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Synthesis of Heterocycles for OLED Applications

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Abstract

Organic light-emitting diodes (OLEDs) have in recent decades gained increasing importance in lightning and in displays, spreading fast outside simple laboratory research. This thesis concentrates on the synthesis of substituted heterocycles and their use in OLED applications.

The first chapter describes the basic principles behind OLEDs and their development and uses up to date. It also provides an overview of the classes of organic compounds – both polymers and small molecules – used in OLED applications, and describes the effects of heterocycles in organic molecules used in OLED applications. The second chapter describes the synthesis and optical characterisation of trisubstituted triazines, and the synthesis of gold nanoparticles functionalised with substituted triazines. Physical and optical characterisation of most interesting compounds is also included.

The third chapter concentrates on new synthetic strategies for the synthesis of functionalised indoles. The optical properties of indole, together with the fact that inserting a nitrogen heterocycle onto a compound lowers its LUMO and HOMO levels, make it an attractive substituent in OLED applications. In the third chapter a new synthetic approach to quinolines is described, exploiting a Ru-catalysed cross-dehydrogenative coupling between two different primary alcohols, whereas the fifth chapter is dedicated to a one-pot synthesis of β-lactams using benzylic amines as the imine source, and ketenes formed *in situ*.

Abbreviations

Ac	acetyl
AIE	aggregation-induced emission
Ar	aryl
BIHEP	biphenylphosphine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BQ	benzoylquinine
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
CPME	cyclopentylmethyl ether
d	doublet
DABCO	Diazabicyclo[2.2.2]octane
DBA	dibutylamine
DBU	18-diazabicycloundec-7-ene
DCE	dichloroethane
DIPEA	di-isopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
EL	electroluminescence
EML	Light emitting layer
ES	electrospray
Et	ethyl
eq.	equivalents

ET	electron transporting
GC	gas chromatography
h	hour
HBET	hole blocking electron transporting
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HT	hole transporting
Hz	Hertz
ICP-MS	inductively coupled mass spectrometry
IR	infrared spectroscopy
J	coupling constant
L(n)	ligand
LCD	Liquid Crystal Display
LUMO	Lowest unoccupied molecular orbital
m	multiplet
m-	meta
M	metal
Me	methyl
mol.	molar
m.p.	melting point
Ms	methanesulfonyl
MW	microwave, microwave induction
n-	normal
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NP	nanoparticle
Nu	nucleophile
o-	ortho
OLED	Organic light emitting diode
p-	para
P3AT	Poly(3-alkythiophene)
PA	trans-polyacetylene
PDA	Personal digital assistant
PF	polyfluorene polymer
PFPV	Poly(2-fluoro-1,4-phenylenevinylene)
Ph	phenyl
PhOLED	phosphorescent organic light emitting diode
Phth	phthalimido
PL	photoluminescence
PLED	Polymer organic light emitting diode
PPE	poly(*p*-phenylene-ethynylene)
ppm	parts per million
PPP	Poly(paraphenylene)
PPV	poly(*p*-phenylene vinylene)
Pr	propyl
PT	polythiophene polymer
q	quartet

quint.	quintuplet
RO-PPV	poly(2,5-dialkoxy-p-phenlyenevinylen)
rt	room temperature
s	singlet
sat.	saturated
SFX	spiro[fluorene-9,9'-xanthene]
smOLED	small molecule organic light emitting diode
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
t	triplet
t-	tertiary
TAA	tert-amyl alcohol
TADF	thermally activated fluorescence
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	tetramethylguanidine
TMS	tetramethylsilane
TRPL	time resolved photoluminescence
Ts	toluenesulfonyl
Å	Ångström

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1. Introduction

Light emitting diodes, and in particular organic light-emitting diodes (OLEDs), have in recent decades gained increasing importance in lightning and in displays, spreading fast outside simple laboratory research. In fact, new commercially available displays using OLED technology have projected this novel technology to the "top ten" in materials science. For the majority of people, OLEDs are simply used in displays, but in reality nowadays there are many more appealing applications for them. These include energy-efficient lighting and the trendy, sought-after light decoration. Simultaneously, since OLEDs are among the few existing flexible light emitters, this opens applications in fields never imagined before.

Although the first OLEDs discovered employed small molecules as emitters, in the first commercial technological products polymeric materials were extensively used for almost all purposes. Currently the research and production of OLEDs are looking for different organic electroluminescent materials that are simultaneously able to deliver high colour purity across the colour spectrum, brightness, easy synthesis with good chemical and electrical stability, low cost, and simple processing.[1]

The OLEDs currently in use are mostly complexes based on rare earth and transition metals. However, rare earth metals and transition metals are very expensive, and in addition their production is laborious and produces vast quantities of toxic waste. Rare earth metal are produced almost exclusively in China, and so the and production of OLEDs and LEDs is wholly dependent on the market of one single country. Moving from rare earth metal OLEDs to metal free OLEDs or solutions using more easily available metals would both decrease the toxic waste produced even indirectly in the production of these materials, make them economically more viable to manufacture, and stabilise the market of the starting materials.

OLEDs have the potential to outperform all other light sources. They can be considered light emitting media that do not sacrifice the aesthetic appeal and essential lighting properties: lumen maintenance, sustainability, low cost and efficiency.[2] Reported record efficiencies of 110 lm/W for green light and performance targets of ongoing research and development activities focused on white emission indicate the potential of OLEDs to emerge as a solid state lighting source for a wide variety of potential applications, including ambient and technical lighting as well as signage applications, such as exit signs or logos.[2]

The following introduction is written from the point of view of an organic chemist, and aims to provide a brief overview of the classes of molecules used in OLEDs, rather than concentrating on their physical properties and the practical side of constructing and optimising the devices.

1.1. OLEDs and their history

1.1.1 What is an OLED

An organic light-emitting diode is a small light emitting unit consisting of a film of organic molecules sandwiched in between two charged electrodes, i.e. a metallic cathode and a transparent anode (usually glass), to allow the light emitted by the diode to shine through. The organic film is made of a hole-injection layer, a hole-transport layer, an emissive layer and an electron-transport layer. When voltage is applied to the OLED cell, the positive and negative charges recombine in the emissive layer (in this case made of organic molecules) and create electroluminescent light. OLEDs are used to create digital displays in devices such as television screens, computer monitors, as well as portable systems such as mobile phones, handheld game consoles and PDAs. A major area of research is the development of white OLED devices for use in solid-state lighting applications.[1,3-6]

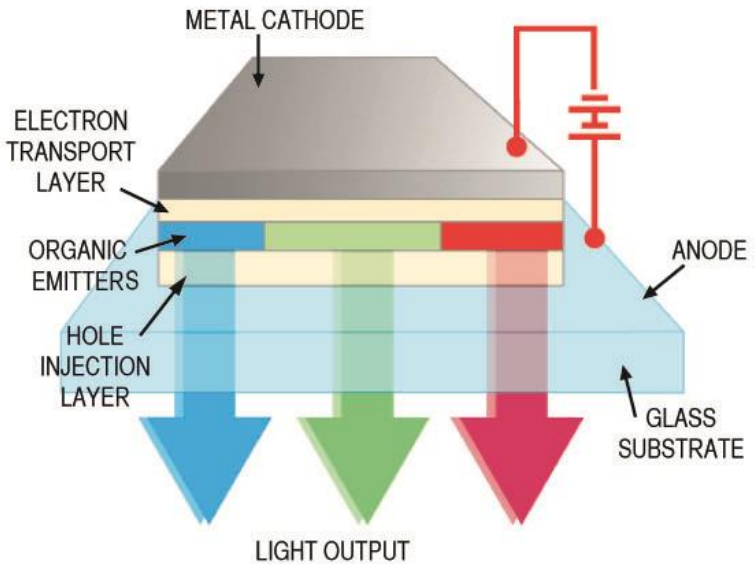


Figure 1.1 Structure of an OLED

Electron transport layer, emissive layer and hole injection layer are made of polymers or small organic molecules. An electronic current is applied across the OLED, causing the holes and electrons to combine in the emissive layer as exiton pairs. Decay of this stage results in a relaxation of the energy levels of the electron, accompanied by emission.

Unlike a LED, an OLED display works without a backlight, generating all the necessary light by emissions from the organic emitting layer. This allows it to display deep black levels and to be thinner

and lighter than a liquid crystal display (LCD). In low ambient light conditions (such as a dark room), an OLED screen can also achieve a higher contrast ratio than an LCD.

1.1.2. The Working Principle of OLEDs

A standard OLED is composed of a layer of organic materials situated between two electrodes, the anode and cathode, deposited on a support that is normally metal. The organic molecules - that normally have highly conjugated double and triple bonds - are electrically conductive as a result of delocalization of π-electrons caused by the conjugation over either one part or all of the molecule. The conductivity levels in these materials range from insulators to conductors, and they can therefore be considered as organic semiconductors. The highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of organic semiconductors are analogous to the valence and conduction bands of inorganic semiconductors. In an organic semiconductor, holes and electrons are transported via the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), respectively, of closely-packed, highly-conjugated aromatic molecules. The absorption and emission of light normally involves the creation and destruction of an exciton (bound electron-hole pair) by electronic transfer between the LUMO and HOMO of a single molecule. Charge-carrier transport and light-emission depend not only on the energy and wavefunction of the molecular orbitals, but also crucially on how the molecules are packed together, i.e. on the thin film morphology.[7] In fact, one of the reasons for loss of function is quenching of the exciton from a neighbouring molecule due to the packing of the organic molecules. To avoid quenching, the organic layer must present a certain degree of morphological irregularity.

When a voltage is applied across the OLED, the charges start moving through the device. A current of electrons flows through the device from cathode to anode (or, in other words, the holes move from the anode to the cathode), as electrons are injected into the LUMO of the organic layer at the cathode, and withdrawn from the HOMO at the anode. This can also be considered – as is often done – as the injection of electron holes into the HOMO. Electrons and holes then recombine creating an exciton, a bound state of the electron and a hole. Holes are generally more mobile than electrons in organic semiconductors, and so the holes and electrons are recombined close to the emissive layer. The decay of this excited state results in a relaxation of the energy levels of the electron, creating a photon with a frequency determined by the energy gap ($E = h\nu$) between the LUMO and HOMO levels of the emitting molecules. In short, the electrical power applied to the electrodes is transformed into light (Figure 1.2). Different materials and dopants can be used to generate different colours and the combination of them allows building up a white light source.[8]

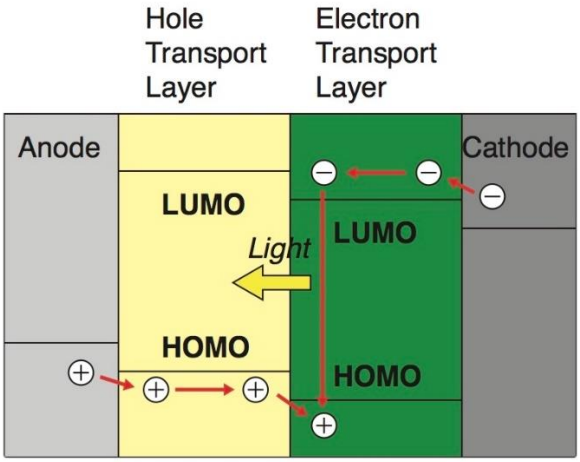


Figure 1.2

Charge transport and light generation in OLEDs.

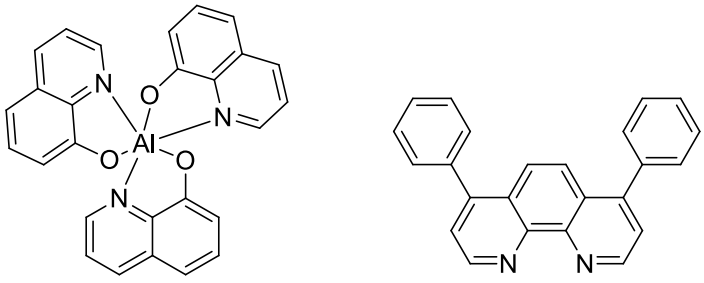
The first basic polymer OLEDs consisted of a single organic layer,[8] like the first light-emitting device synthesised by J. H. Burroughes *et al.*[9] that consisted of a single layer of poly(p-phenylene vinylene). However, the efficiency of OLEDs increases when the organic layer is fabricated in a multilayer fashion. This enables to select materials with different electronic properties to aid charge injection at electrodes by providing a more gradual electronic profile, or block a charge from reaching the opposite electrode and being wasted.[10] In fact, many modern OLEDs incorporate a simple bilayer structure, consisting of a conductive layer and an emissive layer.[10] In the past decade, however, the architecture of the light emitting layer (EML) was studied for better power efficiency and device lifetime, and another method that arose for improving the efficiency of OLEDs both in terms of power efficiency and device lifetime is graded heterojunction in the emissive layer. This means that the composition of the hole- and electron-transport materials varies throughout the emissive layer with a dopant emitter. In these structures, the organic layer can be mixed either uniformly, step-wise in grades, or it can be continuously graded. The common feature in these is that the emissive layer is basically a bipolar transport layer, whereas the distribution of the hole- and electron- transport materials differs. This approach combines the benefits of both the monolayer- and multilayer emitters by improving charge injection while simultaneously balancing charge transport within the emissive region.[11,12]

One of the most common anode materials is indium tin oxide. It is transparent, allowing the light emitted to shine through, and it also has a high work function, which promotes the injection of holes into the HOMO level of the organic layer. The cathode does not need to be transparent, and the metals commonly used as a cathode are barium and calcium. They have low work functions, which promote injection of electrons into the LUMO of the organic layer. Both barium and calcium are reactive metals, and are often capped by a layer of aluminium to avoid degradation.[8,13]

1.1.3. The History of OLEDs

Electroluminescence is widely present in nature, both in animals and plants. Some well know examples include luminous bacteria, fireflies and moonlight mushrooms. Electroluminescence in organic materials was first discovered by Bernanose *et al.*[14,15] in the 1950s. They applied high alternating voltages in air to materials such as acridine orange, either deposited on or dissolved in cellulose or cellophane thin films. The proposed mechanism was either direct excitation of the dye molecules or excitation of electrons.[14,16,17]

OLED technology was invented by Tang and Van Slyke[18] at Eastman Kodak in the early 1980s, when they reported the first functioning diode device. This device used a novel two-layer structure with separate hole-transporting and electron-transporting layers, so that recombination and light emission occurred in the middle of the organic layer. This resulted in a reduction in operating voltage and improvements in efficiency that led to the current era of OLED research and device production. In fact, OLED technology is fast replacing LCD technology in handheld devices (for example mobile phones) because OLED technology is brighter, thinner, faster and lighter than LCDs, it uses less power, offers higher contrast and in addition OLED devices are also cheaper to manufacture. The first OLEDs designed by Easman Kodak were so called small molecule OLEDs, sm-OLEDs. They were made of small molecules such as Alq_3 and Biphen (figure 1.3).



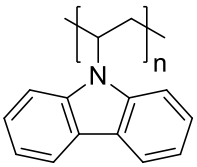
1.1 **1.2**

Figure 1.3

Alq3(1.1) and Biphen (1.2), the first small molecule OLEDs used in commercial applications.

Partridge[19] made the first observation of electroluminescence from polymer films at the National Physical Laboratory in the United Kingdom. The device he constructed consisted of a film of poly(N-vinylcarbazole) (Figure 1.4) up to 2.2 micrometres thick located between two charge injecting electrodes.

The polymer was doped with antimony tetrachloride. The results of the project were patented in 1975, and published a few years later.[20-23]

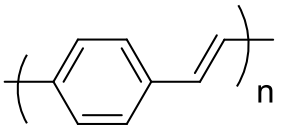


1.3

Figure 1.4

poly(N-vinylcarbazole)

Research into polymer electroluminescence culminated in 1990 with J. H. Burroughes *et al.*[9] at the Cavendish Laboratory in Cambridge reporting a high-efficiency green light-emitting polymer-based device using 100 nm thick films of poly(*p*-phenylene vinylene) (PPV) Figure 1.5. They demonstrated for the first time that an organic semiconductor could be used in electroluminescent devices. They hypothesised that moving from small molecules to polymers would increase the long-term stability of the organic layer on the OLED device.



1.4

Figure 1.5

Structure of poly(*p*-phenylenevinylene)

After Burroughes' discovery on polymer OLEDs, the field of electroluminescence has gained even greater importance, and the research into both polymer OLEDs (PLEDs) and small molecule OLEDs (smOLEDs) has exploded, with new inventions coming to light at a fast pace. OLEDs and PLEDs are now used in commercial applications worldwide, and their importance in everyday life is undeniable. Figure 1.6 shows some of the most important moments in the history of OLEDs and their commercial applications.

