, 135.0 (ArCH), 130.9 (ArCH), 127.7, 125.9 (ArCH), 122.5 (ArCH), 109.2, 51.9 (OCH₃), 26.1 (CH₃).

Methyl 2-acetylbenzoate



[2.16]

Method A

Isolated from the above reaction the *title compound* (0.159 g, 29%) as a colourless oil (Found: M^+ , 178.0631. $C_{10}H_{10}O_3$ requires M , 178.0630); ν_{\max} (Neat) 1722, 1700, 1277, 760 cm^{-1} ; δ_H (250 MHz; CDCl_3) 7.83 (1H, dd, J 7.2, 1.3 Hz, Ar-H), 7.58-7.44 (2H, m, Ar-H), 7.40 (1H, dd, J 7.2, 1.3 Hz, Ar-H), 3.90 (3H, s, OCH_3), 2.54 (3H, s, CH_3); δ_C (62.9 MHz; CDCl_3) 202.5, 167.5, 142.7, 132.4 (ArCH), 130.2 (ArCH), 129.8 (ArCH), 129.2, 126.6 (ArCH), 52.9 (OCH_3), 30.3 (CH_3); m/z (EI) 178 (M^+ , 4%), 164 (28), 163 (100), 161 (30), 147 (54), 135 (20), 133 (27), 105 (23), 104 (19), 92 (14), 91 (32), 78 (10), 77 (41), 76 (30), 74 (11), 51 (13), 43 (31).

Method B

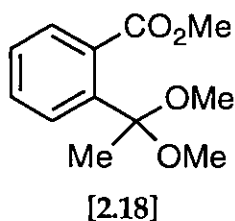
Potassium carbonate (0.842 g, 6.09 mmol) was added to a suspension of 2-acetyl benzoic acid (1.00 g, 6.09 mmol) in water (10 ml) and stirred for 1 h to give a colourless solution. The solvent was removed under reduced pressure and the colourless solid dried. Dimethylformamide (50 ml) was added and the mixture stirred for 5 min. Methyl iodide (1.729 g, 12.18 mmol, 0.76 ml) was added with cooling from an ice-water bath and the reaction mixture was then stirred for 5 h at room temperature. Added water (200 ml) and extracted with diethyl ether (3 x 150 ml) and each ether layer was washed with brine (3 x 150 ml). The combined organic layers were dried (MgSO_4) and the solvent removed under reduced pressure to yield the *title compound* (0.684 g, 63%) as a colourless oil. Identical by ^1H NMR and IR with the same compound prepared by Method A.

Method C

Potassium carbonate (4.630 g, 33.5 mmol) was added to a suspension of 2-acetyl benzoic acid (5.00 g, 30.5 mmol) in water (10 ml) as in Method C. The

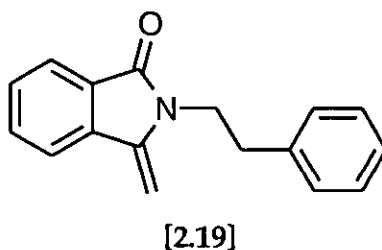
carboxylic acid salt formed was then added to dimethylsulfoxide (50 ml) and reacted with methyl iodide (8.65 g, 61.0 mmol, 3.8 ml) as in Method C yielding the title compound (4.671 g, 86%) as a colourless oil. Identical by ^1H NMR and IR with the same compound prepared by Method A.

Methyl 2-(1,1-dimethoxyethyl)benzoate



Trimethyl orthoformate (5 ml, 4.840 g, 0.046 mole), montmorillonite clay K-10 (3 g) and methyl 2-acetyl benzoate [2.16] (1.500 g, 0.008 mole) in hexane (15 ml) gave after stirring for 16 h the *title compound* (1.481 g, 78%) as colourless oil (Found: M^+ , 223.9827. $\text{C}_{12}\text{H}_{16}\text{O}_4$ requires M , 224.1049); ν_{max} (Neat) 2950, 2833, 1732, 1433, 1117 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.48-7.46 (1H, m, Ar-H), 7.45-7.26 (3H, m, Ar-H), 3.83 (3H, s, CO_2CH_3), 3.13 (6H, s, OCH_3), 1.64 (3H, s, CH_3); δ_{C} (100.0 MHz; CDCl_3) 171.2, 140.2, 132.9, 129.2 (ArCH), 127.7 (ArCH), 126.8 (ArCH), 102.2, 51.9 (OCH_3), 49.0 (OCH_3), 25.1 (CH_3); m/z (EI) 224 (M^+ , 5%), 210 (34), 209 (100), 207 (19), 195 (18), 194 (86), 192 (24), 177 (22), 175 (18), 162 (41), 161 (90), 149 (13), 147 (14), 133 (21), 129 (14), 91 (13), 90 (11), 89 (84).

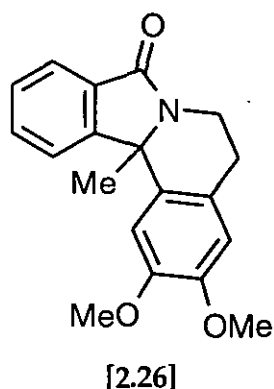
2,3-Dihydro-3-methylene-2-phenylethylisoindol-1-one



Scandium triflate (0.061 g, 0.125 mmol, 5 mol%) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] (0.561 g, 2.5 mmol) and 2-phenylethylamine (0.303 g, 2.5 mmol, 0.31 ml) in xylene (30 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å

molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (dichloromethane) yielded the *title compound* (0.471 g, 75%) as a yellow solid, m.p. 84-85°C (Found: M^+ , 249.1156. $C_{17}H_{15}NO$ requires M , 249.1154); ν_{\max} (KBr Disc) 2938, 1702, 1642, 702 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.82 (1H, d, J 7.0 Hz, Ar-H), 7.70-7.67 (1H, m, Ar-H), 7.60-7.46 (2H, m, Ar-H), 7.33-7.20 (5H, m, Ar-H), 5.18 (1H, d, J 2.2 Hz, C=CH), 4.82 (1H, d, J 2.2 Hz, C=CH), 4.00 (2H, t, J 8.0 Hz, CH_2), 2.97 (2H, t, J 8.0 Hz, CH_2); δ_C (100.0 MHz; $CDCl_3$) 166.9, 141.8, 138.6, 136.4, 133.9, 131.9 (ArCH), 129.7 (ArCH), 129.4 (ArCH), 129.1 (ArCH), 126.7 (ArCH), 123.2 (ArCH), 119.9 (ArCH), 88.6 (CH_2), 41.1 (CH_2), 34.6 (CH_2); m/z (EI) 249 (M^+ , 64%), 159 (11), 158 (100), 145 (12), 129 (10), 104 (37), 103 (18), 77 (16).

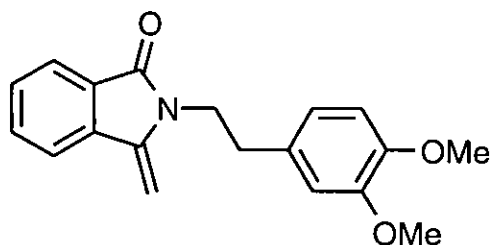
2,3-Dimethoxy-12b-methyl-5,6,8,12b-tetrahydroisoindolo[1,2-a]isoquinolin-8-one



Scandium triflate (0.120 g, 0.25 mmol, 10 mol%) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] (0.561 g, 2.5 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (0.453 g, 2.5 mmol, 0.42 ml) in xylene (30 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (2:1) yielded the *title compound* (0.415 g, 54%) as a yellow solid, m.p. 197-200°C (Found: M^+ , 309.1368. $C_{19}H_{19}NO_3$ requires M , 309.1364); ν_{\max} (KBr Disc) 2939, 1681, 1517, 755 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.87-7.83 (2H, m, Ar-H), 7.72 (1H, dt, J 7.5, 1.1 Hz, Ar-H), 7.45 (1H, t, J 7.4 Hz, Ar-H), 7.18 (1H, s, Ar-H), 6.58 (1H, s, Ar-H), 4.62 (1H, ddd, J 13.1, 6.5, 1.2 Hz, NCH H), 3.94 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.37 (1H, ddd, J 13.1, 11.9, 4.5 Hz, NCHH), 3.11-2.97 (1H, ddd, 16.0, 11.9, 6.5 ArCH H),

2.72 (1H, m, ArCHH), 1.81 (3H, s, CH₃); δ_C (62.9 MHz; CDCl₃) 167.4, 150.7, 148.2, 147.7, 131.9 (ArCH), 131.1, 130.9, 128.2 (ArCH), 125.8, 123.8 (ArCH), 122.2 (ArCH), 112.0 (ArCH), 109.5 (ArCH), 63.6, 56.3 (OCH₃), 55.8 (OCH₃), 35.0 (NCH₂), 29.2 (CH₂), 28.7 (CH₃); m/z (EI) 309 (M⁺, 12%), 295 (23), 294 (100), 278 (8), 250 (7), 155 (5), 130 (15), 51 (8), 31 (7).

2,3-Dihydro-3-methylene-2-(3,4-dimethoxyphenyl)ethylisoindol-1-one



[2.27]

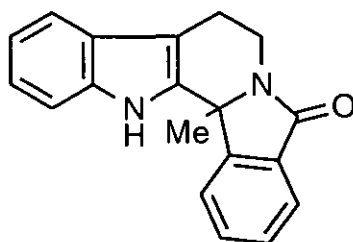
Isolated from the above reaction the *title compound* (0.121 g, 16%) as a pale yellow solid, m.p. 138-141°C (Found: M⁺, 309.1366. C₁₉H₁₉NO₃ requires M, 309.1364); ν_{\max} (KBr Disc) 2940, 1708, 1663, 768 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.84-7.80 (1H, m, Ar-H), 7.72-7.66 (1H, m, Ar-H), 7.60-7.45 (2H, m, Ar-H), 6.79 (2H, d, J 1.0 Hz, Ar-H), 6.73 (1H, s, Ar-H), 5.18 (1H, d, J 2.4 Hz, C=CH), 4.82 (1H, d, J 2.4 Hz, C=CH), 3.98-3.91 (2H, m, CH₂), 3.85 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 2.97-2.89 (2H, m, CH₂); δ_C (62.9 MHz; CDCl₃) 166.9, 149.0, 147.7, 141.7, 136.3, 133.8, 131.9 (ArCH), 131.0, 129.5 (ArCH), 123.1 (ArCH), 120.8 (ArCH), 119.8 (ArCH), 112.1 (ArCH), 111.4 (ArCH), 88.7 (CH₂), 55.9 (OCH₃), 55.8 (OCH₃), 41.1 (CH₂), 34.0 (CH₂); m/z (EI) 309 (M⁺, 58%), 165 (30), 164 (100), 158 (47), 151 (60), 149 (23), 145 (11), 107 (12), 103 (21), 91 (12), 103 (21), 91 (12), 77 (19), 51 (10).

2,3-Dimethoxy-12b-methyl-5,6,8,12b-tetrahydroisoindolo[1,2-a]isoquinolin-8-one [2.26]

Scandium triflate (0.015 g, 0.03 mmol, 10 mol%) was added to a solution of 2,3-dihydro-3-methylene-2-(3,4-dimethoxyphenyl)ethylisoindol-1-one [2.27] (0.115 g, 0.37 mmol) in xylene (30 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl

acetate) (2:1) yielded the *title compound* (0.093 g, 81%) as a yellow solid. Identical by ^1H NMR and IR to the same compound prepared directly from the methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] above.

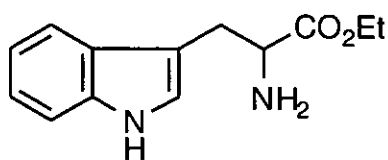
13b-Methyl-7,8,13,13b-tetrahydrobenzo[1,2]indolizino[8,7-b]indol-5-one



[2.28]

Scandium triflate (0.03 g, 0.06 mmol, 10 mol%) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] (0.140 g, 0.62 mmol) and tryptamine (0.100 g, 0.62 mmol, 0.31 ml) in xylene (50 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (2:1) yielded the *title compound* (0.163 g, 91%) as a colourless solid, m.p. 285-287°C (Lit.,¹³⁸ 282-283°C) (Found: M^+ , 288.1267. $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ requires M , 288.1263); ν_{max} (KBr Disc) 3223, 1670, 744 cm^{-1} ; δ_{H} [250 MHz; $(\text{CD}_3)_2\text{SO}$] 11.35 (1H, s, NH), 8.29 (1H, d, J 8.0 Hz, Ar-H), 7.74-7.68 (2H, m, Ar-H), 7.51 (1H, t, J 7.5 Hz, Ar-H), 7.39-7.34 (2H, m, Ar-H), 7.08 (1H, t, J 7.4 Hz, Ar-H), 6.96 (1H, dd, J 7.8, 6.9 Hz, Ar-H), 4.51 (1H, dd, J 13.1, 4.9 Hz, NCHH), 3.38 (1H, m, NCHH), 2.76-2.70 (2H, m, CH_2), 1.84 (3H, s, CH_3); δ_{C} [100.0 MHz; $(\text{CD}_3)_2\text{SO}$] 170.2, 152.3, 139.2, 138.1, 135.2 (ArCH), 133.2, 131.6 (ArCH), 129.0, 126.1 (ArCH), 125.7 (ArCH), 124.6 (ArCH), 121.9 (ArCH), 121.3 (ArCH), 114.2 (ArCH), 109.3, 65.0, 38.4 (NCH_2), 28.9 (CH_3), 24.4 (CH_2); m/z (EI) 288 (M^+ , 28%), 274 (21), 273 (100), 271 (7), 143 (4), 130 (4), 108 (4), 102 (4), 31 (4).