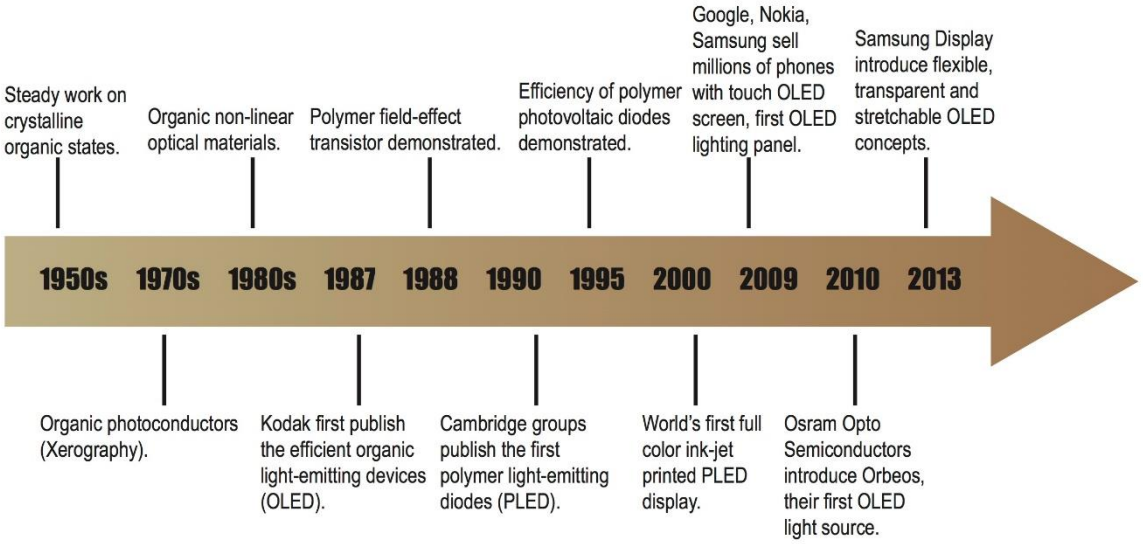


Figure 1.6

Major discoveries in the field of electroluminescence and advances in the commercial applications of OLEDs.

1.2 Different types of OLED

There are two main families of OLED: those based on small molecules and those employing polymers. The first studies on OLEDs were done on small molecules, but in the late 1980s and early 1990s witnessed the insurgence of polymeric materials for OLEDs, and the first commercial applications of PLEDs came to the market in the early 2000s. After the initial excitement on polymer OLEDs their limitations became clearer and the emphasis on the research on small molecule OLEDs became once again more important.

1.2.1 PLEDs

Since the first successful fabrication of a polymer-based OLED, a PLED, there has been great interest in the research on using polymers for OLED applications. The first PLED was made using poly(*p*-phenylenvinylene) (PPV) in the active layer.[9] Polymers had already been used as conductors in various applications, and in the late 1980s Burroughes and Friend *et al.*[9,24] discovered that they could also be used for electroluminescent purposes. They demonstrated that the semiconductive conjugated polymer poly(*p*-phenylenevinylene) had electroluminescent characteristics if an appropriate choice of contact layers was made.

After Friend's discovery, there was a boom in the research field of polymer OLEDs, and a lot of progress was made in a relatively short time in this field in order to realise commercial applications, opportunities for processing, device structures and performances - in addition to new conjugated polymers and their derivatives as electroluminescent materials (Table 1.1).[2,3,25-34] PPV is a bright yellow, fluorescent conjugated polymer. Its emission maxima at 551 nm (2.25 eV) and 520 nm (2.4 eV) are in the yellow-green region of the visible spectrum, and so PPV PLED emits green light. PPV is the only polymer of this type that has so far been successfully processed into a highly ordered crystalline thin film. Presently, PPV and its derivatives are the only conjugated polymers that have been successfully processed in film with high levels of crystallinity, and indeed most polymers that are currently studied – with very few exceptions- are PPV derivatives. Although PPV is a very promising light emitting conjugated polymer, the processing is still somewhat problematic. The unsubstituted form of PPV is insoluble in organic solvents, but with proper chemical modifications of the polymer backbone it can be dissolved in organic solvents and the physical and electronic properties of PPV derivatives can also be altered by insertion of functional side groups[7,35,36]

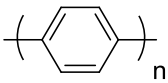
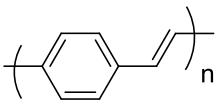
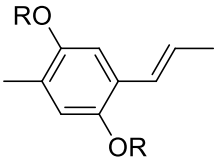
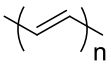
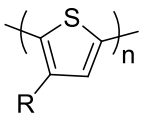
Polymer	Chemical Name	Structure	Emission Peak
PPP	Poly(paraphenylene)		465
PPV	Poly(paraphenylenevinylene)		565
RO-PPV	poly(2,5-dialkoxy-p-phenlyenevinylen)		580
PA	trans-polyacetylene		600
P3AT	Poly(3-alkythiophene)		690

Table 1.1 Some common conjugated polymers and their emission peaks.

Several other classes of light-emitting conjugated polymers have also been developed, for example polycarbazoles[37], poly fluorenes[27,38,39], poly(phenylene ethynylenes)[39-41] and polythiophenes[30,31,39]. While PPV and its derivatives are still the leading materials for green light-emitting PLEDs, polyfluorenes are

one of the most important blue emitters. Also, some very high-efficiency PLEDs made from polythiophene derived copolymers have been reported.[42]

Despite its popularity, the PPV polymer still presents some problems, such as its tendency to aggregate, formation of excitation in the solid state leading to blue-green emission, fluorescence quenching, and the decrease in electroluminescence efficiency.[43-45] Recently, hyperbranched polymers have drawn much attention and consideration due to their ability to diminish the formation of interchain interactions owing to their high degree of branching, which can improve the solubility and thermal stability of PPV and reduce chain aggregation caused by fluorescence quenching.[46]

Modified PPVs containing electron-withdrawing groups such as fluorine atoms, cyano groups, and heterocycles display high electron affinities and electron-transport properties as a result of increasing the polymer's electron deficiency.[47] In particular, fluorine atoms lower both the HOMO and LUMO energy levels. Consequently, the electron injection is made easier, the materials display a greater resistance against the degradative oxidation processes and organic n-type (electron transporting) or ambipolar (consisting of both n-type and p-type layers) semiconducting materials may result. Moreover, the C–H… interactions play an important role in the solid state supramolecular organization, originating a typical π-stack arrangement which enhances the charge carrier mobility.[47,48]

Kang and Shim[49] synthesized the fluorine-substituted PPV derivative, Poly(2-fluoro-1,4-phenylenevinylene) (PFPV), that emits light in the yellow region of the light spectre. They examined the effect of the fluorine atom on the photoluminescence and electroluminescence properties of this polymer by comparing it with a poly(1,4-phenylenevinylene), and found that the relative electroluminescence efficiency of the PFPV was 10 times higher than PPV, whereas the photoluminescence properties were quite similar. The enhanced EL efficiency of PFPV is due to the decrease of band offset between polymer and electron injection electrode.

Since the nitro moiety is also a strong electron-withdrawing group, in order to improve efficiency, processability, and stability of PPV polymers, Li et al.[50] synthesised two groups of novel poly(p-phenylene vinylene) derivatives (**1.5** and **1.6**) with hyperbranched structure and containing a nitro substituent. The band gaps of the PPV derivatives with a nitro substituent were decreased and the polymers had higher molecular weights, showing excellent solubility in common organic solvents, good film-forming ability, and better thermal stability. Introducing a trisubstituted benzene with a nitro substituent increased the absorption range and lowered the polymer band gap. The maximum absorption peak of polymers with a nitro substituent is sharper than that of polymers without this substituent, which is why introducing the strong electron-withdrawing nitro group is good for the polymer π–π* interaction.

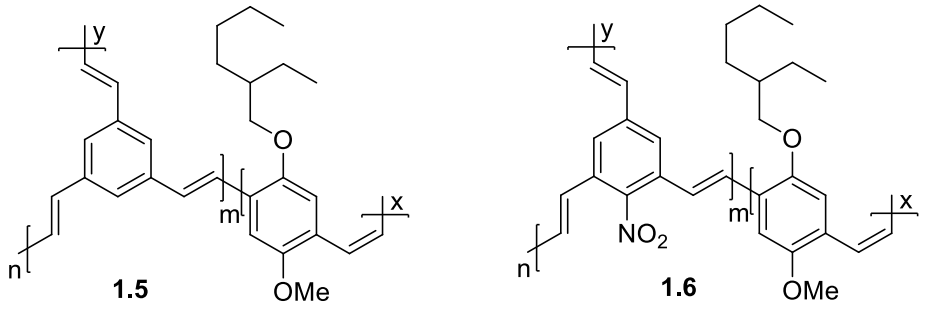


Figure 1.7

Polymers studied by Li *et al.*

Recently Rodrigues[36] has combined the effects of a PPV polymers with those of fluorene by synthesising a PPV polymer with fluorene substituents (Scheme 1.8). They studied the electrochemical, thermomechanical, optical and structural properties of this polymer, as well as its possible applications in PLEDs, with promising results that confirmed that these polymers can indeed be used in electroluminescent devices. The ester groups in the PPV-fluorene polymer could in addition be thermally cleaved, improving the morphology of the material by decreasing the density of chromophores and thus avoiding quenching. Comparison of PPV-Fluorene polymer with the results of polyfluorene homopolymer and derivatives indicate that this new PPV fluorene structure can be more explored to fabricate efficient electroluminescent polymers.

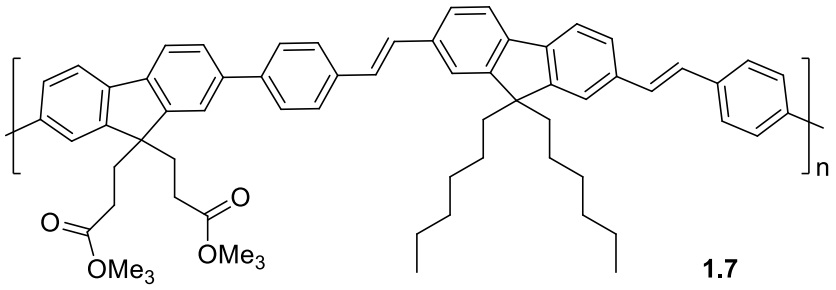


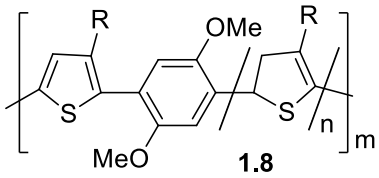
Figure 1.8

PPV-Fluorene polymer

Some of the polymers that are not PPV derivatives that show promising characteristics for applications in PLEDs are the abovementioned polythiophene polymers (PT)[42,51,52] (Table 1.1) and polyfluorene polymers (PF).[27,38,52] Even though PT can produce a red light that is difficult to achieve

with other polymers, they still have not been studied as extensively as PPV and its derivatives. Some thiophene-derived copolymers have also been used in the manufacture of very high-efficiency PLEDs. Copolymers are polymers used in the emissive layer for their electroluminescence properties, while other polymers are used as electron and hole carriers. Generally, PTs are one of the most studied and important classes of linear conjugated polymers,[53] and they are slowly finding their way also into electroluminescence applications. Polythiophene polymers have been studied not only for their electroluminescence properties, but also because they have possible applications in memory devices and in solar cells.[31,30]

Hardeman[51] has studied the effect of phenyl substituent on the polythiophene polymer (Figure 1.9). The phenyl groups were introduced into the polymer in a random fashion. Hardeman synthesised polymers with 50%, 40%, 30%,20% and 0% of phenyl rings in the PT chain, and compared the results achieved on different substitution levels. The effect on the bandgap was remarkable, and a linear relation between the bandgap and the percentage of introduced phenyl rings was observed, with the band gap increasing with increased phenyl content. Aggregation and crystallization behaviour were also affected by the introduction of phenyl rings. Aggregation was still possible with 20% of phenyl rings, albeit to a small extent, while crystallization was already completely inhibited at that point.



1.8

Figure1.9

Polythiophene polymer studied by Hardeman.

Towns[27] and co-workers, as well as Lindgren[38] and his group, have studied different polyfluorene polymers (Figure 1.10) for applications in PLED. Lindgren synthesised a series of fluorene-based conjugated copolymers, and tested them in light-emitting devices. The polymers consisted of alkoxyphenyl-substituted fluorene units together with different amounts of a hole-transporting triphenylamine-substituted fluorene unit: 0%, 10%, 25% and 50%. All of these polymers showed good photoluminescence efficiency and light emission in the blue spectral region with no changes. Instead, the electroluminescence quantum efficiencies of the devices increased six times going from 0% to 10% triphenylamine-substituted fluorene groups. After that, they decreased again, indicating an optimal polymer composition between 10% and 25% of the triphenylamine moiety, where the charge carrier mobilities in the PLED are balanced.

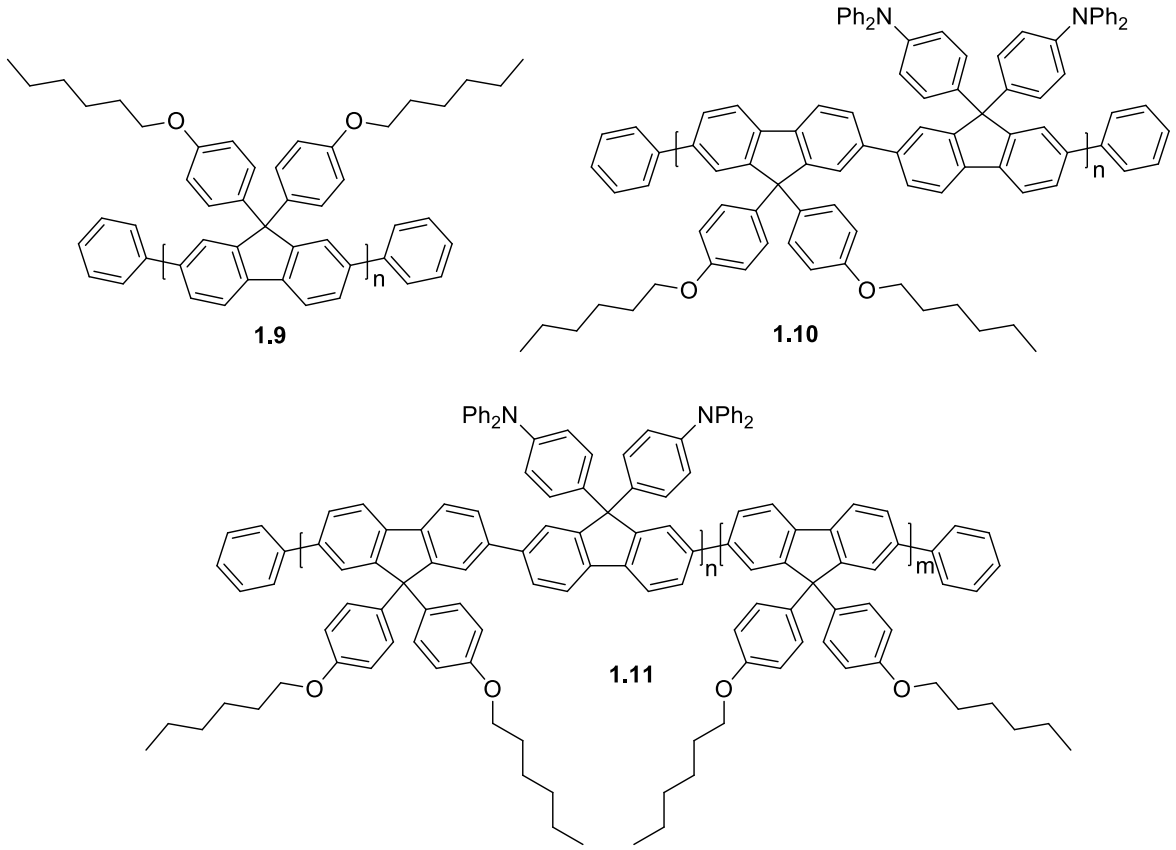


Figure 1.10

Structures of the polymers studied by Lindgren. **1.10** and **1.11** contain 10% and 25% of triphenylamine-substituted fluorene units, respectively.

One example of a poly(*p*-phenylene-ethynylene) polymer are the polystyrene-grafted polymers studied by Breen et al.(Figure 1.11)[40,41] These copolymers, like other poly(*p*-phenylene-ethynylene) (PPE) polymers, emit in the blue region when used with an efficient hole-transport matrix. Compared with simple PPE polymers, the grafting onto styrene shifted the emission peak more towards the blue region. The grafting also rendered these polymers liquid also in the solid state, thus removing some of the problems encountered with traditional PPE polymers and increasing their electroluminescence (EL) by external quantum efficiencies that were several orders of magnitude greater than those recorded for their non-grafted counterparts.

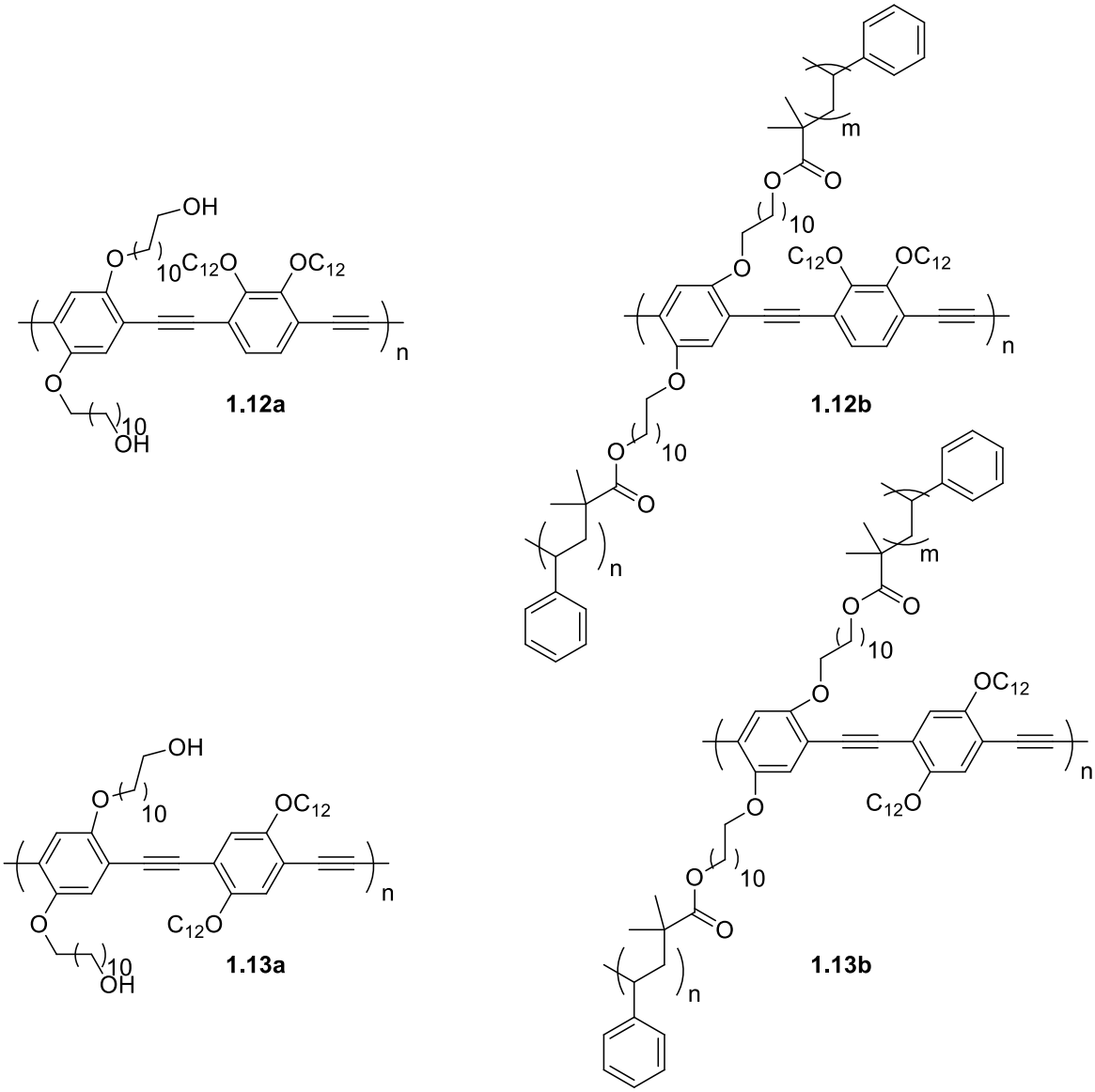
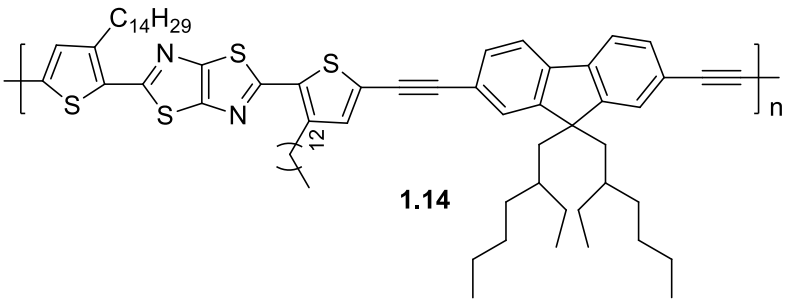


Figure 1.11

The structures of the simple *ortho*- and *para*- PPE polymers (**1.12a** and **1.13a**) studied by Breen *et al.*, and their grafted counterparts (**1.12b** and **1.13b**, respectively).

Palai[39,52] has combined fluorene and thiophene units in a polyarylene ethynylene polymer as a copolymer, in the hope of thus combining the best traits of all three classes of polymers. One example of the polymers studied is shown in figure 1.12. These molecules had high molecular weight, good solubility, and thermal stability. They were also optically active and fluorescent in nature, with electroluminescence maxima at 600nm, in the orange region. The combination of excellent solubility in common organic solvents, appropriate HOMO/LUMO energy level, and narrow band gap of these copolymers renders them promising active materials for polymer optoelectronic device applications.

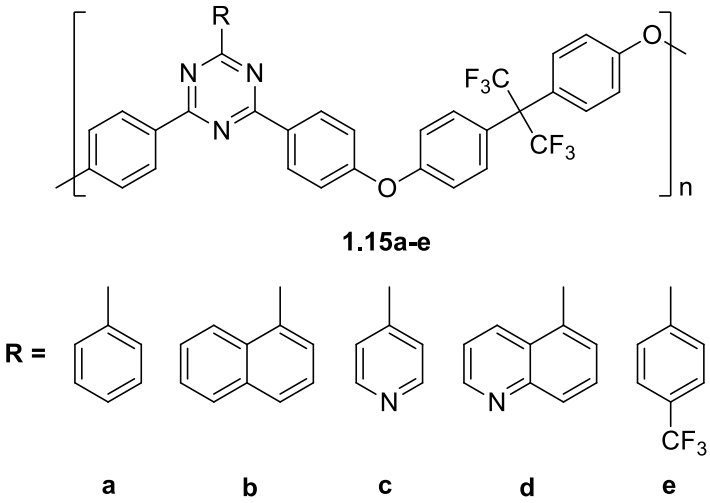


1.14

Figure 1.12

One of the heterocycle containing thionyl- fluorene- ethynylene polymers studied by Palai.

The first published studies with triazines as part of polymers for OLED applications were conducted by Schmidt *et al.*[54] in the late 1990s (Figure 1.13). They synthesised various polyethers with triazine units, and used them as hole-blocking layer in OLED devices with good results, showing that the high electron-affinities of the triazine moieties improved the efficiency of the two-layer PLEDs constructed.



1.15a-e

Figure 1.13

Polyethers studied by Schmidt.

An interesting development was published by Kim *et al.*[55] in 2002, when they synthesised a small library of heterocycle-containing (including triazine) polymers and oligomers with both hole- and electron-transporting units in the main chain (Figure 1.14). All the polymers and oligomers synthesized exhibit remarkable thermal stability ,with EL emission maximum peaks of the materials in the range of

535–560 nm, corresponding to green–yellowish-green. Among the three electron-transporting moieties, the 1,3,4-oxadiazole unit showed the best electron injection and transporting properties.

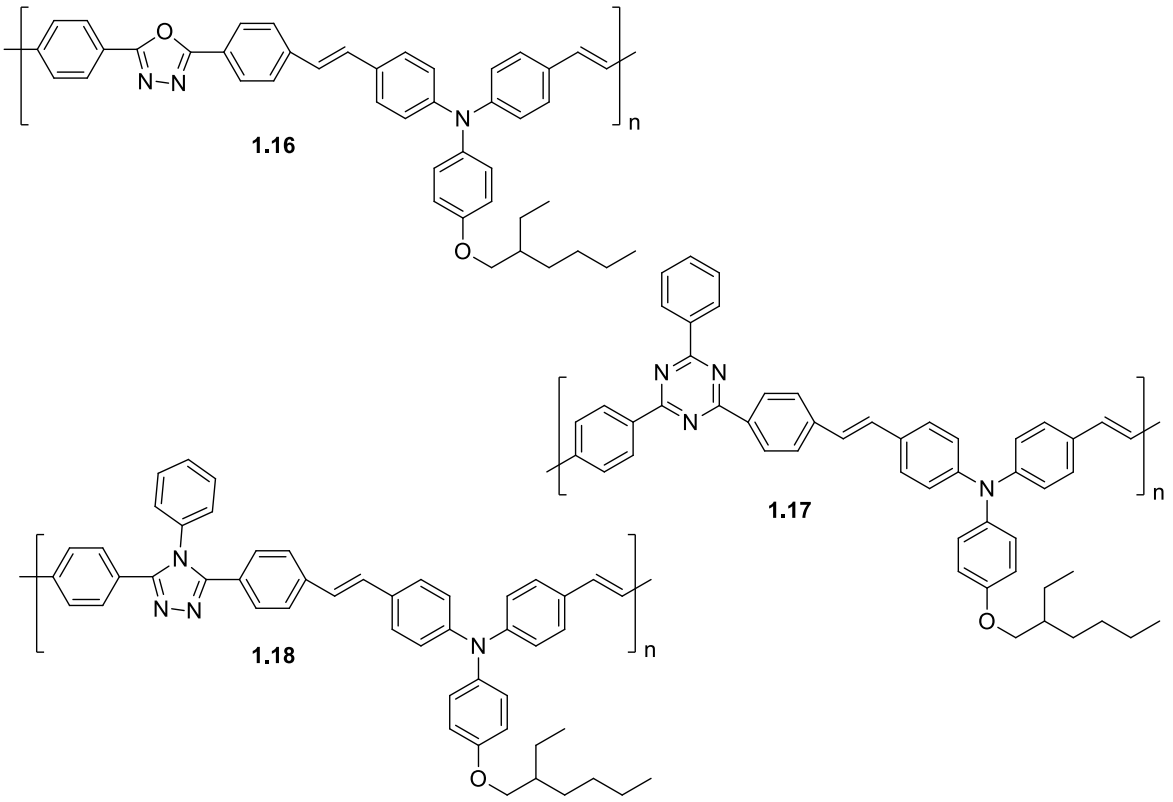


Figure 1.14

Oligomers and polymers studied by Kim *et al.*

The compounds described above represent just a small fraction of all the polymers studied for OLED applications. Regardless, it would be not purposeful nor productive to create an exhaustive list of all the polymer classes used in lightning applications, as the polymers discussed give a reasonably good view on what type of compounds are generally used in OLEDs, the properties that are important for a well-functioning device, and also on the general on the general outlines of the research that is ongoing in the field.

1.2.2 smOLEDs

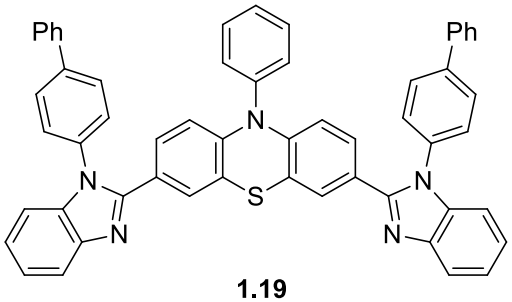
The research on small molecules for OLED applications is constantly evolving, and the amount of published papers and patents in this field is overwhelming. Therefore, as with the polymers, this chapter will serve the purpose of providing an introduction to the topic with some examples selected from the papers published in the last 5 years. The compounds discussed come from the most interesting groups in this field, and contain both emitting molecules and compounds used as hole blockers and electron transfer materials. In many cases, these molecules are used together with metal complexes, most often iridium and its salts.

1.2.2.1 Small molecule organic emitters

In many cases, the emission from an OLED is not derived only from the organic molecules, but from other substances, called dopants, used to enhance the efficiency of the device. In these cases the host molecule releases its energy to the dopant for emitting light. However, in many cases an organic molecule can be used directly as an emitter without the need for a dopant.

For highly efficient and durable OLEDs, it is desirable for the emissive materials to have high capability of accepting both electrons and holes, which means that the material should be able to inject and transport both charge carriers to the emitting centre.[56-59] To satisfy this requirement, an emitter needs to have both electron donor and acceptor type properties. This can be achieved simply by combining electron donor and acceptor moieties in the same molecule. As the electron donor and acceptor moieties are separated in the same molecule, the emission of donor-acceptor type emitters generally originates from intramolecular charge transfer between electron donating and accepting groups.[60] The utilisation of bipolar materials offers the attractive possibility to achieve efficient and stable single-layer OLEDs, which is highly desirable for simplifying the manufacturing process and reducing production costs.

Kim *et al.*[61] synthesised a donor–acceptor type green fluorescent emitter **1.19** (Figure 1.15), which consists of phenyl-phenothiazine as an electron donor and biphenylbenzimidazole as an acceptor. Its thermal and photophysical properties, and energy band structure were studied, and also organic light-emitting diodes (OLEDs) with various device structures were fabricated using **1.19** as an emitting layer.

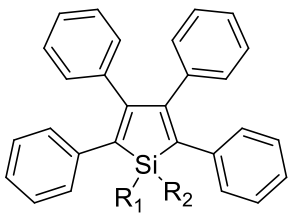


1.19

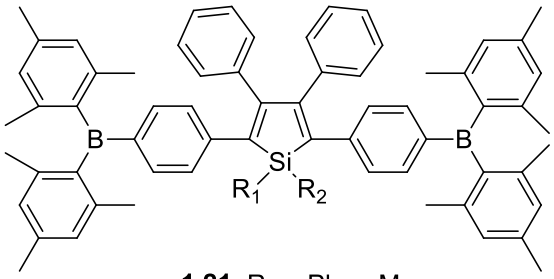
Figure 1.15

Donor–acceptor type green fluorescent emitter synthesised by Kim.

In aggregation-induced emission (AIE), the emission only takes place when the molecules are in close contact with each other, and in solution no emission is observed. This kind of molecules normally function only as light-emitting layer, but lately Chen[62] reported the synthesis and characterisation of novel 2,3,4,5-tetraphenylsiloles with improved efficiency by functioning also as electron-transporting layer in an organic light-emitting diode (OLED). They synthesised three emitters with 2,3,4,5-tetraphenylsilole and dimesitylboryl functional groups (Figure 1.16). The siloles are weakly fluorescent in solution but become highly emissive in the aggregate state, presenting AIE characteristics. They also possess lower LUMO energy levels than their parents, 2,3,4,5-tetraphenylsiloles, and due to the synergistic effect between the silole ring and the dimesitylboryl groups, the LUMO energy levels of the new siloles were lowered, resulting in improved electron transporting ability. These traits enable them to serve as bifunctional materials, functioning simultaneously as a light emitter and an electron transporter in an OLED.



1.20, R_1 = Ph or Me
R_2 = Ph or Me

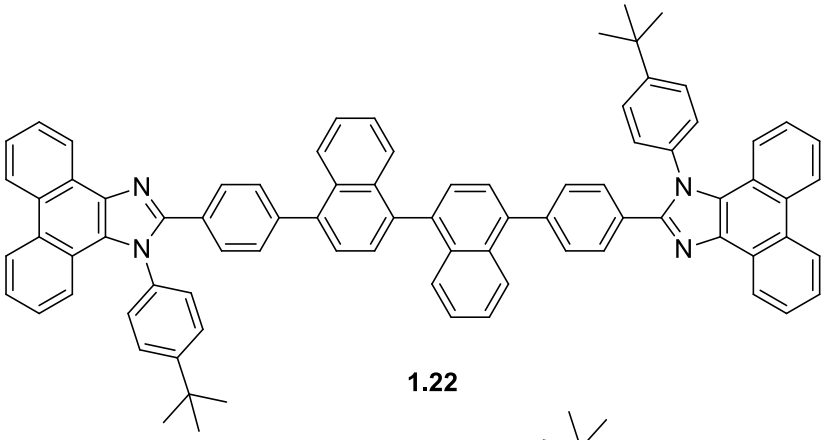


1.21, R_1 = Ph or Me
R_2 = Ph or Me

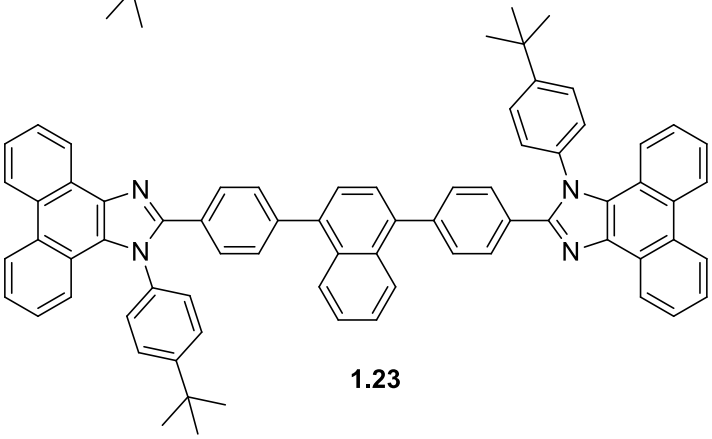
Figure 1.16

Emitters with 2,3,4,5-tetraphenylsilole and dimesitylboryl functional groups synthesised by Chen.

One of the main research areas in smOLEDs is the search for efficient blue fluorescent emitters. These are important especially for creating pure white light. Both red and green organic emitters capable of sufficient efficiency, color purity, and lifetime have been developed for commercial application, whilst their blue organic counterparts are still on their way towards commercialisation.[63] Chen et al.[64] studied the effect of a naphthyl unit on an ambipolar deep-blue emitter, a binaphthalene compound, with fluorescent phenanthroimidazole units joined by either a naphthyl- or a binaphthyl bridge (Figure 1.17). Replacing the naphthyl unit with a binapthtyl unit gave a high thermal stability, deep blue emission as well as spatially separated HOMO and LUMO orbitals with more balanced charge transport properties, better colour purity and higher external quantum efficiency. This compound exhibited OLED performances that are comparable to the best reported non-doped deep-blue emitters.



1.22



1.23

Figure 1.17

Compounds studied by Chen as blue emitters.

Also Muangpaisal *et al.*[65] have used the binaphthyl moiety as a central unit in bipolar transporting materials. The molecules studied had an electron-donating arylamine, an electron-accepting N-phenyl-benzimidazole, and an in-between binaphthalene bridge (Figure 1.18). The highly twisted binaphthalene

bridge is beneficial for its amorphous morphology, good solubility, high thermal stability and high photoluminescence quantum efficiency. The fluorescence properties of these compounds were dependent on the solvent polarity, and the physical properties of the compounds could be tuned by binding the benzimidazole with binaphthalene group via either C-or N- linkage. Three-layered blue-emitting OLEDs using the studied molecules as the emitting layer exhibited good performance.