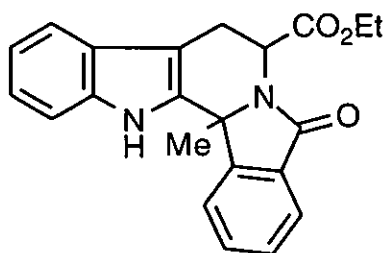
Ethyl 2-amino-3-(1H-3-indolyl)propanoate



[2.29]

Thionyl chloride (14.56 g, 122.4 mmol, 8.9 ml) was added dropwise to a stirred suspension of D,L-tryptophan (5.00 g, 24.5 mmol) in ethanol (50 ml) with cooling from an ice-water bath. The red solution was stirred at room temperature for 16 h. The pink suspension that formed was collected by filtration and washed with ethanol to give the *title compound* (5.121 g, 78%) as a pink solid of the hydrochloride salt, m.p. 219-222°C (decomp.) [Lit.,²¹² 225-226°C (dec.)] (Found: M^+ , 232.1212. $C_{13}H_{16}N_2O_2$ requires M , 232.1212); ν_{\max} (KBr Disc) 3288, 2995, 2932, 1738 cm^{-1} ; δ_H [250 MHz; $(\text{CD}_3)_2\text{SO}$] 11.30 (1H, br s, NH), 8.65 (2H, br s, NH_2), 7.52 (1H, d, J 7.7 Hz, Ar-H), 7.37 (1H, d, J 7.9 Hz, Ar-H), 7.25 (1H, d, J 2.4 Hz, Ar-H), 7.12-6.96 (2H, m, Ar-H), 4.20-4.13 (1H, m, CH), 4.05 (2H, dq, 1.0; 7.1 Hz, OCH_2) 3.33-3.21 (2H, m, ArCH_2), 1.07 (3H, t, J 7.1 Hz, CH_3); δ_C [100.0 MHz; $(\text{CD}_3)_2\text{SO}$] 170.1, 137.0, 127.8, 125.8 (ArCH), 121.9 (ArCH), 119.4 (ArCH), 118.9 (ArCH), 112.4 (ArCH), 107.3, 62.4 (OCH_2), 53.4 (CH), 27.0 (CH_2), 14.5 (CH_3); m/z (EI) 232 (M^+ , 43%), 216 (12), 159 (16), 131 (27), 130 (100), 103 (10), 77 (11), 36 (13).

Ethyl 9b-methyl-1-oxo-3,4,9,9b-tetrahydro-1H-isoindolo[1,2-a] β -carboline-3-carboxylate



[2.30]

Scandium triflate (0.120 g, 0.25 mmol, 10 mol%) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] (0.561 g, 2.5 mmol) and ethyl 2-amino-3-(1H-3-indolyl)propanoate hydrochloride salt [2.29] (0.672 g, 2.5 mmol)

in xylene (50 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.104 g, 12%) as a colourless solid, m.p. 300-305°C (decomp.) (Found: M^+ , 360.1470. $C_{22}H_{20}N_2O_3$ requires M , 360.1474); ν_{\max} (KBr Disc) 3303, 2928, 1740, 1695, 1673, 1210 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 8.89 (1H, br s, NH), 7.93-7.87 (2H, m, Ar-H), 7.60 (1H, m, Ar-H), 7.51-7.42 (2H, m, Ar-H), 7.32 (1H, m, Ar-H), 7.16-7.08 (2H, m, Ar-H), 5.81 (1H, dd, J 1.4, 8.1 Hz, NCH), 4.18 (2H, q, J 7.1 Hz, OCH_2), 3.61 (1H, dd, J 1.4, 16 Hz, ArCH H), 3.12 (1H, dd, J 8.1, 16.0 Hz, ArCHH), 1.87 (3H, s, CCH_3), 1.23 (3H, t, J 7.1 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 171.5, 169.1, 149.1, 136.5, 133.5, 132.8 (ArCH), 129.8, 128.9 (ArCH), 126.6, 124.6 (ArCH), 122.6 (ArCH), 121.6 (ArCH), 119.9 (ArCH), 118.9 (ArCH), 111.2 (ArCH), 106.0, 62.7, 61.8 (OCH_2), 49.8 (CH), 28.1 (CH_3), 22.1 (CH_2), 14.1 (CH_3); m/z (EI) 360 (M^+ , 48%), 346 (19), 345 (67), 287 (18), 272 (42), 271 (100), 270 (14), 242 (12), 214 (20), 155 (11), 136 (13), 121 (11), 77 (10), 31 (21), 29 (36), 27 (14).

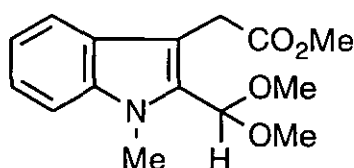
Methyl 2-acetylbenzoate [2.16]

Isolated from the above reaction the *title compound* (0.212 g, 48%) as a colourless oil. Identical by 1H NMR and IR to the same compound prepared directly from 2-acetyl-benzoic acid above.

Ethyl 9b-methyl-1-oxo-3,4,9b-tetrahydro-1H-isoindolo[1,2-a] β -carboline-3-carboxylate [2.30]

Scandium triflate (0.120 g, 0.25 mmol, 10 mol%) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate [2.18] (0.561 g, 2.5 mmol) and ethyl 2-amino-3-(1H-3-indolyl)propanoate (0.581 g, 2.5 mmol) in xylene (50 ml). The reaction mixture was refluxed through a Dean-Stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.324 g, 36%) as a colourless solid. Identical by 1H NMR and IR to the same compound prepared from the tryptophan ethyl ester hydrochloride salt.

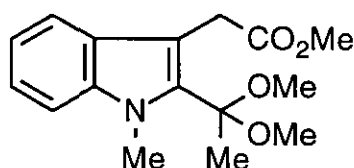
Methyl 2-[2-(dimethoxymethyl)-1*H*-3-indolyl]acetate



[2.35]

Trimethyl orthoformate (5 ml, 4.840 g, 0.046 mole), montmorillonite clay K-10 (1 g) and methyl 2-(2-formyl-1-methyl-1*H*-3-indolyl)acetic acid [3.65] (0.059 g, 0.255 mmole) gave after stirring for 16 h the *title compound* (0.066 g, 93%) as a colourless oil (Found: M^+ , 277.1314. $C_{15}H_{19}NO_4$ requires M , 277.1314); ν_{\max} (Neat) 2950, 2822, 1738, 1100, 742 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.63-7.60 (1H, m, Ar(4)-H), 7.34-7.24 (2H, m, Ar-H), 7.17-7.12 (1H, m, Ar-H), 5.66 (1H, s, CH), 3.94 (2H, s, ArCH₂), 3.82 (3H, s, CO₂CH₃), 3.67 (3H, s, NCH₃), 3.41 (6H, s, OCH₃); δ_C (62.9 MHz; $CDCl_3$) 172.5, 137.2, 131.7, 127.0, 122.5 (ArCH), 119.4 (ArCH), 118.9 (ArCH), 109.1 (ArCH), 107.8, 99.9 (CH), 54.0 (CO₂CH₃), 51.8 (OCH₃), 30.6 (NCH₃), 30.2 (CH₂); m/z (EI) 277 (M^+ , 79%), 247 (22), 246 (100), 218 (58), 202 (34), 188 (59), 172 (53), 144 (66), 85 (37), 84 (51), 47 (15), 36 (20), 31 (22), 29 (27), 28 (30), 15 (58).

Methyl 2-[2-(1,1-dimethoxyethyl)-1*H*-3-indolyl]acetate

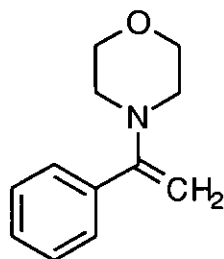


[2.36]

Trimethyl orthoformate (5 ml, 4.840 g, 0.046 mole), montmorillonite clay K-10 (3 g) and methyl 2-(2-acetyl-1-methyl-1*H*-indolyl)acetate [3.62] (0.560 g, 2.28 mmole) gave after stirring for 16 h the *title compound* (0.365 g, 55%) as a yellow oil (Found: M^+ , 291.1469. $C_{16}H_{21}NO_4$ requires M , 291.1471); ν_{\max} (Neat) 2950, 2832, 1734, 1097 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.53 (1H, d, J 7.7 Hz, Ar(4)-H), 7.32-7.19 (2H, m, Ar-H), 7.14-7.08 (1H, m, Ar-H), 4.16 (2H, s, ArCH₂), 3.85 (3H, s, CO₂CH₃), 3.64 (3H, s, NCH₃), 3.19 (6H, s, OCH₃), 1.65 (3H, s, CH₃); δ_C (62.9 MHz; $CDCl_3$) 173.3, 127.8, 122.5, 122.1 (ArCH), 119.4 (ArCH), 118.3 (ArCH), 109.3 (ArCH), 107.7, 101.2, 90.3, 51.4 (CO₂C H₃), 48.3 (OCH₃), 31.0 (CH₂), 30.7 (NCH₃),

23.6 (CH₃); *m/z* (EI) 291 (M⁺, 25%), 260 (32), 259 (37), 245 (15), 228 (19), 202 (22), 201 (17), 200 (100), 186 (39), 185 (30), 168 (20), 157 (24), 144 (53), 115 (16), 89 (16), 84 (15), 43 (21), 31 (18), 15 (59).

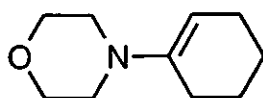
4-(1-Phenylvinyl)morpholine



[2.38]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and morpholine (0.218 g, 2.5 mmol, 0.22 ml) in toluene (30 ml) were reacted as in the general method for imines. Kugelrohr distillation yielded the *title compound* (0.169 g, 36%) as a colourless oil, b.p. 120-125°C/2.0 mmHg (Lit.,²¹³ 96-97°C/1.0 mmHg); ν_{\max} (Neat) 2942, 1590, 1540 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.80-7.13 (5H, m, Ar-H), 4.65 (1H, br s, C=CH), 4.31 (1H, br s, C=CH), 3.72-3.68 (4H, m, C(3)H₂-O-C(5)H₂), 2.83-2.76 (4H, m, C(2)H₂-N-C(6)H₂).

4-(1-Cyclohexenyl)morpholine



[2.39]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1,1-dimethoxycyclohexane [2.6] (0.361 g, 2.5 mmol) and morpholine (0.218 g, 2.5 mmol, 0.22 ml) in toluene (30 ml) were reacted as in the general method for imines. Kugelrohr distillation yielded the *title compound* (0.218 g, 52%) as a colourless oil, b.p. 110-114°C/5.0 mmHg (Lit.,²¹⁴ 93°C/1.5 mmHg); ν_{\max} (Neat) 2935, 1620 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 4.66 (1H, t, J 3.5 Hz, C=CH), 3.73 (4H, t, J 4.8 Hz, CH₂OCH₂),

2.76 (4H, t, J 4.8 Hz, C(2)H₂-N-C(6)H₂), 2.10-2.02 (4H, m, C(12)H₂-C=C-C(9)H₂), 1.71-1.62 (4H, m, C(10)H₂-C(11)H₂).

1-(1-Phenylvinyl)piperidine

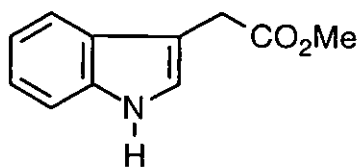


[240]

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%), 1-(1,1-dimethoxyethyl) benzene [2.3] (0.416 g, 2.5 mmol) and piperidine (0.213 g, 2.5 mmol, 0.25 ml) in xylene (30 ml) were reacted as in the general method for imines. Kugelrohr distillation yielded the *title compound* (0.147 g, 31%) as a colourless oil, b.p. 120-125°C/ 2.0 mmHg (Lit.,²¹⁵ 78-79°C/0.3 mmHg); ν_{\max} (Neat) 2938, 1600, 1574 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.56-7.10 (5H, m, Ar-H), 4.23 (1H, br s, C=CH), 4.13 (1H, br s, C=CH), 2.81-2.76 (4H, m, C(2)H₂-N-C(6)H₂), 1.60-1.54 (6H, m, C(3)H₂-C(4)H₂-C(5)H₂).

5.3 Experimental for Chapter 3

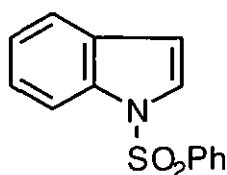
Methyl 2-(1*H*-3-indolyl)acetate



[3.8]

To a solution of indole-3-acetic acid (12.50 g, 71.4 mmol) in methanol (100 ml) was added sulfuric acid (10 M, 10 drops). After refluxing for 3 h the solvent was removed under reduced pressure. Purification by flash chromatography (diethyl ether) yielded the *title compound* (11.88 g, 88%) as pale brown crystals, m.p. 50-51°C [Lit.,²¹⁶ 49-50.5°C (Ethyl acetate)]; (Found: C, 69.43; H, 5.78; N, 7.48%; Calc. for C₁₁H₁₁NO₂ C, 69.84; H, 5.82; N, 7.41%); ν_{\max} (KBr Disc) 3360, 1717, 748 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 8.13 (1H, br s, NH), 7.64 (1H, d, J 8.2 Hz, Ar-H), 7.34 (1H, d, J 8.2 Hz, Ar-H), 7.27-7.14 (3H, m, Ar-H), 3.81 (2H, s, ArCH₂), 3.72 (3H, s, OCH₃); δ_{C} (62.9 MHz; CDCl₃) 172.8, 136.1, 127.1, 123.3 (ArCH), 122.1 (ArCH), 119.6 (ArCH), 118.7 (ArCH), 111.3 (ArCH), 108.0, 52.0 (OCH₃), 31.1 (CH₂); *m/z* (EI) 189 (M⁺, 22%), 130 (100), 77 (11), 51 (10), 28 (14).

1-(Phenylsulfonyl)-1*H*-indole

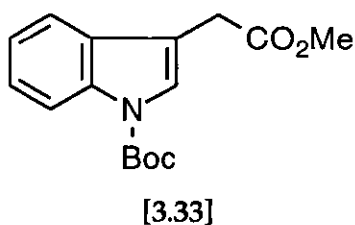


[3.28]

To a solution of indole (2.5 g, 21.3 mmol) in tetrahydrofuran (20 ml) at -78°C was added *n*-butyllithium (2.5 M in hexane; 9.0 ml, 22.5 mmol) over 15 min. The cooling bath was removed and the solution was stirred for 1 h while warming to 0°C. The resulting indole salt precipitated as a fine white solid in a cloudy colourless solution. After the suspension was cooled to -78°C, benzene sulfonyl chloride (4.15 g, 23.5 mmol) was added *via* syringe over 15 min, keeping the internal temperature below -60°C. The resulting colourless mixture was allowed to warm slowly to room temperature overnight, poured

into 2% aqueous sodium bicarbonate (75 ml), and extracted with ether (4 x 30 ml). The combined extracts were washed with 2% aqueous sodium bicarbonate (30 ml), water (2 x 25 ml), and brine (2 x 35 ml), dried over potassium carbonate and the solvent removed under reduced pressure to give an amber oil which crystallised when triturated with hexane-ether (2:1) (20 ml). After standing at 5 °C for 5 h the product was collected by filtration, washed with hexane, and dried at 45°C (20 mmHg) to yield the *title compound* (4.39 g, 80%) as colourless crystals, m.p. 78-80°C (Lit.,¹⁵⁵ 78-79°C); ν_{\max} (KBr Disc) 3139, 1378, 1182, 755 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.00 (1H, d, J 8.2 Hz, Ar-(4)H), 7.88 (1H, d, J 8.2 Hz, Ar-H), 7.86 (1H, m, Ar-H), 7.57-7.39 (5H, m, Ar-H), 7.31-7.22 (2H, m, Ar-H), 6.65 (1H, m, Ar-H); δ_{C} (62.9 MHz; CDCl_3) 138.1, 134.8, 133.8 (ArCH), 130.6, 129.2 (ArCH), 126.7 (ArCH), 126.3 (ArCH), 124.6 (ArCH), 123.4 (ArCH), 121.4 (ArCH), 113.5 (ArCH), 109.2 (ArCH); m/z (EI) 257 (M^+ , 86%), 141 (37), 117 (15), 116 (100), 90 (11), 89 (46), 77 (81), 63 (17), 51 (18).