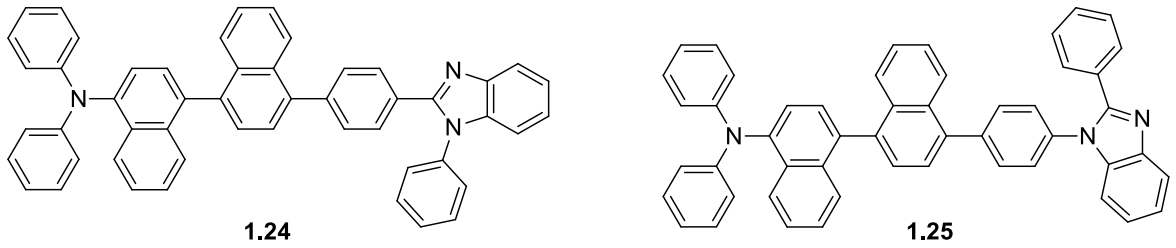


Figure 1.18

Bipolar transporting materials synthesised by Muangpaisal; with C-linkage (**1.24**) and N-linkage (**1.25**).

Sometimes the wavelenght of the light emitted can change noticeably by simply changing the substituent on the emitter. A good example of tuning of the light colour is represented by the study conducted by Anand.[66] He synthesised a group of susbtituted benzoquinolines and benzoacridines (Figure 1.19), and showed that the emission color can be effectively controlled from blue to green to yellow to red by modulating the aromatic p-characteristics not only in solution (photoluminescence) but also in solid electroluminescent devices. The emission maxima shifted from blue (455nm, **1.26**), green (496nm, **1.27**), yellow (545 nm, **1.28**) to red (630 nm, **1.29**) when the substituents on the core were modified (figure 1.19).

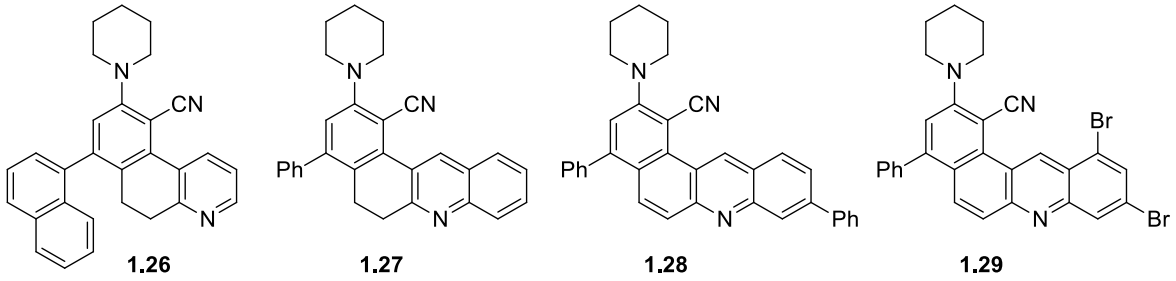


Figure 1.19

Blue (455nm, **1.26**), green (496nm, **1.27**), yellow (545 nm, **1.28**) and red (630 nm, **1.29**) emitters studied by Anand.

1.2.2.2 Host Materials for Emitters

Many OLEDs use small organic molecules as host material doped with emitters. Often these emitters are metal complexes, most commonly with iridium or aluminium.[67-72] Solution-processed phosphorescent OLEDs have been actively developed, since they allow combining both high quantum efficiency of phosphorescent materials and simple fabrication processes of solution processed OLEDs. The device performances of the solution-processed phosphorescent OLEDs have been greatly improved in the last 10 years. This is mostly due to the development of small-molecule host materials for solution processes.[73]

A hybrid host made of polymer and small molecules, a single small molecule host, and a mixed host made of small molecules have effectively enhanced the quantum efficiency of the solution-processed phosphorescent OLEDs. The uses of the small molecule host materials are advantageous over the use of either polymer hosts or hybrid hosts in terms of material purity, chemical stability, triplet energy, and lifetime. The high purity is critical to secure long lifetime in the phosphorescent OLEDs and long lifetime can be obtained using the highly pure small molecule host materials. The chemical stability of the small molecule host materials can also be better than that of hybrid host materials due to the aromatic character of the backbone structure of these host materials. In most small molecules, the molecular structure is made up of the combination of aromatic units with high bonding energy, which is beneficial to the chemical stability of the host materials.[73]

One of the most prominent groups of small molecule hosts are carbazole derivatives. In these molecules, carbazole acts as the donor group. Only recently Yook *et al.*[74] have developed a host material based on a carbazole structure, doped with iridium(III)bis(4-phenylthieno[3,2-c]pyridine)acetylacetonate that has high quantum efficiency. The carbazole derivative (Figure 1.20) was used as a bipolar host material to improve the device performances of yellow phosphorescent OLEDs at a low doping concentration of 1%. During the same time, another group of similar host molecules was synthesised by Huang *et al.*[75] He evaluated the possibilities of grouping carbazole compounds with a pyridine core. The bi-, tri- and tetra- carbazole substituted pyridine derivatives all exhibited good thermal stabilities and comparatively high triplet energy level irrespective of the number of carbazole substituents. When these compounds were used as host materials for blue phosphorescent OLEDs, good current efficiencies were also achieved. The best results were achieved with the bi- and tri-carbazole compounds (**1.32** and **1.33**) shown in figure 1.20.

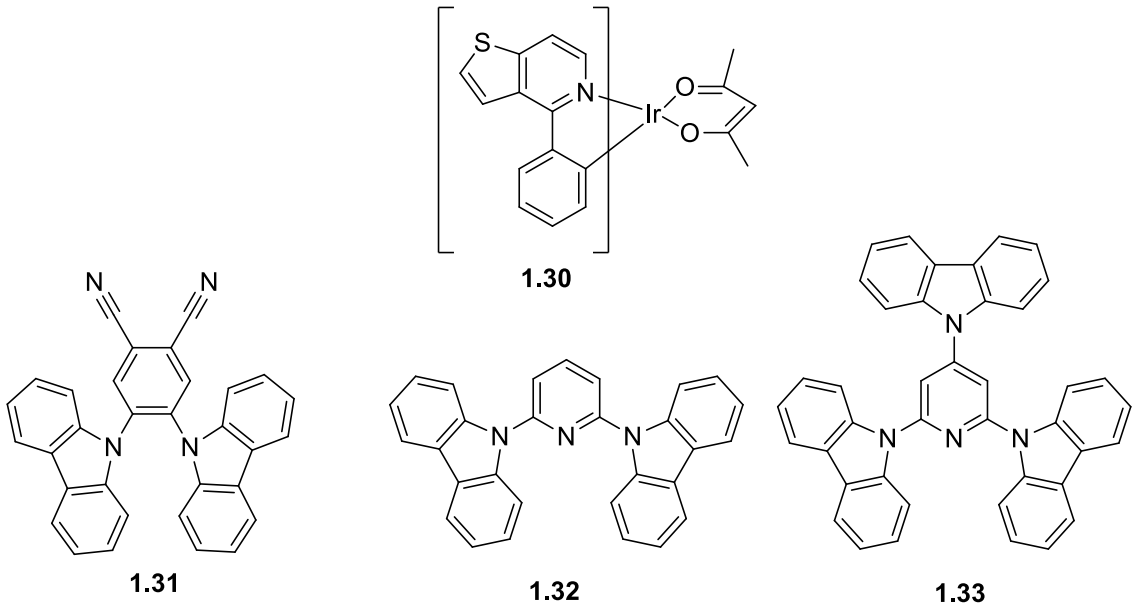


Figure 1.20

The emitter used by Yook (**1.30**), the host material synthesised by Yook (**1.31**), and the two best performing pyridine - carbazole derivatives synthesised by Huang (**1.32** and **1.33**).

Another carbazoyl-based host material was synthesised by Lee *et al.*[76] (Figure 1.21). This carbazolyldibenzofuran-type high-triplet-energy bipolar host material worked well for blue phosphorescent organic light-emitting diodes, with a high triplet energy for energy transfer to a blue phosphorescent dopant, and bipolar charge transport properties for balanced hole and electron density in the emitting layer. High quantum efficiency was obtained at a relatively low doping concentration of 3%.

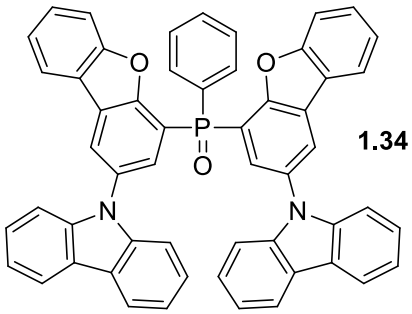


Figure 1.21

carbazolyldibenzofuran-type high-triplet-energy bipolar host material synthesised by Lee.

Adachi et al.[77] combined the carbazole moiety with a triazine core to synthesise novel bipolar host material **1.35** (Figure 1.22), consisting of a dicarbazole donor linked to an electron deficient 1,3,5-triazine acceptor. This design allows the spatial separation of HOMO and LUMO on the donor and acceptor moieties, respectively, giving sufficient triplet energy together with promising physical properties and morphological stability. This material was used as a host for a yellowish-green iridium complex. Fabricated phosphorescent OLEDs demonstrated high performance in trilayer and bilayer device architectures.

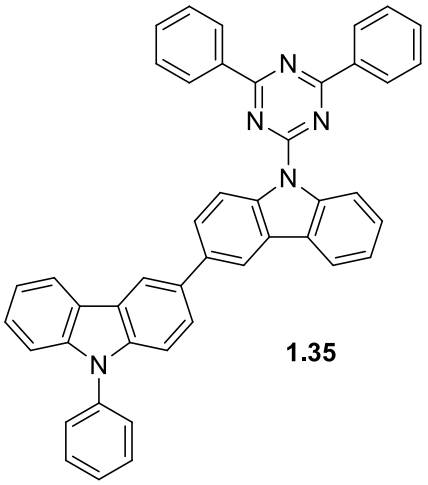
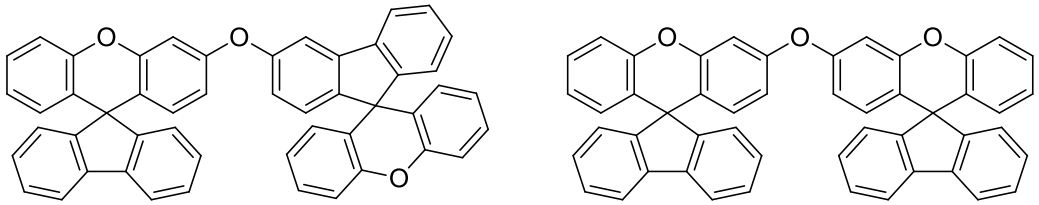


Figure 1.22

Bipolar host material **1.35** consisting of a dicarbazole donor linking to an electron deficient 1,3,5-triazine acceptor synthesised by Adachi.

Most of the recent articles on smOLEDs concentrate their work on carbazole derivatives, with other heterocycles as the acceptor in the molecule.[56,78] There are, however, other interesting compounds that can act as host materials. In 2014 Huang[79] and collaborators reported novel spiro[fluorene-9,9'-xanthene] (SFX)-based compounds as host materials that do not possess the traditional hole- or electron transporting units (Figure 1.23). Diarylfluorene and spiro-systems have the advantage of high thermal and morphological stability for host materials, and they also keep the triplet energy levels of the host materials in the desired range. The compounds tested by Huang proved to be good host materials for efficient and low-voltage blue, green and red phosphorescent OLEDs. Compared with monomeric SFX-based devices, the performance of dimeric SFX-based devices increased nearly 20 times, although the difference of HOMO/LUMO levels and triplet levels between dimeric SFX and SFX was very small.

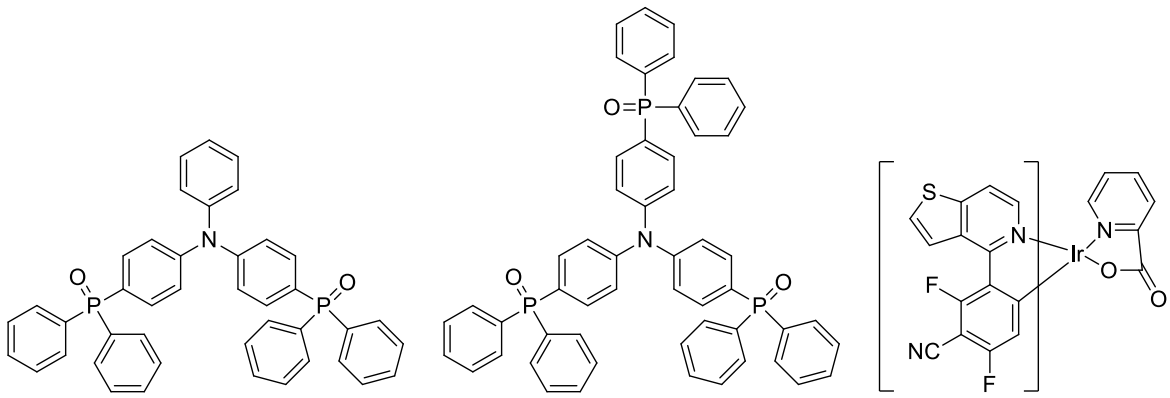


1.36 **1.37**

Figure 1.23

Spiro[fluorene-9,9'-xanthene] (SFX)-based compounds as host materials reported by Huang.

Triphenylamine is another common donor group in host molecules.[56,78,80] Ye[80] has synthesised interesting macrospirocyclic oligomers based on a central triphenylamine structure with peripheral diphenylphosphine oxide and fluorene groups (Figure 1.24). This molecule, with its extended molecular size and nonconjugated structure, improves the solution process ability and thermal stability in comparison with simple monomeric units of substituted triethylamines, without lowering its triplet energy and affecting its optical properties. The solution-processed blue phosphorescent OLED (PhOLED) based on FIrpic and the oligomer demonstrated promising current efficiency and luminance, showing promise as a blue host material.



1.38 **1.39** **1.40**

Figure 1.24

Derivatives with two (**1.38**) and three (**1.39**) diphenyl phosphine oxide units on the triphenylaniline core and FCNIrpic dopant (**1.40**).

Qiu[81] designed and synthesized two new bipolar host materials **1.38** and **1.39** for solution-processed deep blue PhOLEDs. Derivatives with one to three diphenyl phosphine oxide units on the triphenylaniline core all exhibited excellent thermal stability and high triplet energy. Double layer devices constructed with these materials as hosts and FCNIrpic as a dopant showed outstanding current efficiency, with the host material increasing carrier balance in the emitting layer significantly.

The compouds described so far constitute only a little part of the possible structures for both emitters and host materials for smOLEDs. Most emitters are highly conjugated, with heterocyclic structures that function as electron acceptors and electron donors, whereas in host molecules the conjugation is intetionally broken with oxygen, nitrogen or other heteroatoms. The use of heterocycles in the construction of smOLEDs is of paramount importance to their function, and ideed, the amount of heteroatoms on the molecule greatly affects the HOMO and LUMO orbitals of the molecule, with more heteroatoms often lowering these levels and resulting in better electroluminescence and carrier properties.[1,82,83]

1.3 Use of Triazines in smOLEDs

As seen in chapter 1.2.1, the triazine moiety has been introduced into polymers that have interesting EL properties (figure 1.14). The use of triazines in OLED applications has not been limited to polymers, and indeed there are various publications and patents regarding electroluminescent small molecules containing a triazine unit. Triazines can act as electron-transporting material as well as hole-blocking material,[54,55] and have therefore been widely applied in OLED research.

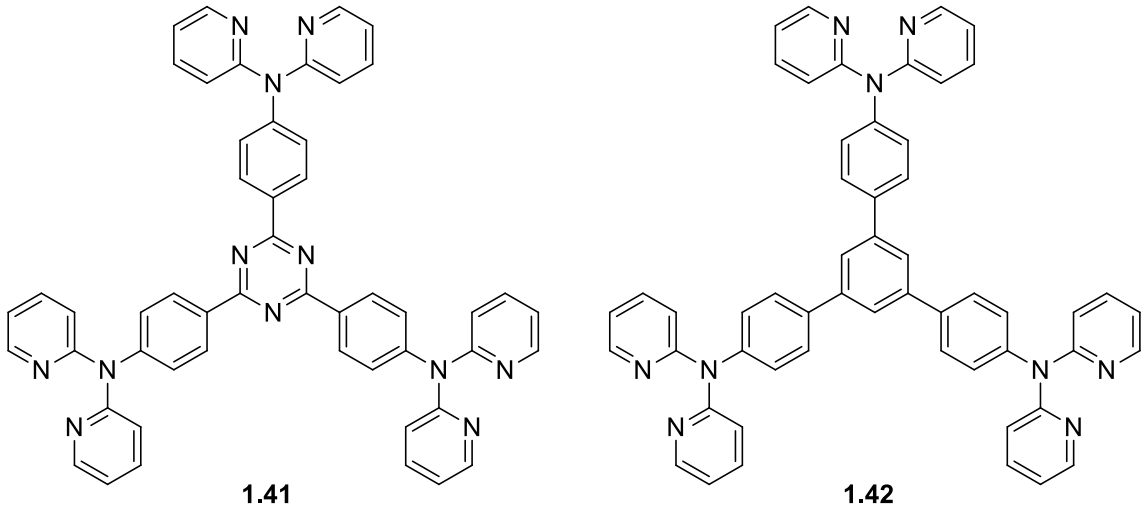
Of the triazine-based molecular materials used inOLED, 2,4,6- triphenyl-1,3,5-triazine is popular and its application in OLED as a hole-blocking material can be traced back to the last century. However, up until recently its use were limited because it shows poor performance in devices.[84] Much effort has been made to improve the properties of the triazine-based materials, mainly concerning introducing different substituents into a triazine ring, for example phenylnaphthalene[85], carbazole[86] and pyridine[87,88] groups. In more recent years, triazine has bee studied also as a possible moiety for hole-blocking material both in polymers and in small molecules.[54,84,87,89-91] However, satisfactory triazine-based materials are still very rare.