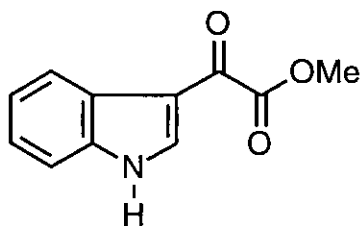
***tert*-Butyl 3-(2-methoxy-2-oxoethyl)-1*H*-1-indolecarboxylate**



Methyl 2-(1*H*-3-indolyl)acetate [3.8] (4.0 g, 21.0 mmol) and 4-dimethylamino-pyridine (0.25 g, 2.1 mmol) were added to a solution of *di-tert*-butyl-carbonate (5.54 g, 25.0 mmol) in acetonitrile (40 ml) and the reaction mixture was stirred for 16 h. Saturated sodium bicarbonate solution (40 ml) was added and the solution was extracted with diethyl ether (3 x 40 ml). The combined diethyl ether layers were dried (MgSO_4) and the solvent was removed under reduced pressure. Purification by flash chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (5.54 g, 90%) as colourless crystals m.p. 55-57°C; (Found: C, 66.29; H, 6.40; N, 4.59%; $\text{C}_{16}\text{H}_{19}\text{NO}_4$ requires C, 66.42; H, 6.62; N, 4.84%); ν_{\max} (KBr Disc) 2982, 1749, 1732, 1610, 750 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.14 (1H, m, Ar-(4)H), 7.57-7.51 (2H, m, Ar-H), 7.35-7.22 (2H, m, Ar-H), 3.72 (2H, s, ArCH_2), 3.71 (3H, s, OCH_3), 1.66 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (62.9 MHz; CDCl_3) 171.5, 149.0, 135.6, 130.1, 124.5 (ArCH), 124.4 (ArCH), 122.6 (ArCH), 118.9 (ArCH), 115.2 (ArCH), 113.2, 83.6, 52.0 (OCH_3), 30.8 (CH_2), 28.1

(CH₃); *m/z* (EI) 289 (M⁺, 9%), 233 (53), 189 (24), 174 (22), 131 (12), 130 (100), 129 (12), 57 (95), 41 (19), 29 (10).

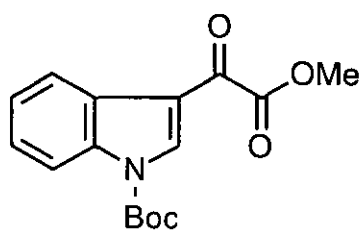
Methyl 2-(1*H*-3-indolyl)-2-oxoacetate



[3.36]

Oxalyl chloride (1.396 g, 11.0 mmol, 0.96 ml) in diethyl ether (10 ml) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in diethyl ether (40 ml) at 0°C over 15 min. After stirring at room temperature for 1 h, the solvent and excess oxalyl chloride were removed under reduced pressure. The resultant yellow solid was dissolved in dichloromethane (50 ml) and cooled to 0°C. A solution of triethylamine (2.277 g, 22.5 mmol, 3.14 ml) and methanol (4 ml) in dichloromethane (10 ml) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 3 h. Water (50 ml) was added and the organic layer was separated, the aqueous layer was extracted with dichloromethane (3 x 30 ml) and the combined organic layers were dried (MgSO₄). The solvent was removed under reduced pressure and the crude product purified by column chromatography (light petroleum : ethyl acetate) (2:1) to yield the *title compound* (1.67 g, 82%) as a light brown solid, m.p. 232-234°C (MeOH) (Lit.²¹⁷ 234-236°C); ν_{\max} (KBr Disc) 2953, 1729, 1621, 757 cm⁻¹; δ_{H} (250 MHz; (CD₃)₂SO) 12.43 (1H, br s, NH), 8.43 (1H, s, Ar-H), 8.17-8.13 (1H, m, Ar-H), 7.54-7.52 (1H, m, Ar-H), 7.29-7.25 (2H, m, Ar-H), 3.88 (3H, s, OCH₃); δ_{C} (62.9 MHz; (CD₃)₂SO) 183.8, 169.2, 143.5 (Ar-H), 141.8, 130.6, 128.9 (Ar-H), 127.9 (Ar-H), 126.3 (Ar-H), 117.9 (Ar-H), 117.6, 57.6 (OCH₃); *m/z* (EI) 203 (M⁺, 12%), 145 (10), 144 (100), 116 (29), 89 (24), 63 (11).

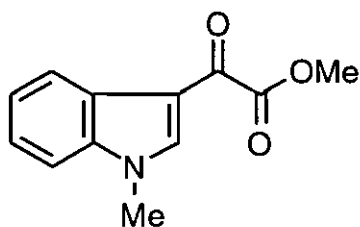
***tert*-Butyl 3-(2-methoxy-2-oxoacetyl)-1*H*-1-indolecarboxylate**



[3.37]

Methyl 2-(1*H*-3-indolyl)-2-oxoacetate [3.36] (0.508 g, 2.50 mmol) and 4-dimethylaminopyridine (0.025 g, 0.21 mmol) were added to a solution of di-*tert*-butyl-carbonate (0.600 g, 2.75 mmol) in acetonitrile (20 ml) and the reaction mixture was stirred for 3 h. Saturated sodium bicarbonate solution (20 ml) was added and the solution was extracted with diethyl ether (3 x 20 ml). The combined diethyl ether layers were dried (MgSO₄) and the solvent removed under reduced pressure. Purification by flash sinter chromatography (dichloromethane) yielded the *title compound* (0.667 g, 88%) as colourless crystals, m.p. 130-131°C (*n*-pentane/ethyl acetate); (Found: C, 63.21; H, 5.42; N, 4.59%; C₁₆H₁₇NO₅ requires C, 63.36; H, 5.65; N, 4.62%); ν_{\max} (Nujol) 1746, 1738, 1731, 1651, 758 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 8.81 (1H, s, Ar-(2)H), 8.42-8.38 (1H, m, Ar-H), 8.18-8.15 (1H, m, Ar-H), 7.46-7.36 (2H, m, Ar-H), 3.98 (3H, s, OCH₃), 1.72 (9H, s, C(CH₃)₃); δ_{C} (62.9 MHz; CDCl₃) 178.6, 162.4, 148.6, 137.0 (ArCH), 135.2, 127.4, 125.9 (ArCH), 124.8 (ArCH), 122.5 (ArCH), 116.0, 115.0 (ArCH), 85.9, 52.9 (OCH₃), 28.0 (CH₃); *m/z* (EI) 303 (M⁺, 17%), 248 (13), 247 (12), 246 (5), 203 (10), 202 (11), 188 (16), 144 (87), 116 (7), 115 (6), 89 (7), 57 (100), 41 (31), 29 (15).

Methyl 2-(1-methyl-1*H*-3-indolyl)-2-oxoacetate

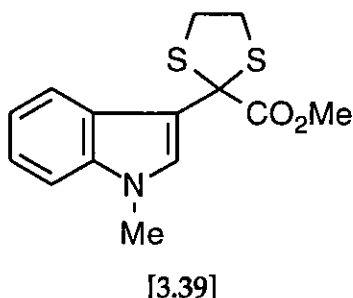


[3.38]

Oxalyl chloride (1.12 g, 8.80 mmol, 0.77 ml) in diethyl ether (10 ml) was added dropwise to a solution of 1-methylindole (1.05 g, 8.00 mmol) in diethyl ether

(40 ml) at 0°C over 15 min. After stirring at room temperature for 1 h, the solvent and excess oxalyl chloride were removed under reduced pressure. The resultant yellow solid was dissolved in dichloromethane (50 ml) and cooled to 0°C. A solution of triethylamine (1.82 g, 18.00 mmol, 2.5 ml) and methanol (4 ml) in dichloromethane (10 ml) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 3 h. Water (50 ml) was added and the organic layer was separated, the aqueous layer was extracted with dichloromethane (3 x 30 ml) and the combined organic layers were dried (MgSO₄). The solvent was removed under reduced pressure and the crude product purified by column chromatography (light petroleum : ethyl acetate) (2:1) to yield the *title compound* (1.38 g, 79%) as a yellow solid, m.p. 94-95°C (Lit.,²¹⁸ 96-97°C) (Found: M⁺, 217.0739. C₁₂H₁₁NO₃ requires M, 217.0739); ν_{\max} (Nujol) 1729, 1701, 1647, 745 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 8.47-8.41 (1H, m, Ar-(4)H), 8.34 (1H, s, Ar-(2)H), 7.38-7.35 (3H, m, Ar-H), 3.91 (3H, s, OCH₃), 3.74 (3H, s, NCH₃); δ_{C} (62.9 MHz; CDCl₃) 176.8, 163.2, 140.3 (ArCH), 137.2, 126.8, 124.0 (ArCH), 123.4 (ArCH), 122.5 (ArCH), 112.4, 109.9 (ArCH), 52.6 (OCH₃), 33.6 (NCH₃); *m/z* (EI) 217 (M⁺, 4%), 158 (40), 131 (29), 119 (28), 100 (10), 69(100), 28 (11).

Methyl 2-(1-methyl-1*H*-3-indolyl)-1,3-dithiolane-2-carboxylate



Method A

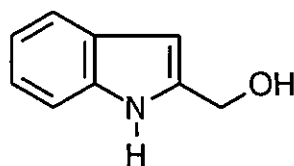
Methyl 2-(1-methyl-1*H*-3-indolyl)-2-oxoacetate [3.38] (0.500 g, 2.30 mmol), 1,2-ethane dithiol (0.216 g, 2.30 mmol) and *p*-toluene sulfonic acid monohydrate (10 mg) in toluene (100 ml) were refluxed through a Dean-Stark trap for 24 h. The solvent was removed under reduced pressure and the crude product purified by column chromatography (light petroleum : ethyl acetate) (3:1) to yield the *title compound* (0.197 g, 29%) as a pale yellow solid, m.p. 129-132°C (Found: M⁺, 293.0566. C₁₄H₁₅NS₂O₂ requires M, 293.0544); ν_{\max} (Nujol) 1731,

1217, 1011 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.65 (1H, d, J 8.1 Hz, Ar-(4)H), 7.37 (1H, s, Ar-(2)H), 7.23-7.11 (3H, m, Ar-H), 3.70 (6H, s, OCH_3 , NCH_3), 3.52-3.39 (4H, m, SCH_2); δ_{C} (62.9 MHz; CDCl_3) 172.6, 137.6, 128.1 (ArCH), 125.2, 122.1 (ArCH), 120.0 (ArCH), 119.6 (ArCH), 113.6, 109.6 (ArCH), 53.6 (OCH_3), 39.8 (CH_2), 32.8 (NCH_3); m/z (EI) 293 (M^+ , 6%), 234 (48), 174 (20), 164 (15), 163 (26), 144 (23), 105 (74), 61 (31), 60 (11), 59 (16), 51 (15), 45 (28), 44 (11), 43 (100), 31 (11), 29 (22), 27 (21).

Method B

1,2-Ethane dithiol (0.096 g, 1.013 mmol) was added to a solution of methyl 2-(1-methyl-1*H*-3-indolyl)-2-oxoacetate [3.38] (0.200 g, 0.921 mmol) in acetic acid (10 ml). Boron trifluoride etherate (0.144 g, 1.013 mmol, 0.12 ml) was added dropwise and the reaction was stirred for 16 h. The solid formed was collected by filtration to yield the title compound (0.084 g, 31%) as a yellow solid. The filtrate was extracted with diethyl ether (25 ml), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.028 g, 10%) as a pale yellow solid. Identical by ^1H and ^{13}C NMR with the same compound prepared above.

1*H*-2-Indolylmethanol

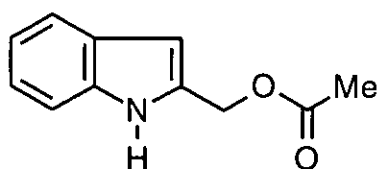


[3.40]

A solution of methyl 1*H*-2-indolecarboxylate [3.45] (10.73 g, 61.23 mmol) in tetrahydrofuran (150 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.79 g, 73.48 mmol) in tetrahydrofuran (100 ml) at a rate such that the mixture achieved gentle reflux. After 2 h, water (1.2 ml), sodium hydroxide (15%, 1.2 ml) and water (3.6 ml), were added to the mixture and the resulting precipitate removed by filtration through a bed of celite. The filtrate was dried (MgSO_4) and the solvent removed under reduced pressure yielding the *title compound* (8.04 g, 89%) as colourless crystals, m.p. 74-76°C (hexane) (Lit.,²¹⁹ 74-76°C); ν_{max} (KBr Disc) 3373, 3248, 1618, 750 cm^{-1} ; δ_{H} (250

MHz; CDCl₃) 8.36 (1H, br s, NH), 7.58 (1H, dd, J 7.9, 0.9 Hz, Ar-(4)H), 7.35-7.31 (1H, m, Ar-H), 7.22-7.07 (2H, m, Ar-H), 6.40 (1H, dd, J 2.1, 0.9 Hz, Ar-(3)H), 4.81 (2H, s, ArCH₂O), 1.94 (1H, br s, OH); δ_C (62.9 MHz; CDCl₃) 137.6, 136.5, 128.0, 122.2 (ArCH), 120.7 (ArCH), 120.0 (ArCH), 111.2 (ArCH), 100.7 (ArCH), 58.4 (CH₂); *m/z* (EI) 147 (M⁺, 51%), 130 (85), 129 (100), 128 (28), 118 (51), 117 (40), 91 (38), 90 (33), 89 (64), 77 (27), 63 (57), 28 (35).