One of the first to study triazine as a possible hole-blocking material was Schmidt[54] who incorporated the triazine moiety into polyether PLED applications. However, for use in multilayer LEDs fabricated by vapor deposition or by blending in a polymer matrix, polymers are not a viable option, and amorphous low molecular weight compounds are needed. Some low molecular weight compounds such as oxadiazoles and triazoles had already previously found an application as hole blocking electron transferring (HBET) material in multilayer LEDs, [92-94] and since 1,3,5-triazines have a comparatively

higher electron affinity than 1,3,4-oxadiazoles and 1,2,4-triazoles, indeed the dimeric triazine ethers synthesised by Schmidt resulted to be good electron-transfer hole-blocking materials in OLED devices.

From the year 2000 onwards, the increase in the use of the triazine moiety in possible electroluminescent small molecules has been exponential, and a simple search of these compounds provides hundreds of articles and patents. The electron carrier properties, as well as the inherent electroluminescence properties of a triazine core, make it an interesting target. In addition, the EL of these compounds can be easily tuned by changing the substitution on the triazine ring.

Starburst or star-shaped organic molecules are an attractive class of molecules for OLEDs mostly because of their good film-forming properties.[95-98]4 In the early 2000s, Wang et al.[87] synthesised a small group of star-shaped organic compounds based on di-2-pyridylamine and 7-azaindole and fabricated electroluminescent devices using these compounds as the emitters. All four compounds synthesised were bright photoluminescent blue emitters. Although all four compounds were capable of functioning as blue emitters in electroluminescent devices, the two large star-shaped molecules shown in figure 1.25 gave the most promising – and very similar – results.



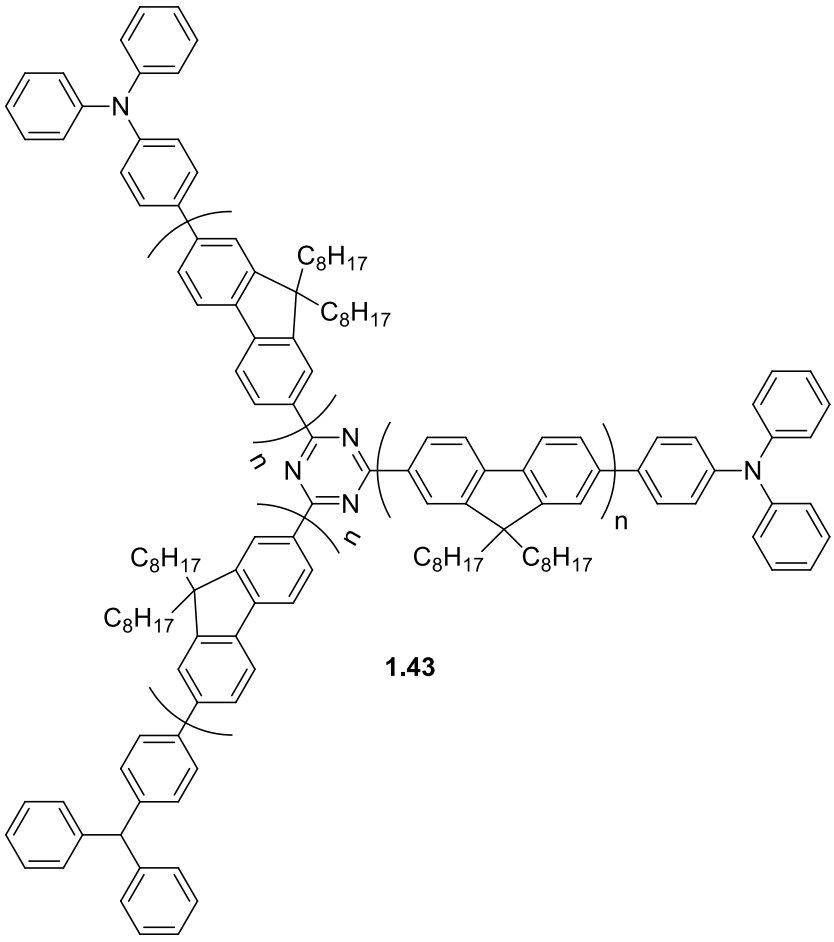
1.41 **1.42**

Figure 1.25

Star-shaped molecules used as blue emitters by Wang et al. **1.41** has a triazine core, whereas **1.42** has a phenyl core.

Some years later also Fang[99] designed and tested star-shaped smOLEDs with a triazine core with good results. The highly soluble compounds synthesised by Fang (Figure 1.26) were also blue-emitting, and when tested in OLED devices showed increased luminance compared to the molecules tested

previously by Wang. The molecules synthesised by Fang are somewhat larger in size, and contain aliphatic side chains that further inhibit aggregation.



1.43

Figure 1.26

Star-shaped molecules studied by Fang. The best results were obtained when n = 1.

Both Fang[99] and Wang[87] have used the triazine unit as a central core in the molecules, whereas Burn *et al.*[100] have tested a molecule where the triazine moiety is used as a peripheral unit in an elongated conjugated system with a distyrylbenzene core (Figure 1.27). In this case, the triazine moieties act as electron transporting components, whereas the distyrylbenzene core functions as a blue emitting component. Burn noted that the triazine moieties with simple substituents rendered the molecule highly soluble, without affecting the EL properties of the chromophore. Unfortunately these molecules were rather unstable, possibly due to the phenoxy linker.

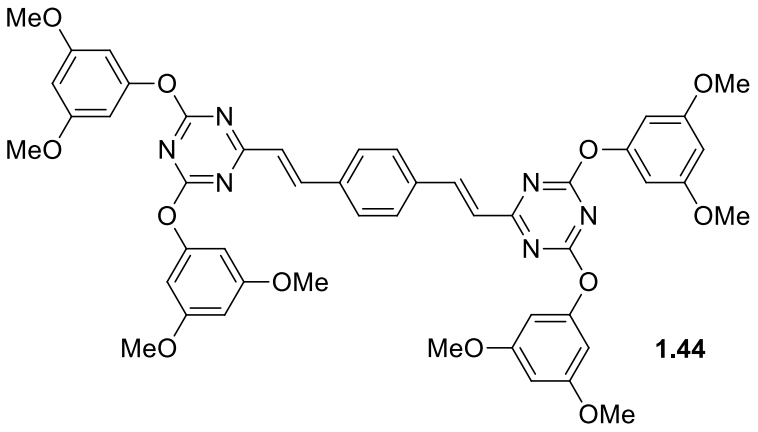


Figure 1.27

Adachi[86] and his coworkers synthesized four 2,4,6-tris(diarylamino)-1,3,5-triazine derivatives with electron-donating substituents and examined their OLED characteristics. Of these, in particular, 2,4,6-tris(carbazolo)-1,3,5-triazine (**1.45**, Figure 1.28) demonstrated a very high external electroluminescent quantum efficiency. The results were hardly surprising, considering that the carbazole units had already given good results PLED applications in earlier studies.[101,102] Also Gong *et al.*[103] have studied carbazole derivatives of triazines and have constructed a white-light emitting OLED combining the red-orange triazine carbazole-based emitter (**1.46**, Figure 1.28) with a blue-green 8-hydroxyquinolinolate lithium emitter. This is a notable achievement, since one of the biggest hurdles in OLED research is the generation of pure white light.

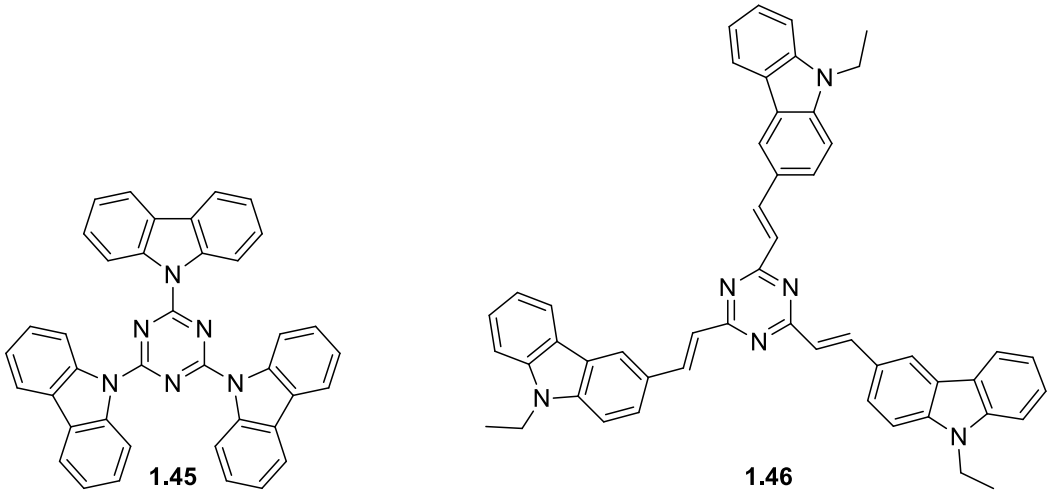


Figure 1.28

The triazine carbazole compounds studied by Adachi (**1.45**) and Gong (**1.46**).

Adachi later extended his research to carbazole and phenoxazine derivatives of triazine that exhibited thermally activated fluorescence (TADF).[77,104-106] TADF materials have attracted attention as third-generation OLEDs because of their high EL efficiency and lack of rare metals such as Ir and Pt. The carbazole substituted triazine **1.47** showed good emitting properties with emission peak in the blue-green region, whereas the mono-, bis- and tris-phenoxazine triazines demonstrated a gradual red-shift going from green to orange when the substituent number increased (figure 1.29).

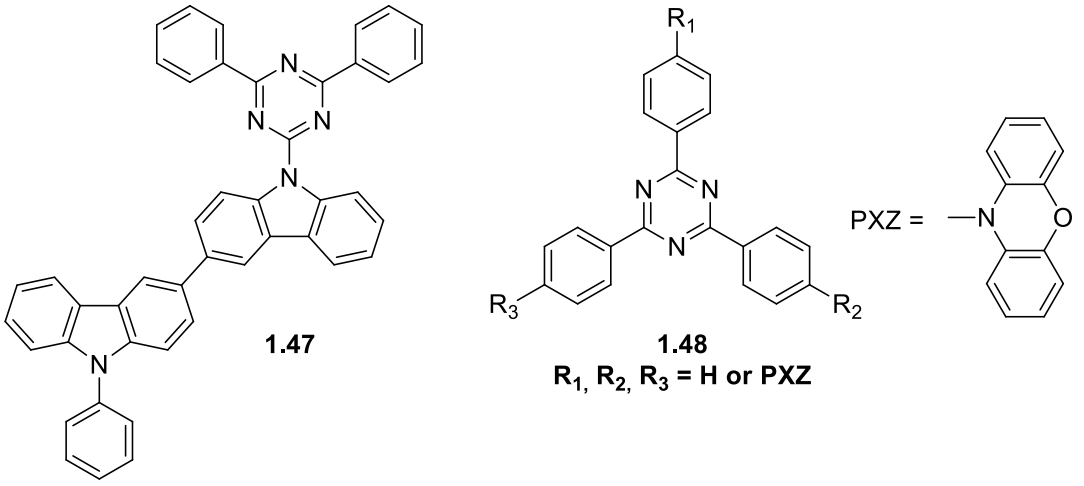


Figure 1.29

Carbazole and Phenoxazine derivatives of triazine that showed good TADF.

Whereas the triazine-based emitter synthesised by Gong functions in the red-orange area, a similar carbazole-substituted triazine synthesised by Strohriegl *et al.*[107] was used as a host for an Iridium blue-green emitter. The compounds synthesised by Strohriegl had both carbazole and phenol substituents. Changing the substituent patterns changed both the physical properties of the molecules as well as their triplet energies; the successive replacement of up to two carbazoles by phenoxy groups (Figure 1.30) yielded asymmetric amorphous materials with glass-transition temperatures up to 170 °C and triplet energies up to 2.96 eV.

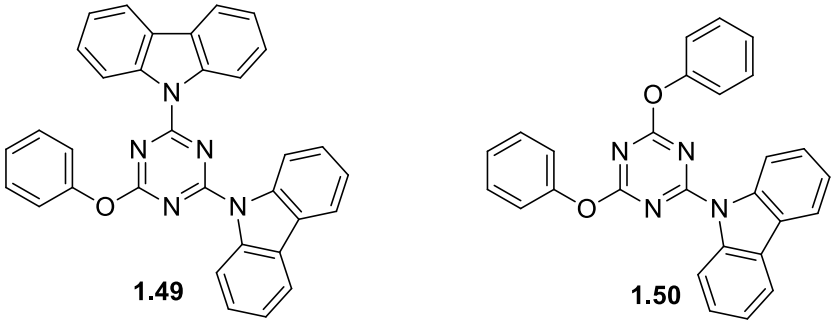


Figure 1.30

Carbazole- and phenoxy-substituted triazines used as host material by Strohriegl.

Zhong *et al.*[90,108] have studied triazines and their applications in OLEDs starting with bitriazines with biphenyl-, phenyl-, or fluorene substituents (**1.51**, Figure 1.31). Later on they extended their studies to conjugated triazines that had phenylfluorene substituents (**1.52** and **1.53**, Figure 1.31). A 1,3,5-triazine unit is a typical electron-accepting unit, and introducing a 1,3,5- triazine unit into the backbone of conjugated compounds usually improves the electron-injection and electron-transportation abilities of the compounds. Zhong hypothesised that the bitriazine derivatives may have stronger electron-accepting ability and ease of forming metal chelates. Unfortunately, overall poor performance of the devices suggested that the reported triazines were not suitable for electron transporting materials. Instead, when the phenylfluorine-substituted triazines were incorporated into OLEDs and PLEDs as electron transport/hole blocking materials, the performance of the OLEDs and PLEDs increased noticeably. Zhong demonstrated that introducing more electron-donating groups and extending π-conjugation into a triazine ring can turn the optimal energy levels and band gaps of the molecules, resulting in the improvement of the optoelectronic properties of the molecules.[90]

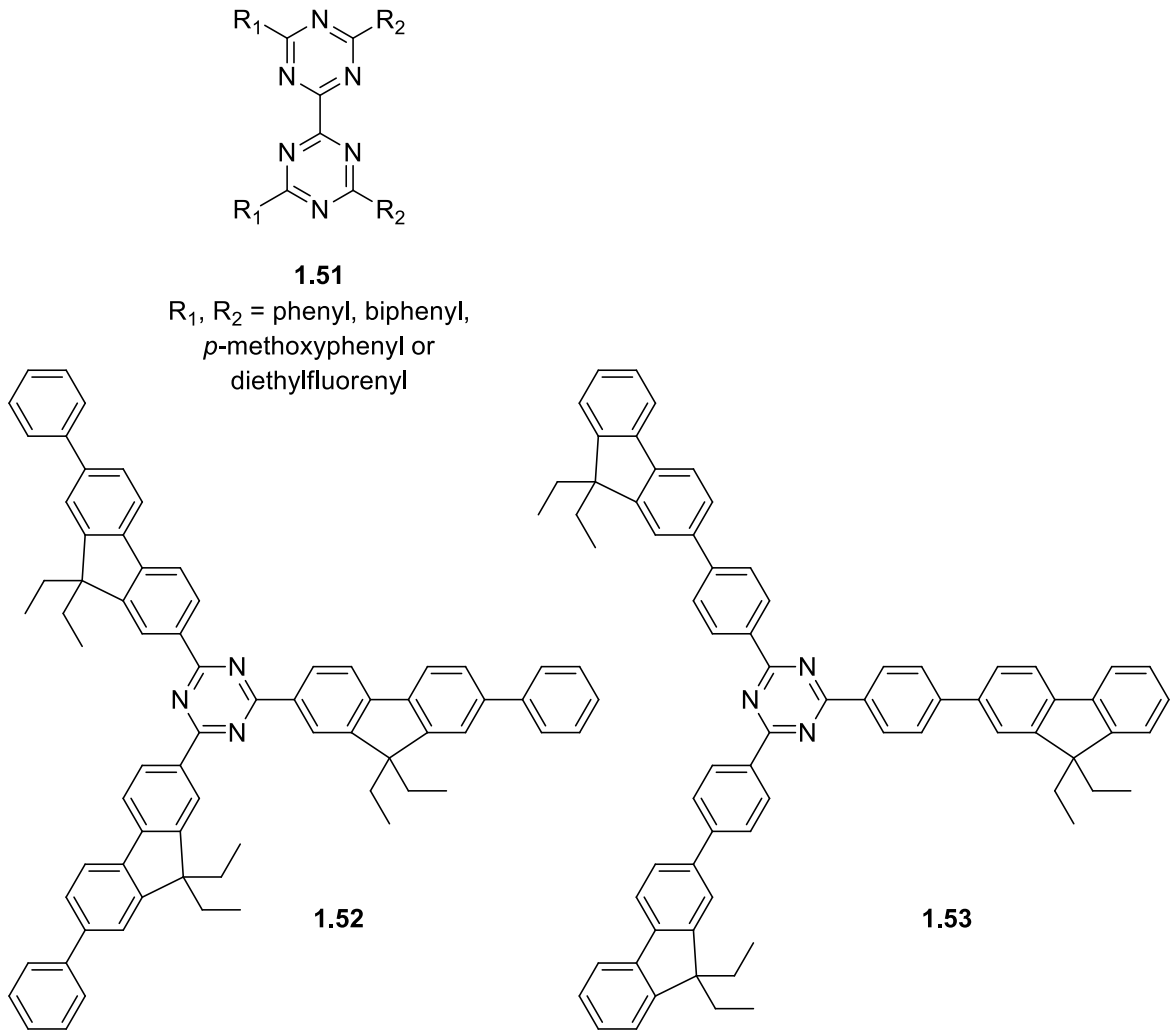
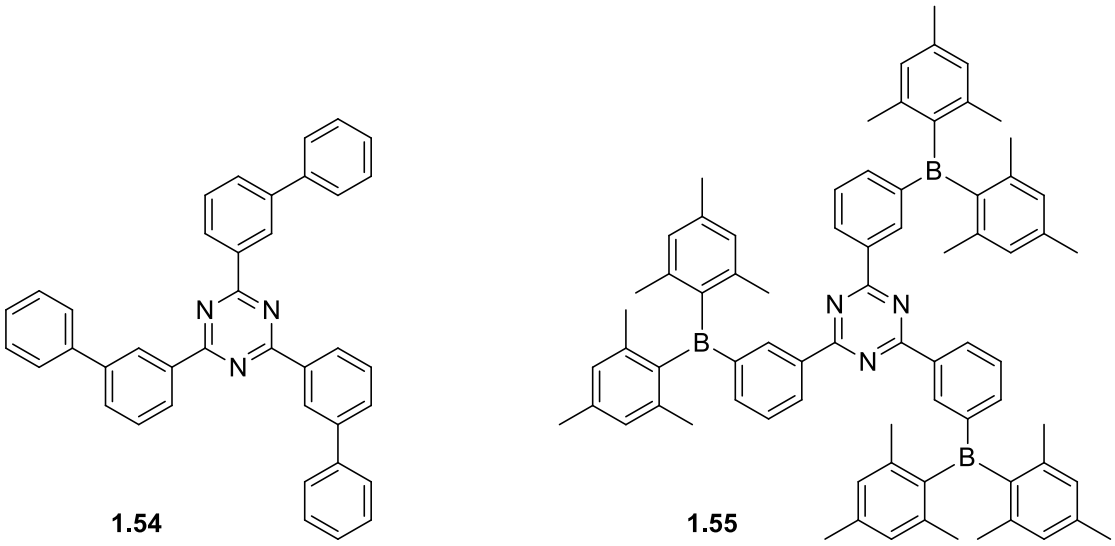


Figure 1.31

bistriazene and substituted triazenes synthesised by Zhong.