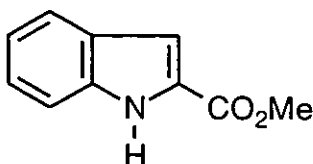
1*H*-2-Indolylmethyl acetate



[3.41]

To a stirred solution of 1*H*-2-indolylmethanol [3.40] (5.03 g, 34.2 mmol), acetic anhydride (3.84 g, 37.6 mmol) and triethylamine (4.15 g, 41.0 mmol) in dichloromethane (250 ml) was added 4-dimethylaminopyridine (0.005 g, 0.041 mmol). The reaction mixture was stirred for 24 h and then saturated aqueous sodium hydrogen carbonate solution (100 ml) was added. The organic layer was separated, washed with hydrochloric acid (2 M, 3 x 100 ml) and water (100 ml) and dried (Na₂SO₄). The solvent was removed under reduced pressure. Flash sinter chromatography (dichloromethane) yielded the *title compound* (6.10 g, 94%) as a colourless solid, m.p. 110-112°C (Lit.,^{166(b)} 112°C); ν_{\max} (Nujol) 3302, 1726, 1235, 740 cm⁻¹; δ_H (250 MHz; CDCl₃) 8.57 (1H, br s, NH), 7.58 (1H, m, Ar-(4)H), 7.34 (1H, m, Ar-H), 7.25-7.16 (1H, m, Ar-H), 7.12-7.06 (1H, m, Ar-H), 6.53 (1H, d, J 2.0 Hz, Ar-(3)H), 5.22 (2H, s, ArCH₂O), 2.10 (3H, s, COCH₃); δ_C (62.9 MHz; CDCl₃) 172.2, 136.6, 133.0, 127.6, 122.7 (ArCH), 120.9 (ArCH), 120.0 (ArCH), 111.1 (ArCH), 103.1 (ArCH), 59.7 (CH₂), 20.3 (CH₃); *m/z* (EI) 189 (M⁺, 79%), 147 (26), 130 (77), 129 (100), 128 (14), 103 (13), 102 (18), 89 (13), 77 (21), 43 (15).

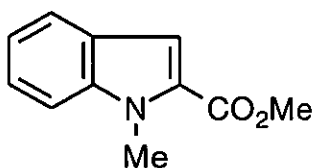
Methyl 1H-2-indolecarboxylate



[3.45]

To a solution of indole-2-carboxylic acid (20.00 g, 0.124 mol) in methanol (200 ml) was added sulfuric acid (10 M, 10 drops) and the mixture was refluxed for 16 h. On cooling a colourless precipitate was formed which was collected by filtration to yield the *title compound* (15.74 g, 72%). The filtrate was concentrated under reduced pressure and purified by flash chromatography (dichloromethane) yielding the title compound (4.04 g, 19%) as colourless crystals, m.p. 149-150°C (Lit.,²²⁰ 151-152°C); ν_{\max} (Nujol) 3331, 1693, 746 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 9.05 (1H, br s, NH), 7.70 (1H, dd, J 7.9, 0.8 Hz, Ar-H), 7.42 (1H, dd, J 8.3, 0.8 Hz, Ar-H), 7.37-7.31 (1H, m, Ar-H), 7.27-7.25 (1H, m, Ar-H), 7.21-7.15 (1H, m, Ar-H), 3.95 (3H, s, OCH_3); δ_{C} (62.9 MHz; CDCl_3) 162.6, 137.0, 127.4, 127.0, 125.4 (ArCH), 122.6 (ArCH), 120.8 (ArCH), 111.9 (ArCH), 108.8 (ArCH), 52.0 (OCH_3); m/z (EI) 175 (M^+ , 64%), 144 (24), 143 (100), 116 (13), 115 (63), 89 (37), 63 (13).

Methyl 1-methyl-1H-2-indolecarboxylate

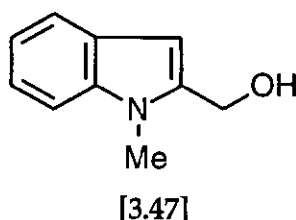


[3.46]

Indole-2-carboxylic acid (3.40 g, 21.1 mmol) in dimethyl sulfoxide (40 ml) was added to a stirred suspension of potassium hydroxide (4.73 g, 84.4 mmol) in dimethyl sulfoxide (5 ml). After 2 h a solution of methyl iodide (12.0 g, 84.4 mmol, 5.3 ml) in dimethyl sulfoxide (5 ml) was added. The reaction was stirred for 3 h. Water (100 ml) was added and the mixture extracted with diethyl ether (3 x 50 ml), the combined organic layers were washed with brine (4 x 50 ml) and dried (MgSO_4). The solvent was removed under reduced pressure yielded the *title compound* (3.84 g, 96%) as colourless crystals,

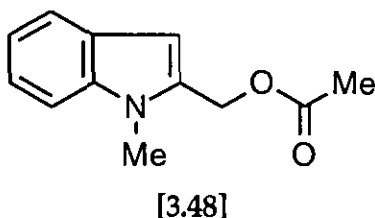
m.p. 97-98°C (Lit.,²²¹ 96.5-97.5°C) (Found: M^+ , 189.0789. $C_{11}H_{11}NO_2$ requires M , 189.0790); ν_{\max} (Nujol) 1708, 1515, 749 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.66 (1H, d, J 7.9 Hz, Ar-H), 7.34-7.27 (3H, m, Ar-H), 7.15-7.11 (1H, m, Ar-H), 4.04 (3H, s, OCH_3), 3.88 (3H, s, NCH_3); δ_C (62.9 MHz; $CDCl_3$) 162.8, 139.6, 128.0, 125.6, 124.9 (ArCH), 122.6 (ArCH), 120.5 (ArCH), 110.2 (ArCH), 110.1 (ArCH), 51.6 (OCH_3), 31.5 (NCH_3); m/z (EI) 189 (M^+ , 73%), 174 (14), 158 (38), 131 (29), 130 (22), 129 (20), 115 (12), 102 (10), 90 (12), 89 (100), 88 (11), 77 (17), 63 (32), 62 (13), 51 (11), 77 (17), 63 (32), 62 (13), 51 (11), 45 (14), 39 (23), 31 (18), 29 (11), 18 (14), 15 (51).

(1-Methyl-1H-2-indolyl)methanol



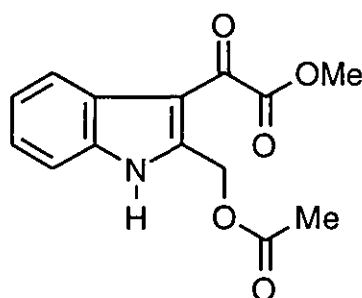
A solution of methyl 1-methyl-1H-2-indolecarboxylate [3.46] (18.94 g, 0.100 mol) in tetrahydrofuran (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (4.18 g, 0.110 mol) in tetrahydrofuran (100 ml) at a rate such that the mixture achieved gentle reflux. After 2 h, water (1.2 ml), sodium hydroxide (15%, 1.2 ml) and water (3.6 ml), were added to the mixture and the resulting precipitate removed by filtration through a bed of celite. The filtrate was dried ($MgSO_4$) and the solvent removed under reduced pressure yielding the *title compound* (15.85 g, 98%) as colourless crystals, m.p. 95-96°C (Lit.,²²² 92-93°C); ν_{\max} (Nujol) 1612, 749 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.59 (1H, d, J 7.8 Hz, Ar-(4)H), 7.37-7.35 (1H, m, Ar-H), 7.21-7.05 (2H, m, Ar-H), 6.43 (1H, m, Ar-(3)H), 4.79 (2H, s, $ArCH_2O$), 3.78 (3H, s, NCH_3), 1.56 (1H, br s, OH).

(1-Methyl-1H-2-indolyl)methyl acetate



To a stirred solution of (1-methyl-1*H*-2-indolyl)methanol [3.47] (15.851 g, 0.098 mol), acetic anhydride (11.042 g, 0.108 mol) and triethylamine (10.945 g, 0.108 mol) in dichloromethane (100 ml) was added 4-dimethylaminopyridine (0.005 g, 0.041 mmol). The reaction mixture was stirred for 15 h and then saturated aqueous sodium hydrogen carbonate solution (50 ml) was added. The organic layer was separated, washed with hydrochloric acid (2 M, 3 x 50 ml) and water (50 ml) and dried (Na₂SO₄). The solvent was removed under reduced pressure. Flash sinter chromatography (dichloromethane) yielded the *title compound* (18.964 g, 95%) as a pale pink solid, m.p. 63-64°C [Lit.,²²³ 63.5-64°C (pentane)] (Found: M⁺, 203.0950. C₁₂H₁₃NO₂ requires M, 203.0946); ν_{\max} (Nujol) 1726, 743 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.59 (1H, dd, J 6.8, 1.1 Hz, Ar-(4)H), 7.29-7.21 (2H, m, Ar-H), 7.13-7.07 (1H, m, Ar-H), 6.58 (1H, s, Ar-(3)H), 5.27 (2H, s, ArCH₂O), 3.74 (3H, s, NCH₃), 2.08 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 170.5, 137.9, 133.6, 127.0, 122.3 (ArCH), 120.9 (ArCH), 119.7 (ArCH), 109.2 (ArCH), 103.7 (ArCH), 58.1 (CH₂), 29.7 (NCH₃), 20.8 (CH₃); *m/z* (EI) 203 (M⁺, 96%), 161 (73), 160 (17), 145 (54), 144 (100), 142 (12), 132 (31), 130 (16), 117 (14), 115 (13), 89 (17), 43 (32), 15 (18).

Methyl 2-[2-[(acetyloxy)methyl]-1*H*-3-indolyl]-2-oxoacetate

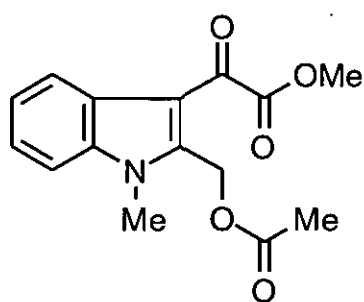


[3.49]

Oxalyl chloride (0.283 g, 2.24 mmol, 0.20 ml) in diethyl ether (5 ml) was added dropwise to a solution of 1*H*-2-Indolylmethyl acetate [3.41] (0.423 g, 2.24 mmol) in diethyl ether (25 ml) at 0°C over 15 min. After stirring at room temperature for 1 h, the solvent and excess oxalyl chloride were removed under reduced pressure. The resultant yellow solid was dissolved in dichloromethane (30 ml) and cooled to 0°C. A solution of triethylamine (0.506 g, 5.00 mmol, 2.5 ml) and methanol (2 ml) in dichloromethane (10 ml) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 3 h. Water (50 ml) was added and the organic layer was

separated, the aqueous layer was extracted with dichloromethane (3 x 30 ml) and the combined organic layers were dried (MgSO₄). The solvent was removed under reduced pressure and the crude product purified by column chromatography (light petroleum : diethyl ether) (1:2) to yield the *title compound* (0.437 g, 70%) as a light brown solid m.p. 135-136°C; (Found: C, 61.05; H, 4.60; N, 4.80%; C₁₄H₁₃NO₅ requires C, 61.09; H, 4.76; N, 5.08%); ν_{\max} (Nujol) 3328, 1732, 1729, 751 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 9.43 (1H, br s, NH), 7.88 (1H, m, Ar-H), 7.43-7.39 (1H, m, Ar-H), 7.33-7.24 (2H, m, Ar-H), 5.58 (2H, s, ArCH₂O), 4.00 (3H, s, OCH₃), 2.18 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 181.4, 170.8, 166.0, 143.7, 135.0, 125.8, 124.1 (ArCH), 123.3 (ArCH), 120.3 (ArCH), 112.0 (ArCH), 110.0, 59.1 (CH₂), 52.8 (OCH₃), 20.6 (CH₃); *m/z* (EI) 275 (M⁺, 62%), 217 (12), 216 (62), 175 (26), 174 (100), 157 (10), 156 (24), 129 (12), 128 (20), 43 (31), 15 (22).

Methyl 2-{2-[(acetyloxy)methyl]-1-methyl-1*H*-3-indolyl}-2-oxoacetate

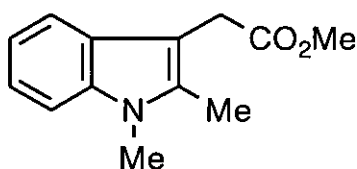


[3.50]

Oxalyl chloride (6.87 g, 54.1 mmol, 0.20 ml) in diethyl ether (75 ml) was added dropwise to a solution of (1-methyl-1*H*-2-indolyl)methyl acetate [3.48] (10.00 g, 49.2 mmol) in diethyl ether (100 ml) whilst keeping the temperature below 5°C. After stirring at room temperature for 1 h, the solvent and excess oxalyl chloride were removed under reduced pressure. The resultant brown oil was dissolved in dichloromethane (100 ml) and cooled to 0°C. A solution of triethylamine (11.208 g, 110.7 mmol, 15.4 ml) and methanol (25 ml) in dichloromethane (25 ml) was added dropwise. The reaction mixture was stirred at room temperature for 12 h. Water (150 ml) was added and the organic layer was separated, the aqueous layer was extracted with dichloromethane (3 x 100 ml), the combined organic layers were washed with water (100 ml) and were then dried (MgSO₄). The solvent was removed under reduced pressure and purification by flash sinter chromatography

(dichloromethane) yielded the *title compound* (11.540 g, 81%) as a yellow solid m.p. 75-76°C; (Found: C, 62.13; H, 5.03; N, 4.56%; C₁₅H₁₅NO₅ requires C, 62.28; H, 5.23; N, 4.84%); ν_{\max} (KBr Disc) 2962, 1747, 1735, 1654, 1610, 760 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.97 (1H, m, Ar-H), 7.35-7.27 (3H, m, Ar-H), 5.47 (2H, s, ArCH₂O), 3.97 (3H, s, OCH₃), 3.78 (3H, s, NCH₃), 2.07 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 181.4, 170.2, 165.8, 141.7, 137.0, 125.7, 124.2 (ArCH), 123.4 (ArCH), 121.0 (ArCH), 111.0, 110.2 (ArCH), 55.3 (CH₂), 52.6 (OCH₃), 30.4 (NCH₃), 20.5 (CH₃); m/z (EI) 289 (M⁺, 42%), 230 (45), 189 (33), 188 (100), 187 (11), 172 (11), 159 (11), 158 (13), 143 (18), 130 (14), 117 (12), 115 (16), 44 (34), 43 (29), 42 (14), 28 (31), 15 (40).