Molecules with a triazine core have been applied to phosphorescent light-emitting diodes by Wong and his collaborators.[109] PhOLEDs have attracted considerable attention because they effectively harvest electrogenerated singlet and triplet excitons to achieve nearly 100% internal quantum efficiency.[1,4] One strategy towards highly efficient PhOLEDs is to suppress detrimental effects such as aggregation quenching and triplet–triplet annihilation by employing suitable host materials that can accommodate the emitters homogeneously.[110-112] Wong constructed devices with $(PPy)_2Ir(acac)$ as the phosphorescent emitter and triazine-based molecules as the electron transfer layer with good efficiencies. The devices featuring compound **1.54** as host material (figure 1.32) provided the best balanced electron/hole recombination within the emitting layer with external quantum efficiency of 17.5%.



1.54 **1.55**

Figure 1.32

Triazine with diphenyl substituents used on a PhOLED by Wong (**1.54**) and a Polyboryl-Functionalized Triazine used as an electron transport material by Wang (**1.55**).

Another host material for phosphorescent emitters was synthesised by Wang and coworkers in 2011.[113] This new pinwheel-like triazine molecule (**1.55**, Figure 1.32) was functionalized by three $BMes_2$(m-Ph) groups and it was found to have a low LUMO (Ea = 3.25 eV) and a deep HOMO (6.73 eV) energy level with a high triplet energy level (3.07 eV) and is thus very promising as an electron transport material for phosphorescent OLEDs. Preliminary studies showed that it is indeed a very effective electron transport material for OLEDs with the green phosphorescent compound $Ir(ppy)_2(acac)$ as the emitter.

An interesting triazine-based emitter was designed and synthesised by Giménez *et al.*[114] (Figure 1.33). This structure is highly electron-deficient – with three triazolyl rings – giving it good electron transfer properties. Extension of the conjugation in the molecules **1.56** with terminal benzyl rings gives them their characteristic luminescent properties. All the tested compounds are luminescent, emitting in the blue-green part of the visible spectrum. A remarkable red-shift in the emission maximum is observed as the number of peripheral alkoxy chains increases. The compounds also show luminescence in thin films at room temperature with emission wavelengths similar to those of the solutions. These materials also showed good liquid crystalline properties, exhibiting ordered columnar mesophases. Electrochemical measurements confirmed the electron-deficient nature of this class of compounds and their potential for electron transport.

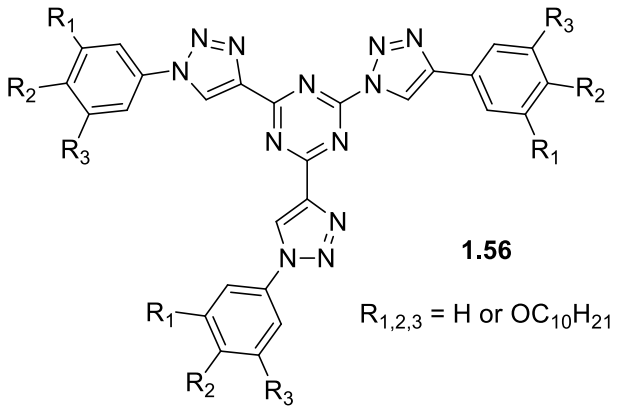


Figure 1.33

Gimenéz et al. synthesised and tested a hybrid triazine molecule with good electron transfer and electroluminescence properties.

1.4 Effect of a Heterocycle in an OLED structure

Most of the organic fluorophores and host materials used for OLEDs are either based on small molecule N-/S-/O-heterocyclic compounds, their metal complexes or polymers containing heterocyclic scaffolds such as carbenes, benzoquinolines, quinoxazolines, oxazoles, fused thiophenes and pyridines.[1,56,115-117] Heterocyclic compounds are particularly interesting because heterocyclic rings give these materials high electron affinity and ionisation potential. These conditions favour electron injection at the cathode and make these compounds attractive as hole blocking/electron transfer layers.[1,83]

One of the most important aspects in the design of OLEDs, as with all lighting applications, is energy efficiency. To improve the electricity-to-light conversion efficiency of PhOLEDs, their external quantum efficiency must be improved, and operating voltage decreased. The improvement of functional materials such as host materials and carrier transport materials, especially electron transport materials, is one of the most important factors in reaching these targets. In order for the OLED to be as efficient as possible, it is important to have both the HOMO and LUMO levels of the emitter as well as the possible host material as low as possible. An efficient way of lowering the HOMO and LUMO levels is introducing nitrogen containing heterocycles into the molecule.[83] Introduction of a nitrogen atom into an aromatic ring lowers its HOMO and LUMO levels, and the introduction of a second and a third nitrogen atom onto the system further lowers these levels, which makes the use of pyridines, pyrimidines, triazines and their various analogs in the research for new functional materials interesting.

One of the less studied heterocycles in OLEDs is quinoline, although there are some examples of benzoquinolines in OLED applications, especially in emitting molecules.[66] Quinolines and poly(quinoline)s have high electron mobilities, good thermal stability, high photoluminescence

efficiencies and good film forming properties, which are crucial for their use in OLEDs.[118-120] Although quinolines and their derivatives are not yet in use on commercial applications, they show great promise in the field of photoluminescence. Another less studied but not less interesting heterocycle is indole. Indoles and their derivatives have been studied as emitters in OLEDs. These small molecules, with both electron-donating and electron-withdrawing substituents on the indole ring, have shown great promise as blue light emitters.[121-123]

The choice of the host material when metal-containing phosphors are used is very important in LEDs and OLEDs. The host material must be designed in a way in which the host material is capable both of transporting holes and electrons, as well as tranferring energy from the host material to the phosphor. In fact, without a suitable host material the metal-containing emitting material can have its exiton stages quenched by a neighbouring emitter. With host materials this problem can be circumvented, since dispersing transition metal-containing phosphors into suitable host materials can reduce the quenching processes associated with the relatively long lifetimes and triplet–triplet annihilations of triplet excited states. This method also allows harvesting both singlet and triplet excitons efficiently, making it possible to prepare organic light-emitting devices (OLEDs) exhibiting 100% internal efficiency. Most of the efficient host materials reported are hole-transporting (HT) compounds with heterocycles embedded in their structures — in particular, carbazole-based organoaryls, whereas electron-transporting (ET) host materials are relatively rare.[124]

Poor charge carrier mobility and unbalanced charge recombination in the emitting layer are detrimental to the power efficiency of OLEDs.[1,125] To improve the carrier drift mobility and achieve good charge balance, ET-type high-triplet-energy host materials with low electron injection barriers, capable of holeblocking, and with high electron mobilities are promising candidates for reducing the operating voltage and improving the device performance. In addition to the triplet energy, suitable thermal stability and energy levels are also critical when designing ET materials. The designed molecules should form morphologically stable and uniform amorphous films when using typical processing techniques. The use of electron-deficient heteroarenes embedded small molecules has proved very useful for improving balanced charge injection and subsequent recombination in OLEDs.[42,86,109,124]

One of the many heterocycles studied for their applications on OLEDs are triazines. Triazine has larger electron affinity than those of other typical electron-deficient heteroaromatic rings like pyridine and pyrimidine. As a result, triazine derivatives are electron-deficient heterocycles that are employed widely as active materials in OLEDs.[109] There are various reports on OLEDs using triazine derivatives as an electron transport-hole/blocking layer.[54,87,91,100] However, most compounds form charge transfer complexes between triazine and the adjacent organic layers, demonstrating that the triazine core has strong electron-accepting characteristics. The triazine ring may be so strong in terms of electron affinity that it prevents fast movement of electrons through the layers. This can be modified to some extent with the substituents on the triazine ring, with polarized molecular structures having slower carrier mobilities.

Introducing electron-donating substitutes may provide a possibility of finding compounds with the electronic properties required for electron transport and host layers that are required for efficient functional materials for OLEDs.[86]

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2. Synthesis of Substituted Triazines

2.1. Introduction

As can be seen in chapter 1.3, substituted triazines have been used in OLEDs both as hole-blocking/electron transfer material, and as emitters. Many of the triazines synthesised are highly conjugated and show promising properties for applications in OLEDs. Triazines can also be used in LEDs as organic phosphors, and therefore it was decided to synthesise a small library of substituted triazines and research their potential first and foremost as possible electron transfer material in OLEDs, and then later on to extend the scope to possible use in LEDs to substitute the rare earth metals on which the LED applications nowadays are highly dependent. As the studies of these compounds in OLED applications are not yet concluded, the results in this chapter will focus mainly on the synthesis of these compounds and on the preliminary data obtained from optical properties studies.

The main structure of the triazines synthesised consists of a triazine core substituted with three anilines, or with two anilines and a two-carbon thiol spacer that is then used to attach the molecules onto gold nanoparticles *via* a sulphur bond. Some triazines with an aromatic ring attached directly onto the triazine core and with phenol ether substituents were also synthesised to evaluate the effect of the NH group. For all of the compounds their absorption spectra, emission spectra and structural and vibrational properties were evaluated. The compounds proved to be more promising for applications in LED as organic phosphors, and therefore in the end the studies were directed more towards the applications in LEDs than in OLEDs.

2.2 Synthesis of substituted triazines

Triazines are very active molecules and readily react with electrophiles. Nucleophilic substitution of either one or all of the chlorine atoms is very easy to carry out with the aid of both organic and inorganic bases. There are various approaches for the synthesis of triazines substituted with either three identical anilines, or with two or three different aniline substituents.[1-4] The degree of substitution can be easily controlled by modifying the reaction temperature. Substitution of the first chlorine occurs readily even at 0 °C, whereas the substitution of the second chlorine in a monosubstituted triazine requires the reaction to be carried out at room temperature. When the temperature of the reaction exceeds 60 °C, even the last chlorine atom will react and a triazine with three aniline substituents will be obtained. The ease of control in the substitution of triazines renders these reactions facile, whereas the low solubility of the trisubstituted products provides some challenge in the isolation and purification of the products.

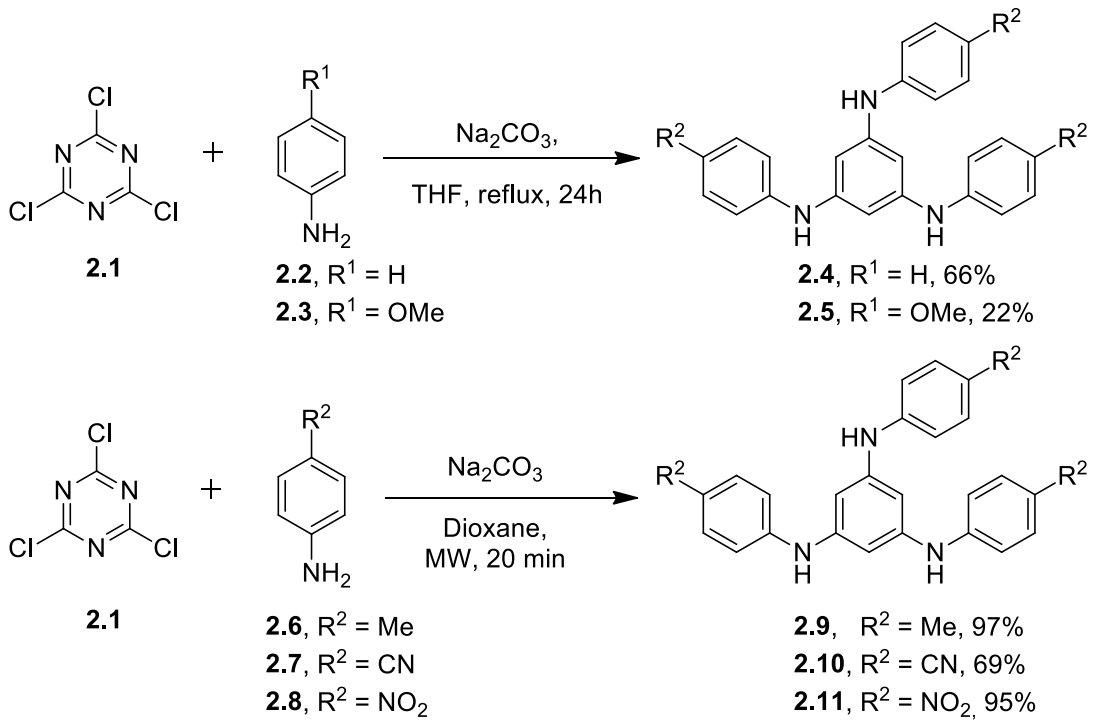
Although there are various existing strategies for the synthesis of triazines,[1,5-8] none was followed directly. The synthesis of each individual molecule was evaluated singularly taking into consideration the solubility of the starting materials and the products, their stability, cost and the ease of purification. Although the choice of method for each individual product presented here can at first sight seem arbitrary, the approach giving the best overall results was chosen (and reported) in each case.

2.2.1 Synthesis of triazines with three aniline substituents

A small group of triazines with three aniline substituents was synthesised to test their optical and electronical properties. Anilines with substituents in position 4 were chosen for these initial studies to have perfectly symmetrical molecules.

Methyl-, methoxy-, nitrile- and nitro substituents, as well as unsubstituted aniline were selected for the synthesis of trisubstituted triazines and testing of their optical properties. The substitution of the first two chlorides on the triazine ring with any of these substituents was very straightforward and worked well with all of the chosen substituted anilines, whereas the substitution of the third position proved challenging due to the low solubility of disubstituted triazines. Therefore either low concentrations or very polar organic solvents were necessary. Also prolonging the reaction time ensured that while the reacted disubstituted triazine crashed out from the solution more disubstituted triazine dissolved and reacted. More equivalents of the anilines were also necessary in some cases to ensure the complete conversion to trisubstituted triazine. As the trisubstituted triazines were highly insoluble, in many cases purification was possible only through washing off unreacted or partly reacted compounds, and subsequent recrystallisation.

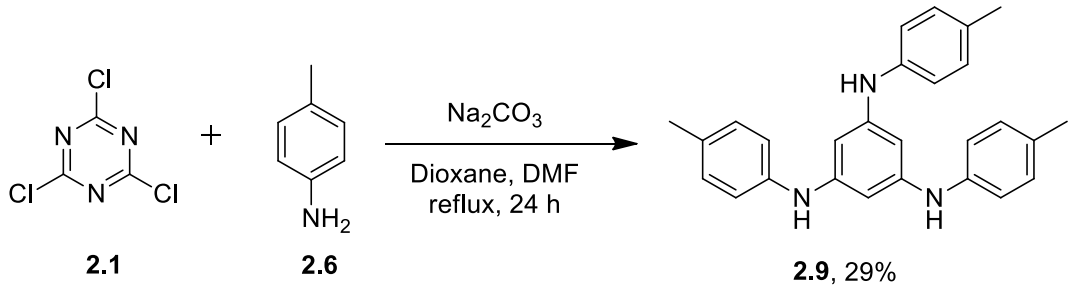
The synthesis of unsubstituted **2.4** and 4-Methoxy- substituted **2.5** proceeded well in THF with DIPEA as a base. A slight excess of both base and aniline was used to ensure the complete transformation to the trisubstituted triazine (Scheme 2.1). Both of these compounds were easy to purify *via* column chromatography, and analytical samples were also recrystallized from ethanol. Nitro- and nitrile substitutions caused some problems of solubility especially in the case of the nitro compound **2.11**, and it was not possible to introduce the third substituent onto the triazine core using the abovementioned method. The pure compounds were instead obtained very easily using a method described by Sha,[2] with dioxane as solvent, an inorganic base and microwave heating (Scheme 2.1).