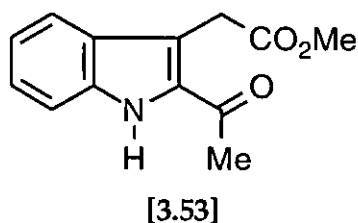
Methyl 2-(1,2-dimethyl-1H-3-indolyl)acetate



[3.52]

A solution of sodium hypophosphite (10.822 g, 102.2 mmol) in water (20 ml) was added to a stirred solution of methyl 2-{2-[(acetyloxy)methyl]-1-methyl-1H-3-indolyl}-2-oxoacetate [3.50] (11.540 g, 39.9 mmol) and palladium on carbon (10%) (2.308 g, 20% w/w based on indole glyoxylate) in 1,4-dioxane (100 ml). The mixture was refluxed, with vigorous stirring, for 4 h. The solution was allowed to cool and a solution of sodium hypophosphite (10.530 g, 99.4 mmol) in water (20 ml) was added and this was again heated to reflux for 4 h. The solution was allowed to cool, filtered through a pad of celite and washed with diethyl ether. The solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : diethyl ether) (2:1) yielded the *title compound* (7.196 g, 83%) as a brown solid (Found: M⁺, 217.1104. C₁₃H₁₅NO₂ requires M, 217.1103); δ_{H} (250 MHz; CDCl₃) 7.57 (1H, m, Ar-H), 7.29-7.26 (1H, m, Ar-H), 7.22-7.09 (2H, m, Ar-H); 3.75 (2H, s, ArCH₂), 3.68 (3H, s, CH₃), 3.67 (3H, s, CH₃), 2.42 (3H, s, ArCH₃); δ_{C} (62.9 MHz; CDCl₃) 172.4, 136.3, 134.3, 127.3, 120.6 (ArCH), 119.0 (ArCH), 117.7 (ArCH), 108.5 (ArCH), 103.4, 51.7 (OCH₃), 30.3 (CH₂), 29.3 (NCH₃), 10.1 (CH₃); m/z (EI) 217 (M⁺, 53%), 159 (20), 158 (100), 143 (10), 115 (6), 15 (10).

Methyl 2-(2-acetyl-1H-3-indolyl)acetate



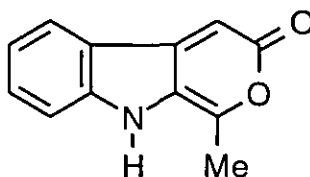
Method A

Acetyl chloride (0.510 g, 6.5 mmol, 0.46 ml) was added to methyl 2-(1H-3-indolyl)acetate [3.8] (0.945 g, 5.0 mmol) in 1,2-dichloroethane (20 ml) at 0°C under nitrogen. Aluminium chloride (0.733 g, 5.5 mmol) was added in small portions over 1 h. The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h. Hydrochloric acid (2 M, 50 ml) was added carefully and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with water (2 x 30 ml), dried (MgSO₄) and the solvent was removed under reduced pressure. Column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (0.591 g, 51%) as a pale yellow solid, m.p. 140-141°C (Lit.,¹⁷⁰ 139°C) (Found: M⁺, 231.0907. C₁₃H₁₃NO₃ requires M, 231.0895); ν_{\max} (Nujol) 1729, 1645, 739 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 9.11 (1H, br s, NH), 7.68-7.65 (1H, m, Ar-(4)H), 7.36-7.33 (2H, m, Ar-H), 7.20-7.13 (1H, m, Ar-H), 4.15 (2H, s, ArCH₂), 3.72 (3H, s, OCH₃), 2.60 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 190.4, 171.6, 135.8, 132.6, 128.2, 126.4 (ArCH), 120.7 (ArCH), 120.6 (ArCH), 114.0, 112.3 (ArCH), 52.3 (OCH₃), 31.0 (CH₂), 28.1 (CH₃); *m/z* (EI) 231 (M⁺, 25%), 199 (28), 188 (5), 172 (67), 171 (12), 130 (27), 32 (31), 28 (100).

Method B

1-Methyl-3,9-dihydropyrano[3,4-b]indol-3-one [3.55] (1.44 g, 7.23 mmol) in methanol (50 ml) was stirred for 16 h. The solvent was removed under reduced pressure and the crude product was purified by flash sinter chromatography (dichloromethane) yielding the *title compound* (1.35 g, 81%) as a pale yellow solid, m.p. 138-139°C (Lit.,¹⁷⁰ 139°C). Identical by ¹H, ¹³C NMR and IR with the same compound prepared by Friedal-Crafts acylation.

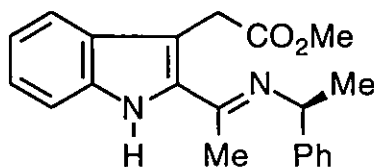
1-Methyl-3,9-dihydropyrano[3,4-b]indol-3-one



[3.55]

To a solution of indole-3-acetic acid (2.0 g, 11.4 mmol) in acetic anhydride (8 ml) at 0°C was added boron trifluoride etherate (2 ml) over 30 min. The reaction was stirred at 0°C for 30 min and then allowed to warm to room temperature over 2 h. Diethyl ether (30 ml) was added and the solid was filtered, triturated with aqueous saturated sodium bicarbonate solution and washed with water and diethyl ether. The solid was dried under reduced pressure yielding the *title compound* (1.64 g, 72%) as a brown solid, m.p. 259-261°C (decomp.) [Lit.,¹⁷⁰ 260°C (decomp.)] (Found: M^+ , 199.0632. $C_{12}H_9NO_2$ requires M , 199.0633); ν_{\max} (KBr Disc) 1701, 1610, 1570 cm^{-1} ; δ_H (250 MHz; $(CD_3)_2SO$) 10.32 (1H, br s, NCH₃), 7.86 (1H, d, J 8.0 Hz, Ar-H), 7.40 (1H, t, J 7.5 Hz, Ar-H), 7.16 (1H, d, J 8.0 Hz, Ar-H), 6.90 (1H, t, J 7.5 Hz, Ar-H), 6.38 (1H, s; Ar-H), 2.49 (3H, s, CH₃); δ_C (62.9 MHz; $(CD_3)_2SO$) 162.6, 148.0, 146.2, 144.4, 133.0 (ArCH), 125.1, 124.5 (ArCH), 119.4, 119.0 (ArCH), 111.4 (ArCH), 95.6 (ArCH), 16.5 (CH₃); m/z (EI) 199 (M^+ , 79%), 171 (57), 170 (15), 143 (73), 128 (33), 115 (22), 102 (18), 101 (34), 75 (36), 74 (20), 52 (17), 51 (37), 44 (15), 43 (100), 39 (21), 31 (18), 28 (34), 18 (42).

Methyl 2-(2-([(1S)-1-phenylethyl]ethanimidoyl)-1H-3-indolyl)acetate

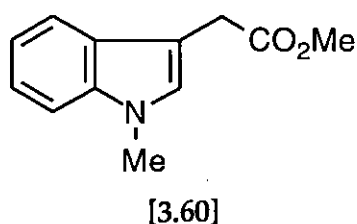


[3.56]

Amberlyst 15 (0.025 g), methyl 2-(2-acetyl-1H-3-indolyl)acetate [3.53] (0.500 g, 2.16 mmol) and S-(1)-phenylethylamine (0.393 g, 3.24 mmol) in dichloromethane (35 ml) containing activated 4 Å molecular sieves were heated to reflux for 16 h. The suspension was filtered and the solvent and excess S-(1)-phenylethylamine were removed under reduced pressure yielding the *title*

compound (0.651 g, 90%) as a pale brown solid, m.p. 138-139°C (Found: M^+ , 334.1680. $C_{21}H_{22}N_2O_2$ requires M , 334.1681); ν_{\max} (Nujol) 1737, 1465 cm^{-1} ; δ_H (250 MHz; CDCl_3) 9.34 (1H, br s, NH), 7.62 (1H, d, J 7.9 Hz, Ar-(4)H), 7.45-7.41 (2H, m, Ar-H), 7.37-7.31 (3H, m, Ar-H), 7.26-7.20 (2H, m, Ar-H), 7.13-7.08 (1H, m, Ar-H), 4.87 (1H, q, J 6.5 Hz, ArCH), 4.05 (2H, s, ArCH_2), 3.66 (3H, s, OCH_3), 2.40 (3H, s, CH_3) 1.55 (3H, d, J 6.5 Hz, CH_3); m/z (EI) 334 (M^+ , 22%), 319 (21), 261 (24), 229 (33), 199 (18), 171 (18), 170 (22), 169 (20), 130 (27), 106 (20), 105 (100), 104 (21), 103 (22), 79 (21), 77 (32), 51 (18), 28 (90).

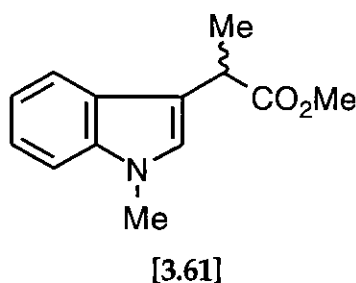
Methyl 2-(1-methyl-1H-3-indolyl)acetate



Method A

Indole-3-acetic acid (8.76 g, 50.0 mmol) in dimethyl sulfoxide (20 ml) was added to a stirred suspension of potassium hydroxide (11.20 g, 200.0 mmol) in dimethyl sulfoxide (80 ml). After 1 h a solution of methyl iodide (28.4 g, 200.0 mmol, 12.5 ml) in dimethyl sulfoxide (10 ml) was added dropwise with cooling from an ice/water bath. After stirred for 12 h, water (100 ml) was added and the mixture extracted with diethyl ether (3 x 100 ml), the combined organic layers were washed with brine (4 x 75 ml) and dried (MgSO_4). The solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (4:1) yielded the *title compound* (2.336 g, 23%) as a yellow oil, (Found: M^+ , 203.0936. $C_{12}H_{13}NO_2$ requires M , 203.0946); ν_{\max} (Neat) 2950, 1735, 740 cm^{-1} ; δ_H (250 MHz; CDCl_3) 7.60 (1H, d, J 7.9 Hz, Ar-(4)H), 7.28-7.22 (2H, m, Ar-H), 7.15-7.11 (1H, m, Ar-H), 7.03 (1H, s, Ar-(2)H), 3.77 (2H, s, ArCH_2), 3.75 (3H, s, OCH_3), 3.69 (3H, s, NCH_3); δ_C (62.9 MHz; CDCl_3) 172.8, 136.8, 127.7 (ArCH), 126.4, 121.8 (ArCH), 119.2 (ArCH), 118.9 (ArCH), 108.3 (ArCH), 106.7, 51.9 (OCH_3), 32.6 (NCH_3), 31.0 (CH_2); m/z (EI) 203 (M^+ , 23%), 155 (17), 151 (10), 145 (13), 144 (100), 124 (10), 113 (15), 51 (30), 31 (18).

Methyl 2-(1-methyl-1H-3-indolyl)propanoate



Isolated the *title compound* (4.423 g, 41%) from the above reaction as a yellow oil (Found: M^+ , 217.1104. $C_{13}H_{15}NO_2$ requires M , 217.1103); ν_{\max} (Neat) 2950, 1735, 740 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.67 (1H, m, Ar-(4)H), 7.30-7.08 (3H, m, Ar-H), 6.98 (1H, s, Ar-(2)H), 4.02 (1H, q, J 6.9 Hz, ArCH), 3.73 (3H, s, OCH_3), 3.65 (3H, s, NCH_3), 1.60 (3H, d, J 6.9 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 175.7, 137.0, 127.7, 126.9 (ArCH), 121.7 (ArCH), 119.3 (ArCH), 119.0 (ArCH), 114.0, 109.3 (ArCH), 51.9 (OCH_3), 36.8 (CH), 32.6 (NCH_3), 18.8 (CH_3); m/z (EI) 217 (M^+ , 91%), 202 (8), 172 (10), 159 (33), 158 (100), 157 (16), 156 (10), 144 (10), 143 (10), 115 (14), 15 (17).

Methyl 2-(1H-3-indolyl)acetate [3.8]

Isolated the *title compound* (2.933 g, 31%) from the above reaction as pale brown crystals, m.p. 50-51°C [Lit.,²¹⁶ 49-50.5°C (Ethyl acetate)]. Identical by 1H NMR and IR to the same compound prepared by esterification above.

Methyl 2-(1-methyl-1H-3-indolyl)acetate [3.60]

Method B

Indole-3-acetic acid (5.00 g, 28.5 mmol) was added to a stirred suspension of potassium hydroxide (9.60 g, 171.1 mmol) in dimethyl sulfoxide (40 ml). After 14 h the reaction mixture was added, with filtration through a sinter to a solution of methyl iodide (12.2 g, 86.0 mmol, 5.33 ml) in dimethyl sulfoxide (30 ml). The reaction was stirred for 3 h. Water (100 ml) was added and the mixture extracted with dichloromethane (3 x 100 ml), the combined organic layers were washed with brine (4 x 100 ml) and dried ($MgSO_4$). The solvent

was removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (4:1) yielded the *title compound* (3.65 g, 63%) as a yellow oil. Identical by ^1H NMR and IR to the same compound prepared by Method A.

Methyl 2-(1-methyl-1*H*-3-indolyl)propanoate [3.61]

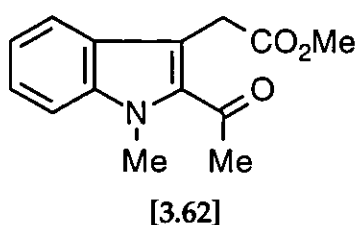
Isolated the *title compound* (1.06 g, 17%) from the above reaction as a yellow oil. Identical by ^1H NMR and IR to the same compound prepared by Method A.

Methyl 2-(1-methyl-1*H*-3-indolyl)acetate [3.60]

Method C

A solution of sodium hypophosphite (4.20 g, 47.8 mmol) in water (4 ml) was added to a stirred solution of methyl 2-(1-methyl-1*H*-3-indolyl)-2-oxoacetate [3.38] (1.63 g, 7.5 mmol) and palladium on carbon (10%) (0.33 g) in 1,4-dioxane (25 ml). The mixture was refluxed, with vigorous stirring, for 4 h. The solution was allowed to cool and a solution of sodium hypophosphite (3.75 g, 42.6 mmol) in water (4 ml) was added and this was again heated to reflux for 4 h. The solution was allowed to cool, filtered through a pad of celite and washed with diethyl ether. The solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : diethyl ether) (3:1) yielded the *title compound* (1.13 g, 74%) as a yellow oil. Identical by ^1H NMR and IR to the same compound prepared by method A.

Methyl 2-(2-acetyl-1-methyl-1*H*-3-indolyl)acetate



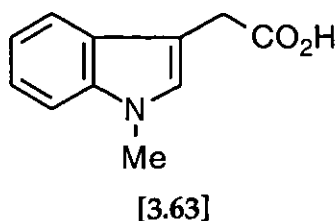
Method A

Acetyl chloride (0.250 g, 3.18 mmol, 0.23 ml) was added to methyl 2-(1-methyl-1H-3-indolyl)acetate [3.60] (0.500 g, 2.46 mmol) in 1,2-dichloroethane (20 ml) at 0°C. Aluminium chloride (0.360 g, 2.71 mmol) was added in small portions over 1 h. The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h. Hydrochloric acid (2 M, 50 ml) was added carefully and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with water (2 x 30 ml), dried (MgSO₄) and the solvent was removed under reduced pressure. Column chromatography (light petroleum : ethyl acetate) (4:1) yielded the *title compound* (0.061 g, 10%) as a white solid, m.p. 112-115°C (Lit.,²¹⁶ 113.5-115°C) (Found: M⁺, 245.1053. C₁₄H₁₅NO₃ requires M, 245.1052); ν_{\max} (KBr Disc) 2940, 1726, 1656, 754 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.68 (1H, dd, J 9.0, 0.8 Hz, Ar-(4)H), 7.39-7.36 (2H, m, Ar-H), 7.21-7.15 (1H, m, Ar-H), 4.11 (2H, s, ArCH₂), 3.97 (3H, s, OCH₃), 3.70 (3H, s, NCH₃), 2.68 (3H, s, CH₃); δ_{C} (62.9 MHz; CDCl₃) 192.3, 171.2, 138.5, 134.4, 126.6, 125.8 (ArCH), 120.6 (ArCH), 120.5 (ArCH), 114.3, 110.3 (ArCH), 52.1 (OCH₃), 32.6 (NCH₃), 31.4 (CH₂), 30.9 (CH₃); *m/z* (EI) 245 (M⁺, 42%), 213 (14), 202 (20), 187 (12), 186 (100), 185 (11), 158 (10), 144 (30), 143 (12), 128 (10), 43 (14), 15 (20).

Method B

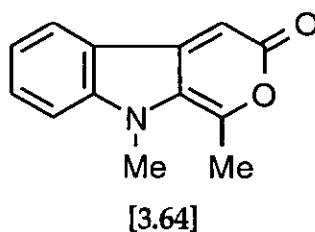
1,9-Dimethyl-3,9-dihydropyrano[3,4-b]indol-3-one [3.64] (0.874 g, 4.10 mmol) in methanol (40 ml) was stirred for 16 h. The solvent was removed under reduced pressure and the crude product was purified by flash sinter chromatography (dichloromethane) yielding the *title compound* (0.914 g, 91%) as a white solid, m.p. 111-113°C (Lit.,²¹⁶ 113.5-115°C). Identical by ¹H, ¹³C NMR and IR with the same compound prepared by Friedal-Crafts acylation.

2-(1-Methyl-1H-3-indolyl)acetic acid



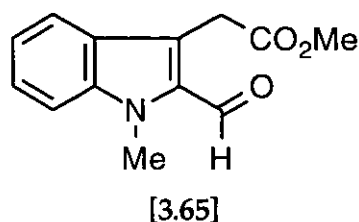
A solution of lithium hydroxide (0.516 g, 12.3 mmol) in water (5 ml) was added to a solution of methyl 2-(1-methyl-1*H*-3-indolyl)acetate [3.60] (0.5 g, 2.46 mmol) in tetrahydrofuran (25 ml). The reaction was stirred for 18 h. The mixture was acidified with hydrochloric acid (10 M) and extracted with dichloromethane (3 x 30 ml), the combined organic layers were washed with water (30 ml), brine (50 ml) and dried (MgSO₄). The solvent was removed under reduced pressure to yield the *title compound* (0.407 g, 87%) as a white solid, m.p. 126-128°C [Lit.,²²⁴ 128°C (aq. EtOH)] (Found: M⁺, 189.0789. C₁₁H₁₁NO₂ requires M, 189.0790); ν_{\max} (KBr Disc) 3125-2800, 2927, 1697, 740 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 10.52 (1H, br s, CO₂H), 7.57 (1H, d, J 7.8 Hz, Ar-(4)H), 7.28-7.22 (2H, m, Ar-H), 7.15-7.11 (1H, m, Ar-H), 7.03 (1H, s, Ar-(2)H), 3.79 (2H, s, ArCH₂), 3.75 (3H, s, NCH₃); δ_{C} (62.9 MHz; CDCl₃) 178.8, 137.3, 128.4 (ArCH), 128.0, 122.3 (ArCH), 119.7 (ArCH), 119.4 (ArCH), 109.8 (ArCH), 106.5, 33.1 (NCH₃), 31.5 (CH₂); m/z (EI) 189 (M⁺, 34%), 144 (100), 129 (6), 115 (6), 102 (7), 77 (7), 28 (6).

1,9-Dimethyl-3,9-dihydropyrano[3,4-*b*]indol-3-one



To a solution of 2-(1-methyl-1*H*-3-indolyl)acetic acid [3.63] (0.150 g, 0.793 mmol) in acetic anhydride (4 ml) at 0°C was added boron trifluoride etherate (0.2 ml) over 10 min. The reaction was stirred at 0°C for 30 min and then allowed to warm to room temperature over 2 h. Diethyl ether (20 ml) was added and the solid was filtered, triturated with aqueous saturated sodium bicarbonate solution and washed with water and diethyl ether. The solid was dried under reduced pressure yielding the *title compound* (0.141 g, 83%) as a yellow solid, m.p. 210-212°C (dec.) [Lit.,²²⁵ 214°C (dec.)] (Found: M⁺, 213.0790. C₁₃H₁₁NO₂ requires M, 213.790); ν_{\max} (Nujol) 1694, 1652, 1547 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.81 (1H, d, J 7.5 Hz, Ar-(4)H), 7.58-7.52 (1H, m, Ar-H), 7.09-7.03 (2H, m, Ar-H), 6.50 (1H, s, Ar-H), 3.68 (3H, s, NCH₃), 2.73 (3H, s, CH₃); m/z (EI) 213 (M⁺, 100%), 185 (53), 184 (18), 157 (43), 156 (52), 142 (23), 128 (16), 115 (22), 101 (15), 75 (16), 51 (15), 43 (34), 18 (22), 15 (17).

Methyl 2-(2-formyl-1-methyl-1H-3-indolyl)acetate



Method A

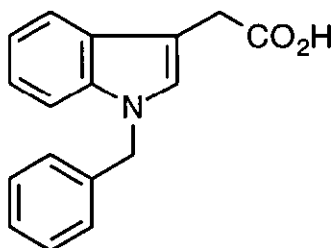
Phosphorus oxychloride (0.609 g, 3.98 mmol, 0.37 ml) was added dropwise to *N,N*-dimethylformamide (2 ml), at 0°C. The reaction mixture was stirred at room temperature for 30 min and then cooled to 0°C. Methyl 2-(1-methyl-1H-3-indolyl)acetate [3.60] (0.699 g, 3.44 mmol) dissolved in *N,N*-dimethylformamide (2 ml) was added and the mixture was then heated to 50°C for 24 h. Aqueous saturated sodium acetate (20 ml) was added and the reaction mixture was stirred for 3 h. The mixture was extracted with dichloromethane (4 x 25 ml). The combined organic layers were washed with water (2 x 50 ml), brine (2 x 50 ml) and dried (MgSO₄). The solvent was removed under reduced pressure and the crude material purified by column chromatography (light petroleum : ethyl acetate) (4:1) to yield the *title compound* (0.531 g, 67%) as a yellow solid, m.p. 90-91°C (light petroleum/ethyl acetate) (Found: C, 67.37; H, 5.26; N, 6.08. C₁₃H₁₃NO₃ requires C, 67.52; H, 5.67; N, 6.06%) (Found: M⁺, 231.0900. C₁₃H₁₃NO₃ requires M, 231.08954); ν_{\max} (Nujol) 1738, 1715, 1660, 756 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 10.19 (1H, s, ArCHO), 7.73 (1H, d, J 8.0 Hz, Ar-(4)H), 7.47-7.35 (2H, m, Ar-H), 7.26-7.16 (1H, m, Ar-H), 4.10 (2H, s, ArCH₂), 4.08 (3H, s, OCH₃), 3.69 (3H, s, NCH₃); δ_{C} (62.9 MHz; CDCl₃) 181.9 (CHO), 171.1, 139.5, 131.7, 127.4 (ArCH), 126.3, 121.2 (ArCH), 121.0, 120.9 (ArCH), 110.5 (ArCH), 52.5 (OCH₃), 31.6 (NCH₃), 29.8 (CH₂); *m/z* (EI) 231 (M⁺, 97%), 202 (11), 200 (7), 199 (38), 173 (13), 172 (100), 144 (46), 143 (20), 103 (12).

Method B

Diphosphoryl chloride (1.00 g, 3.98 mmol, 0.55 ml) was added dropwise to *N,N*-dimethylformamide (2 ml), at 0°C. The reaction mixture was stirred at room temperature for 30 min and then cooled to 0°C. Methyl 2-(1-methyl-1H-3-indolyl)acetate [3.60] (0.699 g, 3.44 mmol) dissolved in *N,N*-dimethylformamide (2 ml) was added and the mixture was then heated to 50°C for 24 h. Work-up and purification as in method A yielded the *title compound*

(0.520 g, 65%) as a yellow solid, m.p. 90-92°C. Identical by ^1H NMR and IR to the same compound prepared by Method A.

2-(1-Benzyl-1H-3-indolyl)acetic acid



[3.66]

Method A

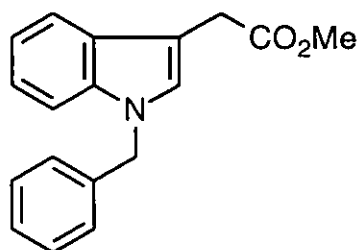
Sodium hydroxide solution (50%, 30 ml), benzyl trimethylammonium chloride (0.10 g, 0.57 mmol) and benzyl chloride (0.723 g, 5.70 mmol) were added to a solution of indole-3-acetic acid (1.00 g, 5.70 mmol) in dichloromethane (30 ml) and the reaction mixture was refluxed for 8 h. The mixture was neutralised with hydrochloric acid whilst cooling with an ice/water bath, and extracted with dichloromethane (3 x 30 ml). The combined dichloromethane layers were washed with brine (30 ml), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography (dichloromethane) yielded the *title compound* (0.456 g, 30%) as colourless crystals, m.p. 153-154°C, (Lit.,¹⁷⁵ 152-153°C) (Found: M^+ , 265.1103. $\text{C}_{17}\text{H}_{15}\text{NO}_2$ requires M , 265.1103); ν_{max} (CH_2Cl_2) 3350, 1701, 734 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.61 (1H, dd, J 1.5, 7.0 Hz, Ar-(4)H), 7.30-7.09 (9H, m, Ar-H), 5.27 (2H, s, NCH_2), 3.79 (2H, m, ArCH_2); δ_{C} (100.0 MHz; CDCl_3) 177.7, 137.4, 136.6, 129.0 (ArCH), 128.2, 127.8 (ArCH), 127.6 (ArCH), 127.1 (ArCH), 122.1 (ArCH), 119.6 (ArCH), 119.0 (ArCH), 109.8 (ArCH), 106.9, 50.0 (NCH_2), 31.1 (ArCH_2); m/z (EI) 265 (M^+ , 24%), 221 (8), 220 (33), 174 (2), 129 (7), 91 (100), 65 (12), 28 (11).

Method B

Sodium hydride (60%, 0.55 g, 13.8 mmol) was added to a stirred solution of indole-3-acetic acid (1.00 g, 5.71 mmol) in N,N -dimethylformamide (10 ml) at 0°C. The reaction mixture was stirring for 30 min at 0°C. Benzyl bromide (1.17 g, 6.84 mmol, 0.81 ml) was added and the reaction stirred for 2 h at 0°C. The reaction mixture was poured into water (100 ml), acidified with hydrochloric

acid (10% solution) and left to stand at 5°C for 18 h. The solid was filtered washed with water and dried in a vacuum desiccator. Recrystallisation from light petroleum/ethyl acetate gave the *title compound* (1.41 g, 90%) as a white solid, m.p. 152-153°C (Lit.,¹⁷⁵ 152-153°C). Identical by ¹H NMR and IR to the same compound prepared by Method A.

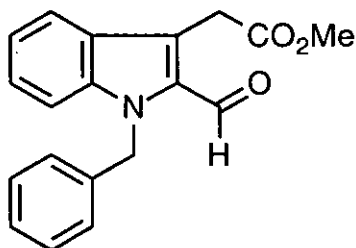
Methyl 2-(1-benzyl-1*H*-3-indolyl)acetate



[3.67]

To a solution of 2-(1-benzyl-1*H*-3-indolyl)acetic acid [3.66] (0.439 g, 1.65 mmol) in methanol (25 ml) was added sulfuric acid (10 M, 5 drops). After refluxing for 3 h the solvent was removed under reduced pressure. Purification by flash chromatography (dichloromethane) yielded the *title compound* (0.449 g, 97%) as a brown oil, (Found: M^+ , 279.1260. $C_{18}H_{17}NO_2$ requires M , 279.1260); ν_{\max} (Neat) 3030, 2950, 1738, 741 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.67-7.63 (1H, m, Ar-(4)H), 7.31-7.26 (4H, m, Ar-H), 7.24-7.14 (5H, m, Ar-H), 5.29 (2H, s, NCH_2), 3.81 (2H, s, $ArCH_2$), 3.72 (3H, s, OCH_3); δ_C (62.9 MHz; $CDCl_3$) 172.5, 137.6, 136.4, 128.7 (ArCH), 127.6 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 122.0 (ArCH), 119.6, 119.4 (ArCH), 119.1 (ArCH), 109.8 (ArCH), 107.8, 51.9 (OCH_3), 49.9 (NCH_2), 31.1 (CH_2); m/z (EI) 279 (M^+ , 27%), 221 (9), 220 (51), 129 (8), 92 (9), 91 (100), 65 (12).