Scheme 2.1

Synthesis of symmetrical trisubstituted triazines with *para*-substituted anilines.

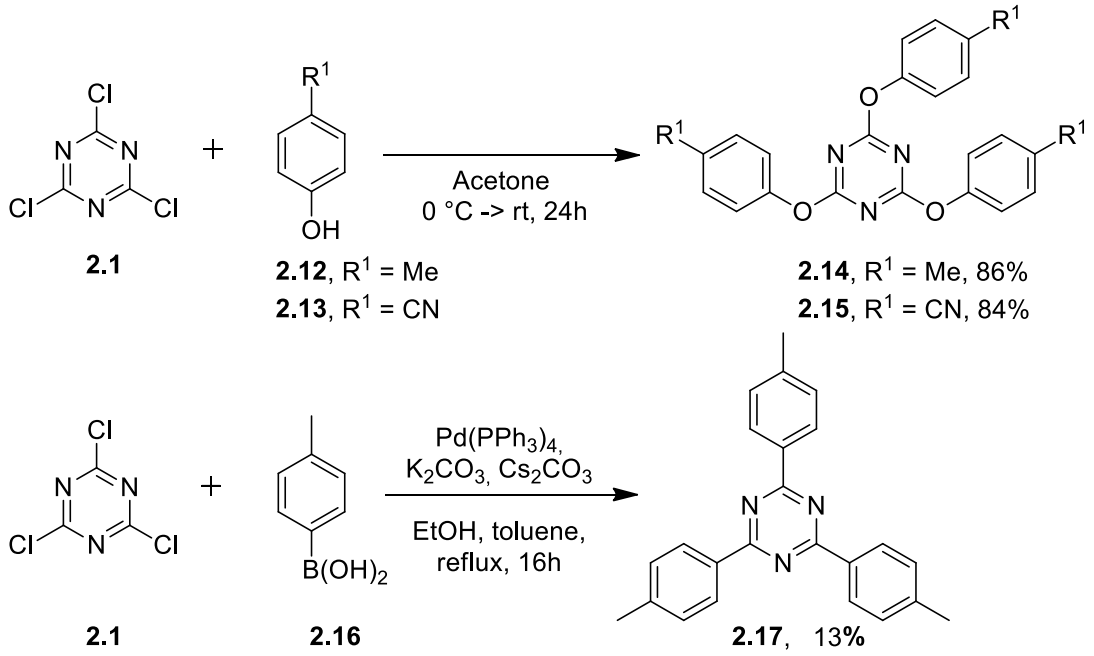
2.9 could also be synthesised using an alternative method where the reagents were heated at reflux in a mixture of dioxane and DMF (Scheme 2.2). An excess of reagents was used to ensure complete conversion, although the reaction can probably be carried out also with stoichiometric quantities.



Scheme 2.2

Synthesis of **2.9** *via* traditional heating.

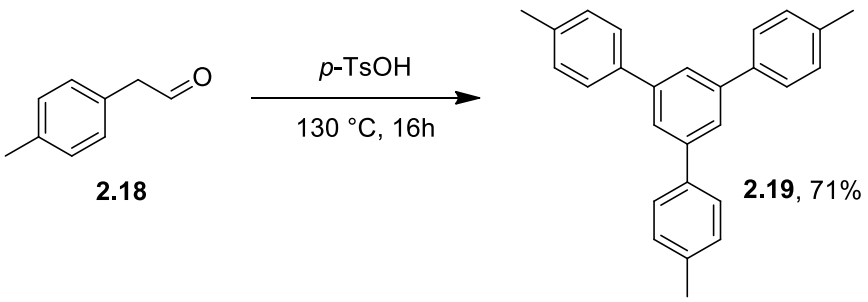
To study the effect of the NH group on the properties of the molecules, a selection of compounds where the NH bridge was either replaced with an ether bridge or eliminated altogether were also synthesised (Scheme 2.3).



Scheme 2.3

Synthesis of substituted triazines without NH bridge.

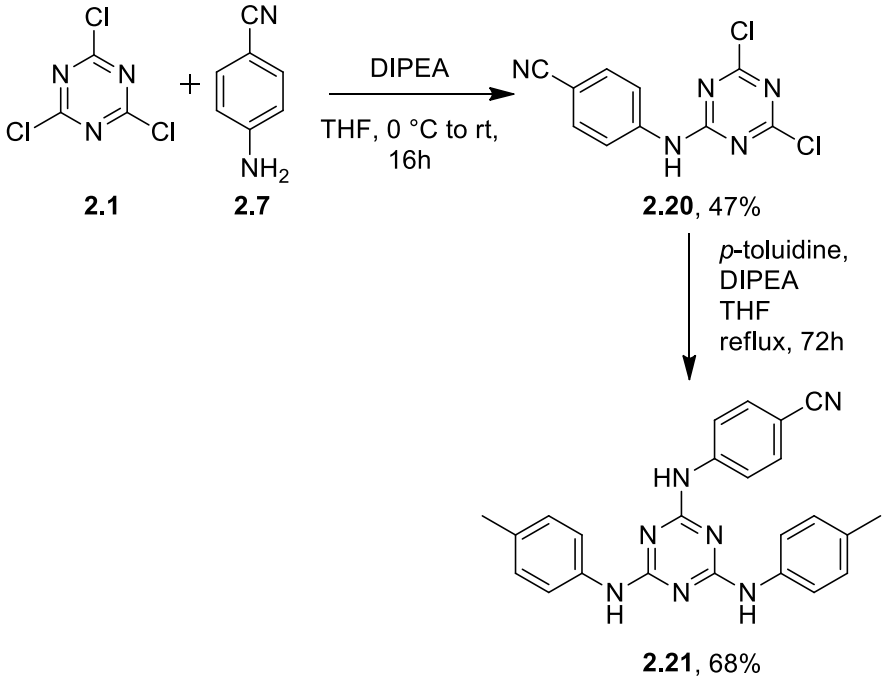
Although the yield for compound **2.17** was poor, since the compound was obtained in a sufficient amount, the reaction was not optimised. Also, a control compound without neither the triazine ring nor the NH bridge was synthesised (Scheme 2.4). A methyl substituted compound, **2.19**, was chosen because of the promising initial results of **2.9**.



Scheme 2.4

Synthesis of control compound **2.19**.

One unsymmetrical trisubstituted triazine was also synthesised, with one 4-cyanoaniline and 2 toluidine substituents (Scheme 2.5).



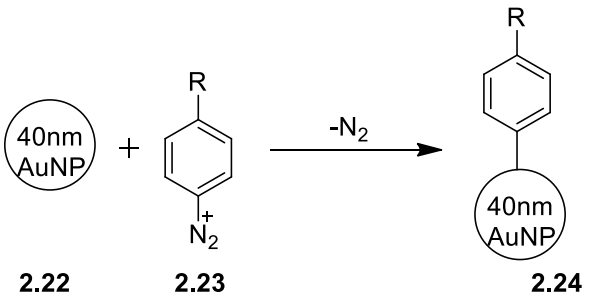
Scheme 2.5

Synthesis of unsymmetrical trisubstituted triazine **2.21**.

2.2.2 Synthesis of Disubstituted Triazines Linked onto Gold Nanoparticles

Many of the existing small molecules used as emitters in OLEDs are metal complexes.[9-16] On the other hand, also gold nanoparticles have interesting optical properties that can be exploited in optoelectronics.[17] Attaching a substituted triazine or another heterocycle onto a gold nanoparticle may be able to combine the properties of both the gold nanoparticle, and the organic molecule.

A recent publication by Laurentius *et al.*[18] reports a method for forming a covalent bond between a gold nanoparticle and an aromatic ring via a reaction between a diazonium salt of the aromatic compound and gold nanoparticles (Scheme 2.5).

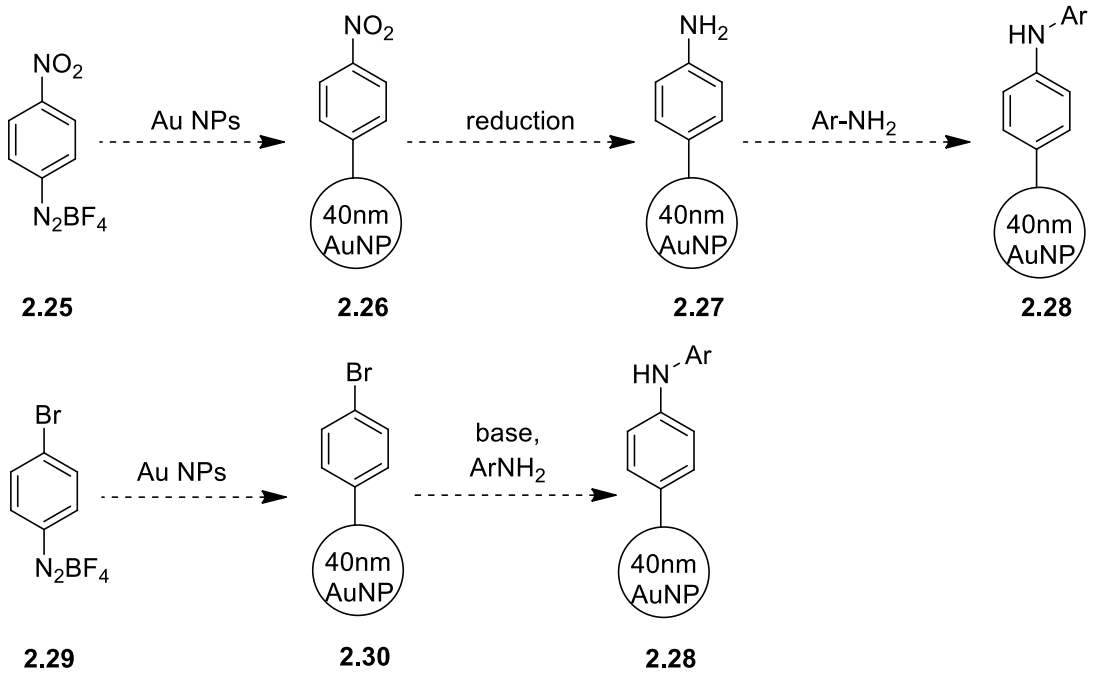


2.22 **2.23** **2.24**

Scheme 2.5

Synthesis of functionalised gold nanoparticles using diazonium salts.

Since the studies on the synthesis of functionalised gold nanoparticles with simple aromatic compounds by Laurentius[18] were promising, it was decided to synthesise a gold nanoparticle functionalised with either a nitro group or a halide (in particular, a bromide). The nitro group could be subsequently reduced to an amine that could in turn react with a triazine to give a gold nanoparticle with substituted triazines on the surface (Scheme 2.6). However, the reduction of a nitro group on a gold support can be challenging. An alternative route, a reaction of an aromatic halide on the surface of a gold nanoparticle with an aromatic amine was chosen as the more promising synthetic route to the desired compounds (Scheme 2.6).



2.25 **2.26** **2.27** **2.28**

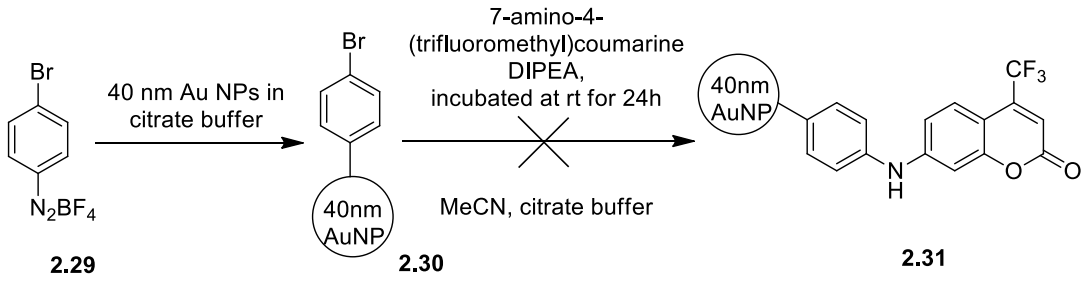
2.29 **2.30** **2.28**

Scheme 2.6

Possible synthetic approaches for functionalisation of gold nanoparticles.

Coumarins were chosen as the test compound in these reactions due to their optical properties. It is relatively easy to detect if a coumarin is attached onto the gold nanoparticle, and as coumarins themselves are strong chromophores their complex with gold nanoparticles may itself prove interesting in optoelectronic applications. The reasoning was that once the synthetic method is validated with the test compound, the synthesis can be extended also to triazines.

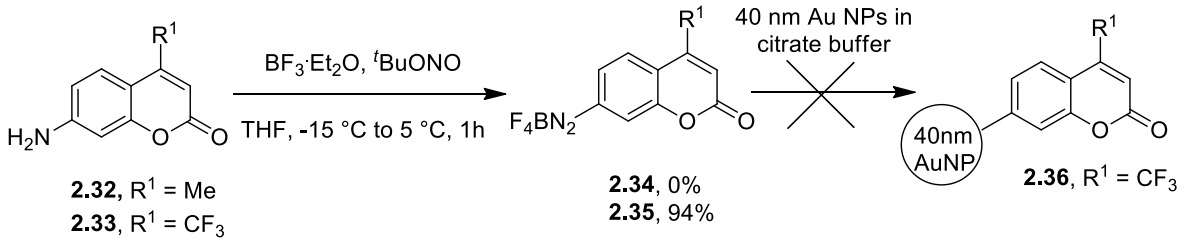
The synthesis of gold nanoparticles functionalised with a diazonium salt derived from 4-bromoaniline gave good results both in the yields and stability of the compounds (Scheme 2.7). However, the reaction of **2.30** with a 7-amino-4-(trifluoromethyl)coumarin did not give the expected results. In addition there were problems with the solubility of the other coumarins that were studied (7-amino coumarins and 7-amino-4-methylcoumarin), with only 7-amino-4-(trifluoromethyl)coumarin being soluble enough in the reaction conditions. Changing the base in the reaction to inorganic bases caused deterioration of the functionalised nanoparticles.



Scheme 2.7

Synthesis of diazonium salts and functionalisation of gold nanoparticles.

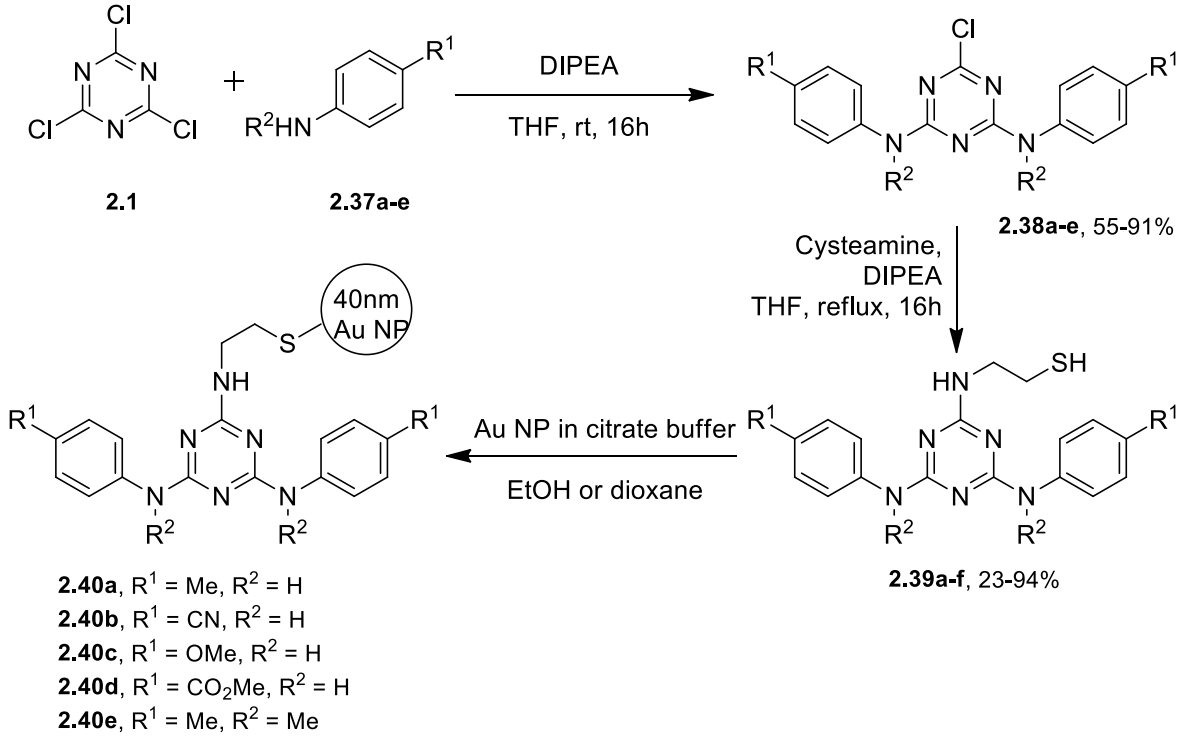
An alternative route to functionalisation would be the direct diazotisation of the aromatic molecule that is to be attached to the gold nanoparticle. To test this route a diazonium salt of a trifluoromethyl coumarin **2.33** was synthesised, as the diazotisation of methyl coumarin **2.32** did not give satisfactory results due to problems in solubility of the starting material. The diazotisation of **2.33** proceeded smoothly giving **2.35** in excellent yields. However, even after repeated attempts the reaction of **2.35** with gold nanoparticles failed to give the expected results, the main problem being the poor solubility of the diazonium salt. After these initial studies with substituted coumarins and anilines this route was abandoned. With the problems encountered already with simple molecules such as coumarins this synthetic approach was deemed not feasible with neither substituted triazines nor more complex heterocycles.