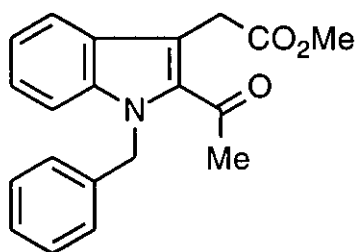
Methyl 2-(1-benzyl-2-formyl-1*H*-3-indolyl)acetate



[3.68]

Phosphorus oxychloride (0.609 g, 3.98 mmol, 0.37 ml) was added dropwise to *N,N*-dimethylformamide (2 ml), at 0°C. The reaction mixture was stirred at room temperature for 30 min and then cooled to 0°C. Methyl 2-(1-benzyl-1*H*-3-indolyl)acetate [3.67] (0.960 g, 3.44 mmol) dissolved in *N,N*-dimethylformamide (2 ml) was added and the mixture was heated to 50°C for 24 h. Aqueous saturated sodium acetate (20 ml) was added and the reaction mixture was stirred for 3 h. The mixture was extracted with dichloromethane (4 x 25 ml). The combined organic layers were washed with water (2 x 50 ml), brine (2 x 50 ml) and dried (MgSO₄). The solvent was removed under reduced pressure and the crude material purified by column chromatography (light petroleum : ethyl acetate) (4:1) to yield the *title compound* (0.202 g, 19%) as a red oil, (Found: *M*⁺, 307.1208. C₁₉H₁₇NO₃ requires *M*, 307.1208); ν_{\max} (Neat) 2952, 1738, 1732, 1667, 750 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 10.17 (1H, s, ArCHO), 7.76 (1H, d, *J* 8.0 Hz, Ar-(4)H), 7.39-7.36 (2H, m, Ar-H), 7.25-7.17 (4H, m, Ar-H), 7.09-7.05 (2H, m, Ar-H), 5.81 (2H, s, NCH₂), 4.14 (2H, s, ArCH₂), 3.70 (3H, s, OCH₃); δ_{C} (62.9 MHz; CDCl₃) 181.5 (CHO), 170.8, 139.3, 137.7, 131.2, 128.6 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 126.5 (ArCH), 125.8, 121.7, 121.3 (ArCH), 121.2 (ArCH), 110.9 (ArCH), 52.4 (OCH₃), 47.8 (NCH₂), 29.7 (CH₂); *m/z* (EI) 307 (*M*⁺, 23%), 278 (9), 248 (9), 218 (8), 155 (8), 91 (100), 65 (9), 31 (9).

Methyl 2-(1-benzyl-2-acetyl-1*H*-3-indolyl)acetate

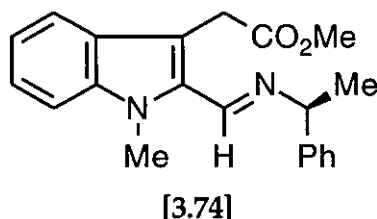


[3.73]

To a solution of 2-(1-benzyl-1*H*-3-indolyl)acetic acid [3.66] (0.380 g, 1.432 mmol) in acetic anhydride (4 ml) at 0°C was added boron trifluoride etherate (0.5 ml) over 20 min. The reaction was stirred at 0°C for 30 min and then allowed to warm to room temperature and stirred for 16 h. Aqueous saturated sodium bicarbonate solution (50 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 30 ml). The organic extracts were washed with water (50 ml), dried (MgSO₄) and the solvent removed under reduced pressure. Methanol (40 ml) was added and the reaction mixture was stirred for

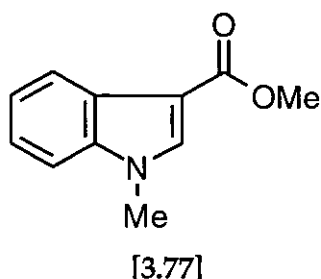
16 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (light petroleum : diethyl ether) (4:1) yielding the *title compound* (0.013 g, 3%) as a pale brown oil; ν_{\max} (Neat) 2954, 1727, 746 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.72 (1H, d, J 8.2 Hz, Ar-(4)H), 7.34-7.14 (7H, m, Ar-H), 7.02-6.98 (1H, m, Ar-H), 5.71 (2H, s, NCH_2), 4.14 (2H, s, ArCH_2), 3.71 (3H, s, OCH_3), 2.61 (3H, s, CH_3).

Methyl 2-(1-methyl-2-((((1S)-1-phenylethyl)imino)methyl)-1H-3-indolyl)acetate



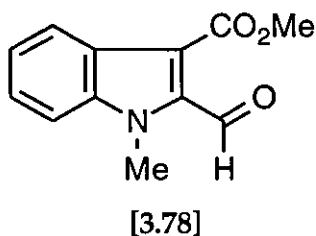
Amberlyst 15 (0.025 g), methyl 2-(2-formyl-1-methyl-1H-3-indolyl)acetate [3.65] (0.416 g, 1.80 mmol) and S-(1)-phenylethylamine (0.327 g, 2.70 mmol, 0.35 ml) in dichloromethane (25 ml) containing activated 4 Å molecular sieves were heated to reflux for 16 h. The suspension was filtered and the solvent and excess S-(1)-phenylethylamine were removed under reduced pressure yielding the *title compound* (0.531 g, 88%) as a brown oil (Found: M^+ , 334.1681. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ requires M, 334.1681); ν_{\max} (Neat) 2969, 1738, 1634, 1611, 743 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.67 (1H, s, $\text{CH}=\text{N}$), 7.65 (1H, d, J 7.9 Hz, Ar-(4)H), 7.47 (2H, m, Ar-H), 7.40-7.23 (5H, m, Ar-H), 7.18-7.12 (1H, m, Ar-H), 4.50 (1H, q, J 6.5 Hz, ArCH), 4.12 (3H, s, OCH_3), 4.01 (2H, s, ArCH_2), 3.66 (3H, s, NCH_3), 1.61 (3H, d, J 6.5 Hz, CH_3); δ_{C} (62.9 MHz; CDCl_3) 172.0, 150.5 (CH), 145.7, 138.7, 131.7, 128.6 (ArCH), 127.1, 127.0 (ArCH), 126.7 (ArCH), 124.3 (ArCH), 120.1 (ArCH), 119.8 (ArCH), 112.9, 109.9 (ArCH), 71.6 (CH), 52.1 (OCH_3), 31.9 (NCH_3), 30.4 (CH_2), 26.0 (CH_3); m/z (EI) 334 (M^+ , 100%), 275 (9), 261 (33), 230 (13), 229 (83), 205 (25), 199 (16), 198 (18), 197 (19), 171 (24), 170 (54), 169 (49), 144 (15), 143 (10), 115 (10), 105 (77), 104 (11), 103 (15), 79 (15), 77 (23), 51 (10).

Methyl 1-methyl-1H-3-indolecarboxylate



Indole-3-carboxylic acid (3.00 g, 18.6 mmol) was added to a stirred suspension of potassium hydroxide (4.18 g, 74.4 mmol) in dimethyl sulfoxide (40 ml). After 1 h a solution of methyl iodide (7.93 g, 55.8 mmol, 3.48 ml) in dimethyl sulfoxide (5 ml) was added whilst cooling with an ice/water bath. The reaction was stirred for 2 h. Water (75 ml) was added and the mixture extracted with dichloromethane (3 x 75 ml), the combined organic layers were washed with brine (4 x 75 ml) and dried (MgSO_4). The solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (2:1) yielded the *title compound* (3.05 g, 87%) as pale orange solid, m.p. 96-97°C (Found: M^+ , 189.0792. $\text{C}_{11}\text{H}_{11}\text{NO}_2$ requires M , 189.0790); ν_{max} (KBr Disc) 2924, 1690, 740 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.19-8.16 (1H, m, Ar-(4)H), 7.78 (1H, s, Ar(2)H), 7.38-7.26 (3H, m, Ar-H), 3.91 (3H, s, OCH_3), 3.83 (3H, s, NCH_3); δ_{C} (62.9 MHz; CDCl_3) 165.4, 137.2, 135.1 (ArCH), 126.6, 122.7 (ArCH), 121.8 (ArCH), 121.6 (ArCH), 109.7 (ArCH), 106.8, 50.9 (OCH_3), 33.3 (NCH_3); m/z (EI) 189 (M^+ , 48%), 159 (11), 158 (100), 130 (10), 103 (10), 77 (14), 51 (15), 32 (17), 31 (16), 28 (34).

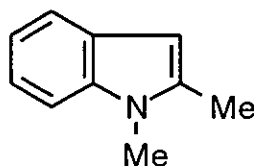
Methyl 2-formyl-1-methyl-1H-3-indolecarboxylate



2-Nitropropane (1.375 g, 15.43 mmol, 1.39 ml) was added to a solution of sodium metal (0.273 g, 11.87 mmol) in ethanol (25 ml) and stirred for 30 min. Methyl 2-(bromomethyl)-1-methyl-1H-3-indolecarboxylate [3.82] (3.349 g, 11.87

mmol) was added and the mixture was heated to reflux for 2h. The mixture was cooled to room temperature and the precipitated product was collected by filtration and washed with water (50 ml). Recrystallisation from propan-2-ol yielded the *title compound* (2.074 g, 80%) as a yellow solid, m.p. 130-132°C (Lit.,¹⁷⁷ 126-128°C) (Found: M^+ , 217.0741. $C_{12}H_{11}NO_3$ requires M , 217.0739); ν_{\max} (KBr Disc) 2949, 2882, 1698, 1676, 752 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 10.83 (1H, s, ArCHO), 8.26 (1H, dd, J 8.3, 0.9 Hz, Ar-(4)H), 7.51-7.42 (2H, m, Ar-H), 7.37-7.30 (1H, m, ArH), 4.13 (3H, s, OCH_3), 4.02 (3H, s, NCH_3); δ_C (62.9 MHz; $CDCl_3$) 186.1 (CHO), 164.4, 138.4, 136.0, 126.6 (ArCH), 125.1, 123.5 (ArCH), 123.0 (ArCH), 114.3, 110.4 (ArCH), 51.5 (OCH_3), 32.1 (NCH_3); m/z (EI) 217 (M^+ , 52%), 189 (18), 186 (16), 159 (13), 158 (100), 157 (17), 130 (18), 129 (11), 114 (10), 103 (15), 89 (15), 77 (16), 15 (14).

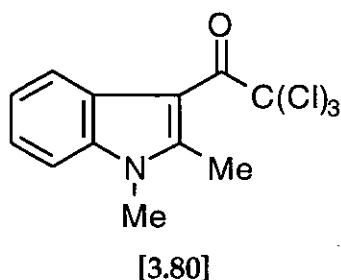
1,2-Dimethyl-1H-indole



[3.79]

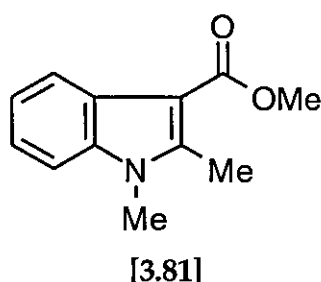
2-Methylindole (5.00 g, 38.1 mmol) was added to a stirred suspension of potassium hydroxide (8.55 g, 152.4 mmol) in dimethyl sulfoxide (75 ml). After 2.5 h a solution of methyl iodide (16.23 g, 114.3 mmol, 7.12 ml) in dimethyl sulfoxide (10 ml) was added whilst cooling with an ice/water bath. The reaction was stirred for 2 h at room temperature. Water (100 ml) was added and the mixture extracted with dichloromethane (3 x 100 ml), the combined organic layers were washed with brine (4 x 100 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (3:1) yielded the *title compound* (4.79 g, 87%) as pale yellow crystals, m.p. 54-55°C (Lit.,¹⁵¹ 54-55°C); ν_{\max} (KBr Disc) 2925, 1654, 747 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 7.59 (1H, d, J 7.7 Hz, Ar-(4)H), 7.31-7.08 (3H, m, Ar-H), 6.30 (1H, s, Ar-(3)H), 3.69 (3H, s, NCH_3), 2.47 (3H, s, $ArCH_3$); δ_C (62.9 MHz; $CDCl_3$) 136.7, 120.4 (ArCH), 119.6 (ArCH), 119.2 (ArCH), 118.5, 117.9, 108.7 (ArCH), 99.5 (ArCH), 29.3 (NCH_3), 12.7 ($ArCH_3$); m/z (EI) 145 (M^+ , 87%), 144 (100), 143 (15), 130 (7), 128 (11), 115 (19), 103 (12), 77 (20), 73 (21), 72 (15).

2,2,2-Trichloro-1-(1,2-dimethyl-1H-3-indolyl)-1-ethanone



1,2-Dimethyl-1H-indole [3.79] (4.64 g, 31.97 mmol) and trichloroacetyl chloride (6.39 g, 35.17 mmol, 3.93 ml) were added with stirring to pyridine (2.78 g, 35.17 mmol, 2.81 ml) in 1,4-dioxane (10 ml) whilst cooling with an ice/water bath. The mixture was stirred for a further 2 h at room temperature. The mixture was then poured into water (50 ml) and the precipitated product was collected, dried and recrystallised from ethanol to yield the *title compound* (7.06 g, 76%) as pale orange crystals, m.p. 158-161°C (Lit.,¹⁷⁷ 156-158°C); ν_{\max} (KBr Disc) 2936, 1647, 751 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.30-8.23 (1H, m, Ar-(4)H), 7.37-7.25 (3H, m, Ar-H), 3.76 (3H, s, NCH_3), 2.78 (3H, s, ArCH_3); δ_{C} (62.9 MHz; CDCl_3) 164.2, 151.2, 136.8, 124.4, 123.8 (ArCH), 122.6 (ArCH), 122.1 (ArCH), 109.5 (ArCH), 30.1 (NCH_3), 14.0 (CH_3); m/z (EI) 290 (M^+ , 1%), 289 (5), 226 (11), 173 (14), 172 (100), 144 (6), 143 (13), 115 (16), 77 (7), 51 (4).

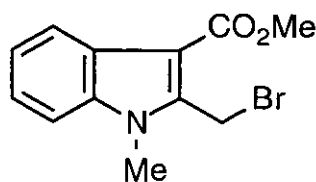
Methyl 1,2-dimethyl-1H-3-indolecarboxylate



2,2,2-Trichloro-1-(1,2-dimethyl-1H-3-indolyl)-1-ethanone [3.80] (6.09 g, 20.97 mmol) and aqueous potassium hydroxide (60%, 0.3 ml) in methanol (100 ml) were heated to reflux for 1 h. The mixture was cooled to room temperature and diluted with water (50 ml). The precipitated product was collected and recrystallised from aqueous methanol to yield the *title compound* (3.88 g, 91%) as colourless crystals, m.p. 146-148°C (Lit.,¹⁷⁷ 144-145°C); ν_{\max} (KBr Disc)

2944, 1686, 1532, 736 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.12-8.07 (1H, m, Ar-(4)H), 7.28-7.12 (3H, m, Ar-H), 3.91 (3H, s, OCH_3), 3.56 (3H, s, NCH_3), 2.68 (3H, s, ArCH_3); δ_{C} (62.9 MHz; CDCl_3) 186.0, 166.8, 145.4, 138.6, 126.4, 121.9 (ArCH), 121.5 (ArCH), 121.3 (ArCH), 109.0 (ArCH), 50.6 (OCH_3), 29.4 (NCH_3), 11.7 (CH_3); m/z (EI) 203 (M^+ , 96%), 188 (13), 173 (11), 172 (100), 171 (14), 144 (15), 143 (22), 115 (19), 102 (11), 77 (11).

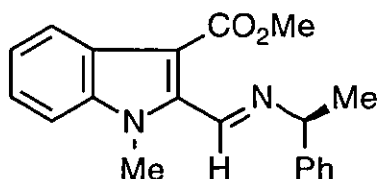
Methyl 2-(bromomethyl)-1-methyl-1H-3-indolecarboxylate



[3.82]

Benzoyl peroxide (20 mg) was added to a solution of *N*-bromosuccinimide (3.050 g, 17.1 mmol) and methyl 1,2-dimethyl-1H-3-indolecarboxylate [3.81] (3.478 g, 17.1 mmol) in carbon tetrachloride (100 ml) and the reaction mixture was refluxed for 4 h. The hot solution was filtered and the solvent removed under reduced pressure, the crude product was recrystallised from carbon tetrachloride yielding the *title compound* (3.488 g, 72%) as a pale brown solid, m.p. 122-124°C (Lit.,¹⁷⁷ 123-124°C) (Found: M^+ , 283.0034. $\text{C}_{12}\text{H}_{12}\text{NO}_2\text{Br}$ requires M , 283.0032); ν_{max} (KBr Disc) 2952, 1690, 754 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.14 (1H, dd, J 6.6, 1.5 Hz, Ar-(4)H), 7.37-7.24 (3H, m, Ar-H), 5.17 (2H, s, CH_2Br), 3.97 (3H, s, OCH_3), 3.80 (3H, s, NCH_3); δ_{C} (62.9 MHz; CDCl_3) 165.8, 141.4, 137.4, 126.1, 124.0 (ArCH), 122.6 (ArCH), 122.5 (ArCH), 109.9 (ArCH), 105.4, 51.5 (OCH_3), 29.9 (NCH_3), 21.5 (CH_2Br); m/z (EI) 283 (M^+ , 25%), 202 (100), 172 (39), 171 (10), 144 (10), 143 (18), 142 (10), 115 (13), 15 (14).

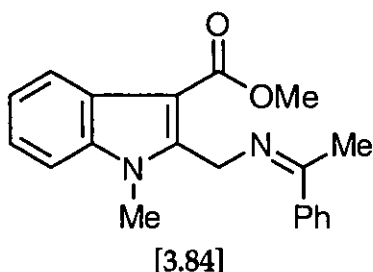
Methyl 1-methyl-2-(((1S)-1-phenylethyl)imino)methyl)-1H-3-indolecarboxylate



[3.83]

Amberlyst 15 (0.025 g), methyl 2-formyl-1-methyl-1*H*-3-indolecarboxylate [3.78] (1.130 g, 5.2 mmol) and *S*-(1)-phenylethylamine (0.788 g, 6.5 mmol, 0.83 ml) in dichloromethane (35 ml) containing activated 4Å molecular sieves were heated to reflux for 16 h. The suspension was filtered and the solvent and excess *S*-(1)-phenylethylamine were removed under reduced pressure yielding the *title compound* (1.621 g, 97%) as an orange oil (Found: M^+ , 320.1524. $C_{20}H_{20}N_2O_2$ requires M , 320.1525); ν_{\max} (Neat) 2970, 1700, 1685, 1654, 1636, 751 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 9.40 (1H, s, CH=N), 8.18 (1H, dd, J 8.9, 0.8 Hz, Ar-(4)H), 7.49-7.46 (2H, m, Ar-H), 7.41-7.24 (6H, m, ArH), 4.63 (1H, q, J 6.6 Hz, CH), 4.20 (3H, s, OCH_3), 3.97 (3H, s, NCH_3), 1.64 (3H, d, J 6.6 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 165.7, 153.4 (CH=N), 145.0, 138.6, 138.4, 128.5 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 125.6, 124.4 (ArCH), 122.5 (ArCH), 122.2 (ArCH), 110.0 (ArCH), 109.0, 71.3 (CH), 51.1 (OCH_3), 32.9 (NCH_3), 25.4 (CH_3); m/z (EI) 320 (M^+ , 37%), 289 (11), 288 (38), 216 (15), 215 (100), 214 (16), 183 (94), 171 (17), 156 (25), 106 (16), 105 (64), 103 (21), 79 (18), 77 (26), 15 (15).

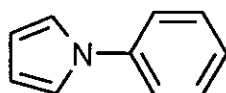
Methyl 1-methyl-2-(((1-phenylethylidene)amino)methyl)-1*H*-indole-3-carboxylate



Sodium methoxide powder (0.050 g, 0.92 mmol) was added to a solution of methyl 1-methyl-2-(((1*S*)-1-phenylethyl]imino)methyl)-1*H*-3-indolecarboxylate [3.83] (1.00 g, 3.12 mmol) in methanol (50 ml) and refluxed for 6 h. Water (100 ml) was added and the mixture extracted with dichloromethane (3 x 100 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was recrystallised from light petroleum/ethyl acetate yielding the *title compound* (0.953 g) as a white solid; ν_{\max} (Nujol) 2920, 1694, 1621, 751 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 8.15-8.13 (1H, m, Ar-H), 7.81-7.78 (2H, m, Ar-H), 7.37-7.35 (4H, m, ArH), 7.29-7.24 (2H, m, ArH), 5.39 (2H, s, CH_2), 3.93 (6H, s, 2 x CH_3), 2.47 (3H, s, CH_3).

5.4 Experimental for Chapter 4

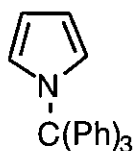
1-Phenylpyrrole



[4.3]

Trimethylsilyl trifluoromethanesulfonate (0.067 g, 0.3 mmol, 0.06 ml, 10 mol%) was added with cooling from an ice/water bath to a stirred solution of aniline (0.279 g, 3.0 mmol), 2,5-dimethoxytetrahydrofuran (0.397 g, 3.0 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1.220 g, 6.0 mmol) in 1,2-dichloroethane (10 ml). The reaction mixture was then refluxed with stirring for 16 h. Water (15 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were washed with water (25 ml), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (15:1) yielded the *title compound* (0.086 g, 20%) as a solid, m.p. 61-62 °C (Lit.,²²⁶ 62 °C); ν_{max} (Nujol) 1603, 1552, 1405 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.45-7.37 (4H, m, ArH), 7.27-7.20 (1H, m, ArH), 7.09 (2H, t, J 2.2 Hz, C(2), C(5)H), 6.35 (2H, t, J 2.2 Hz, C(3), C(4)H).

1-Tritylpyrrole



[4.18]

Method A²⁰¹

Tritylamine (1.50 g, 5.8 mmol) and 2,5-dimethoxytetrahydrofuran (0.90 g, 6.9 mmol) in glacial acetic acid (4.2 ml) and benzene (9 ml) were refluxed with stirring for 16 h. The solvent was removed under reduced pressure and the black solid was recrystallised from benzene (with charcoal) yielding the *title compound* (1.08 g, 60%) as a colourless needles, m.p. 245-246°C (Lit.,²⁰¹ 245-

246°C); δ_{H} (250 MHz; CDCl_3) 7.34-7.21 (9H, m, Ar-H), 7.21-7.17 (6H, m, Ar-H), 6.63 (2H, t, J 2.3 Hz, C(2), C(5)H), 6.15 (2H, t, J 2.3 Hz, C(3), C(4)H).

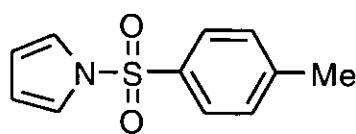
Method B : Typical Procedure Using TMSOTf

Trimethylsilyl trifluoromethanesulfonate (0.067 g, 0.3 mmol, 0.06 ml, 10 mol%) was added with cooling from an ice/water bath to a stirred solution of tritylamine (0.778 g, 3.0 mmol), 2,5-dimethoxytetrahydrofuran (0.397 g, 3.0 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1.220 g, 6.0 mmol) in 1,2-dichloroethane (10 ml). The reaction mixture was then refluxed with stirring for 6 h. Water (15 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were washed with water (25 ml), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (35:1) yielded the *title compound* (0.326 g, 35%) as a colourless solid, m.p. 244-246°C (Lit.,²⁰¹ 245-246°C) (Found: M^+ , 309.1516. $\text{C}_{23}\text{H}_{19}\text{N}$ requires M , 309.1517); ν_{max} (KBr Disc) 3060, 3032, 1595, 1488 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.32-7.27 (9H, m, Ar-H), 7.20-7.15 (6H, m, Ar-H), 6.60 (2H, t, J 2.2 Hz, C(2), C(5)H), 6.14 (2H, t, J 2.2 Hz, C(3), C(4)H); m/z (EI) 309 (M^+ , 6%), 244 (31), 243 (100), 241 (10), 166 (11), 165 (54), 91 (8), 51 (8), 39 (17).

Method C : Using $\text{Sc}(\text{OTf})_3$

Scandium triflate (0.061 g, 0.125 mmol, 5 mol%) was added to a solution of 2,5-dimethoxytetrahydrofuran (0.330 g, 2.5 mmol) and tritylamine (0.684 g, 2.5 mmol) in toluene (30 ml). The reaction mixture was refluxed through a dean-stark trap containing activated 4 Å molecular sieves for 16 h. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (35:1) yielded the *title compound* (0.191 g, 25%) as a colourless solid, m.p. 243-245°C (Lit.,²⁰¹ 245-246°C). Identical by ^1H NMR with the same compound prepared using Method A.

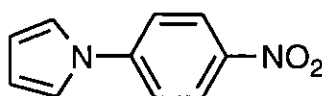
1-(4-Tolylsulfonyl)pyrrole



[4.20]

Trimethylsilyl trifluoromethanesulfonate (0.067 g, 0.3 mmol, 0.06 ml, 10 mol%) was added with cooling from an ice/water bath to a stirred solution of *p*-toluenesulfonamide (0.514 g, 3.0 mmol), 2,5-dimethoxytetrahydrofuran (0.397 g, 3.0 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1.220 g, 6.0 mmol) in 1,2-dichloroethane (10 ml). The reaction mixture was then refluxed with stirring for 16 h. Water (15 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were washed with water (25 ml), dried (MgSO₄) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (15:1) yielded the *title compound* (0.127 g, 19%) as a pale yellow solid, m.p. 98-101°C (Lit.,¹⁸³ 100-101°C) (Found: M⁺, 221.0511. C₁₁H₁₁NSO₂ requires M, 221.0511); δ_{H} (250 MHz; CDCl₃) 7.74 (2H, d, J 8.2 Hz, ArH), 7.28 (2H, d, J 8.2 Hz, ArH), 7.17 (2H, t, J 2.8 Hz, C(2), C(5)H), 6.31 (2H, t, J 2.8 Hz, C(3), C(4)H), 2.42 (3H, s, ArCH₃); *m/z* (EI) 221 (M⁺, 5%), 171 (31), 155 (30), 109 (16), 108 (20), 107 (28), 92 (27), 91 (100), 89 (16), 83 (15), 77 (15), 67 (25), 65 (50), 63 (16), 60 (17), 59 (21), 44 (32), 43 (54), 39 (32), 28 (15), 15 (24).

1-(4-Nitrophenyl)pyrrole



[4.22]

Trimethylsilyl trifluoromethanesulfonate (0.067 g, 0.3 mmol, 0.06 ml, 10 mol%) was added with cooling from an ice/water bath to a stirred solution of 4-nitroaniline (0.414 g, 3.0 mmol), 2,5-dimethoxytetrahydrofuran (0.397 g, 3.0 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1.220 g, 6.0 mmol) in 1,2-dichloroethane (10 ml). The reaction mixture was then refluxed with stirring for 16 h. Water (15 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic layers were washed with

water (25 ml), dried (MgSO_4) and the solvent removed under reduced pressure. Purification by column chromatography (light petroleum : ethyl acetate) (15:1) yielded the *title compound* (0.080 g, 14%) as a pale yellow solid, m.p. 182-184°C (light petroleum/ethyl acetate) (Lit.,²²⁷ 182-183°C) (Found: M^+ , 188.0589. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$ requires M , 188.0586); ν_{max} (KBr Disc) 1609, 1508, 1316 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.31 (2H, dd, J 7.0, 2.1 Hz, ArH), 7.52 (2H, dd, J 7.0, 2.1 Hz, ArH), 7.18 (2H, t, J 2.2 Hz, C(2), C(5)H), 6.43 (2H, t, J 2.2 Hz, C(3), C(4)H); δ_{C} (100 MHz; CDCl_3) 145.2, 144.7, 125.5 (ArCH), 119.4 (ArCH), 119.1 (ArCH), 112.5 (ArCH); δ_{C} (100 MHz; CDCl_3) 145.2, 125.6 (ArCH), 119.4 (ArCH), 119.1 (ArCH), 112.5 (ArCH); m/z (EI) 188 (M^+ , 100%), 142 (37), 141 (24), 116 (12), 115 (32), 89 (9), 76 (8), 63 (9), 39 (9).

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Appendix

Appendix 1

A. Crystal Data

Empirical Formula	C ₂₃ H ₂₁ N ₂ O ₃ Cl ₃
Formula Weight	479.79
Crystal Colour, Habit	clear, plate
Crystal Dimensions	0.20 X 0.20 X 0.20 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2 θ range)	24 (42.5 - 50.2°)
Omega Scan Peak Width at Half-Height	0.36°
Lattice Parameters	$a = 9.442(2)\text{\AA}$ $b = 16.802(1)\text{\AA}$ $c = 14.915(2)\text{\AA}$ $\beta = 103.88(1)^\circ$
Space Group	$V = 2297.1(4)\text{\AA}^3$ $P2_1/c$ (#14)
Z value	4
D_{calc}	1.387 g/cm ³
F_{000}	992.00
$\mu(\text{CuK}\alpha)$	38.42 cm ⁻¹

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuK α ($\lambda = 1.54178\text{\AA}$) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0 kV, 0 mA
Temperature	20.0°C

Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.05 + 0.35 \tan \theta)^\circ$
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 3809 Unique: 3570 ($R_{int} = 0.089$)
Corrections	Lorentz-polarisation Absorption (trans. factors: 0.4899-1.0000) Decay (2.02% decline) Secondary Extinction (coefficient: 1.11082e-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma \omega (F_o - F_c)^2$
Least Squares Weights	$\omega = \frac{1}{\sigma^2(F_o)} = [\sigma_c^2(F_o) + \frac{p^2}{4} F_o^2]^{-1}$
p-factor	0.0000
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 1.50\sigma(I)$)	1600
No. Variables	281
Reflection/Parameter Ratio	5.69
Residuals: R; R_w	0.088; 0.052
Goodness of Fit Indicator	3.07
Max. Shift/Error in Final Cycle	0.03
Maximum peak in Final Diff. Map	$0.37 \text{ e}^-/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.41 \text{ e}^-/\text{\AA}^3$