Scheme 2.8

Functionalisation of gold nanoparticles with coumarins.

Another common method for linking molecules onto gold nanoparticles in the use of sulphur bridges.[19-21] Gold-sulphur bond has been shown to be very stable, almost covalent in its nature,[21-26] and therefore it was decided to attempt the synthesis of disubstituted triazines attached onto gold nanoparticles by a gold-sulphur bond *via* a short spacer. Synthesis of the disubstituted triazines proceeded smoothly giving good yields of the product. Once two aromatic substituents were inserted onto the triazine moiety, the remaining chloride was substituted with cysteamine to give compounds **2.39a-e** in excellent purity (Scheme 2.7).

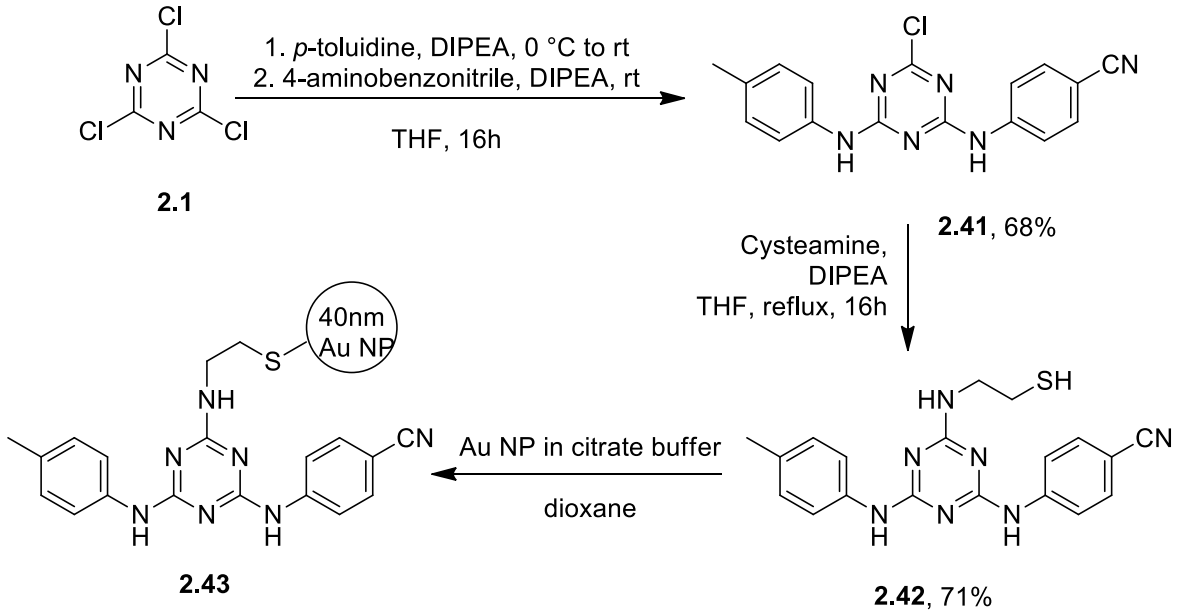


Scheme 2.7

Synthesis of gold nanoparticles functionalised with disubstituted triazines

Although it has been show that dithiol compounds bind to gold equally well, to avoid the formation of dimers the reaction with cysteamine was carried out in very dilute solutions.

Also **2.40f** with N-methyl groups was synthesised using the same strategy (Scheme 2.7). Gold nanoparticles functionalised with asymmetrically substituted triazine **2.42** were also synthesised, by reacting the trichlorotriazine **2.1** first with one equivalent of toluidine on ice, and subsequently with 4-aminobenzonitrile at room temperature. This gave disubstituted **2.41**, which was in turn reacted with cysteamine at reflux to give compound **2.42** (Scheme 2.8). The synthesised disubstituted triazines with a thiol linker were dissolved into either ethanol or dioxane, and reacted with gold nanoparticles in citrate buffer following literature procedures (Scheme 2.7 for compounds **2.40a-e** and Scheme 2.8 for compound **2.43**).[27] The initial studies on the gold linked triazines were promising, but unfortunately the compounds proved unstable during the optical studies, and the research was not continued further.



Scheme 2.8

Synthesis of **2.43**

2.3. Structural Characterisation of Trisubstituted Triazines

The structural characterisation of the synthesised compounds was carried out at University of Cagliari, Department of Physics by Prof. Carlo Ricci.

2.3.1 Optical Studies

Initial studies were carried out on all of the synthesised trisubstituted triazines. The optical absorbance of the compounds clearly shows that the substitution pattern on the triazines has a marked effect on the absorbance of the compounds (Figure 2.1).

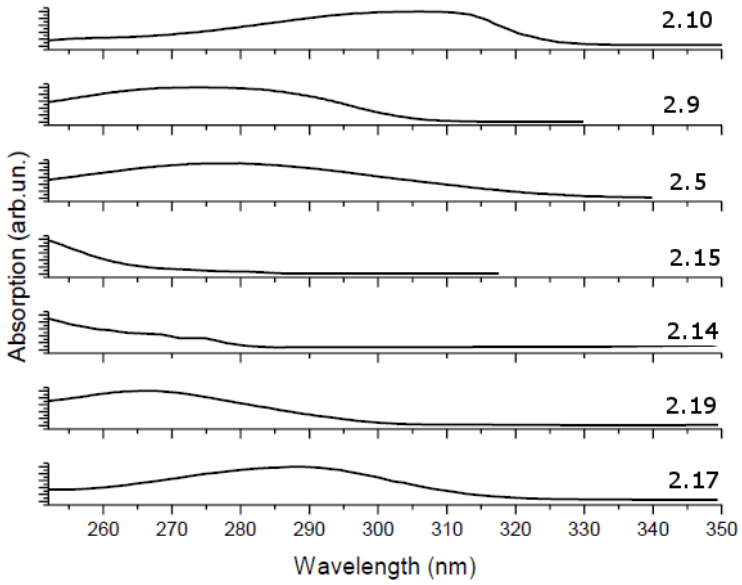


Figure 2.1

Optical absorbance of the trisubstituted triazines and reference compound **2.19**

A closer look at the absorption spectra of compounds **2.10**, **2.9** and **2.5** shows even more clearly the effect of the substituent on the absorption spectra, with the nitrile group in **2.10** giving a strong red-shift towards the visible region spectrum in comparison with the methyl substituted **2.9** and the methoxy substituted **2.5** (Figure 2.2).

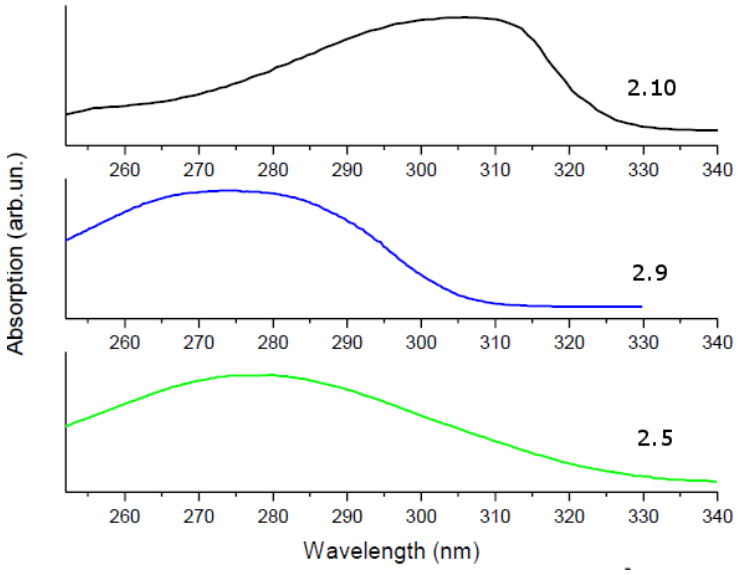
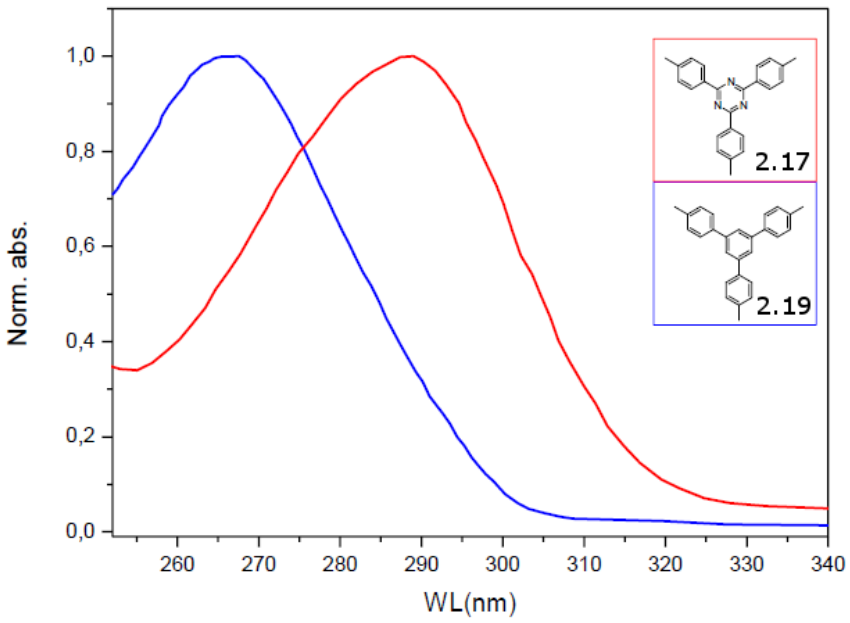


Figure 2.2

Optical absorbance of **2.5**, **2.9** and **2.10**.

In figure 2.3 the comparison of the absorption spectra of compound **2.19** with an aromatic benzene core with the absorption spectra of **2.17** that has a central triazine ring shows the effect of the triazine on the absorption spectra.



Scheme 2.3

Optical absorbance of compounds **2.17**and **2.17**.

The absorption of compound **2.19** with a central benzene ring lies in the blue region, with the absorption maximum at 265 nm, whereas with the triazine ring as the core of the molecule, the absorption maximum is shifted noticeably towards the visible region with the maximum at 290 nm.

The comparison of the spectra of compounds **2.10** and **2.15**, as well as compounds **2.9** with **2.14** emphasises the importance of the presence of the NH group between the triazine ring and its aromatic substituents. The optical absorbance of compounds **2.15** and **2.14**, where the NH group has been replaced by an ether bridge, show dramatic decrease in the optical absorbance value.

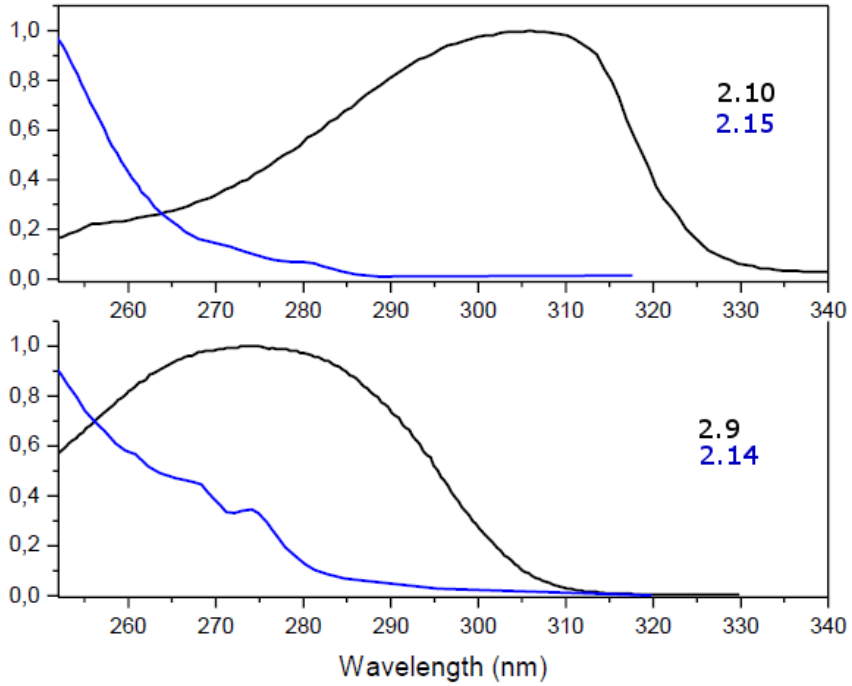


Figure 2.4

Comparison of the optical absorbance of **2.10** with **2.15**, and **2.9** with **2.14**.

The importance of the NH group can be further appreciated when comparing the absorbance of compound **2.14** with an ether bridge (Figure 2.4), compound **2.17** with the aromatic substituent directly attached onto the triazine ring (Figure 2.3) and compound **2.9** with an NH bridge. From these studies it is evident that both the presence of the triazine ring and the NH bridge are essential for optimal absorbance.

The theoretical and experimental absorbance spectra of compounds **2.5**, **2.9** and **2.10** were well in accordance, as can be seen by comparing the theoretical absorbance shown in figure 2.5 with the experimental absorbance shown in figure 2.2.

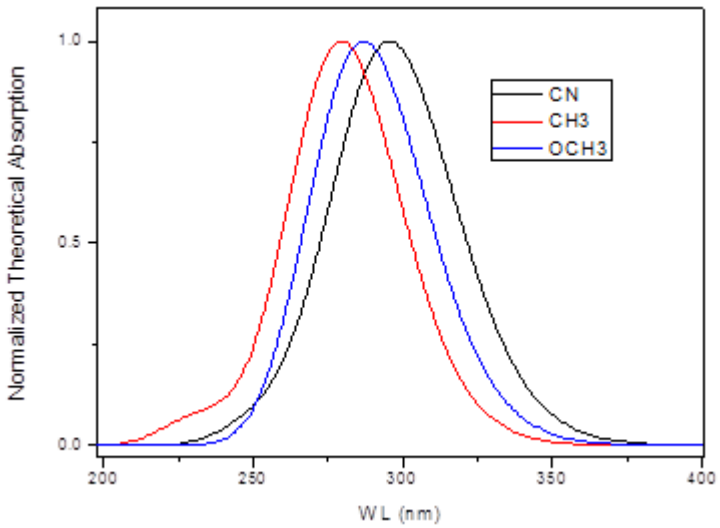


Figure 2.5

Theoretical absorbance of compounds **2.5**(OCH_3), **2.9** (CH_3) and **2.10** (CN).

The absorption-emission spectra of the most promising compounds, **2.5**, **2.9** and **2.10** were measured (Figure 2.5). It can be seen that the methoxy substituent does not give noticeable emission spectra, whereas methyl substituted **2.9** gives an emission with the maximum around 375 nm, and nitrile substituted **2.10** has an emission maximum at 420 nm.

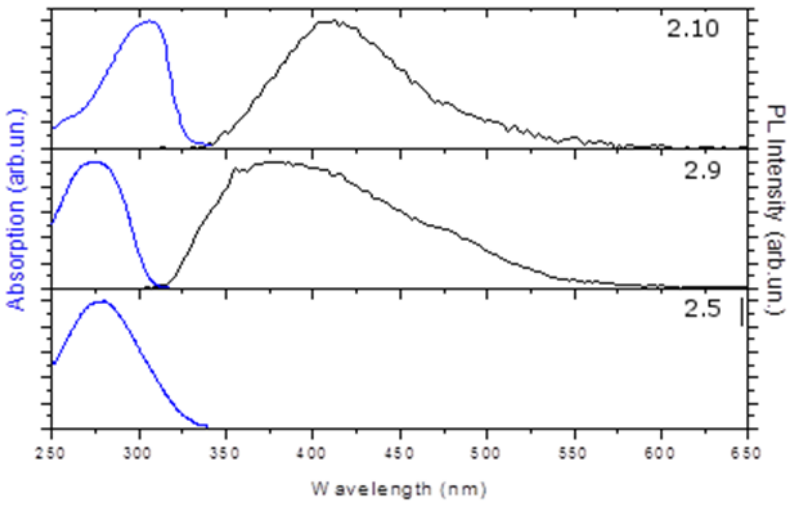


Figure 2.6

Experimental absorption and emission spectra of substituted triazines **2.10** with nitrile-, **2.9** with methyl-, and **2.5** with methoxyanilines as substituents. The excitation wavelength for each PL spectrum was in correspondence of the absorption maximum.

It is important to note again the exact correspondence between the theoretical and experimental data both in the vibrational frequencies and also in the optical absorption. These data further underline the exact structural features of the organic compounds and the main optical properties of the phosphors.

For deeper understanding of the kinetic mechanism, time resolved photoluminescence (TRPL) measurement were performed in the pico-second time domain (Figure 2.7). There are two different types of photoluminescence (PL) measurements: the more common stationary PL measurements, and time resolved photoluminescence measurements. In stationary PL measurements the sample is irradiated with a continuous light and the emission spectra is recorded. Instead, in TRPL the sample is irradiated with a pulsating light, where the length of the light pulse is shorter than the extinction time of the sample. In fact, TRPL is quite simply the measurement of the mean time of the intensities of luminescence rising from all of the recombinations from the optically active centres of the sample. TRPL allows to learn much more of the characteristics of the sample than simple stationary luminescence measurements in the way of quantum efficiency, kinetics of the excitation and time of life of the luminescence, and so even though these measurements require very sophisticated instruments, they are nevertheless very widely used.

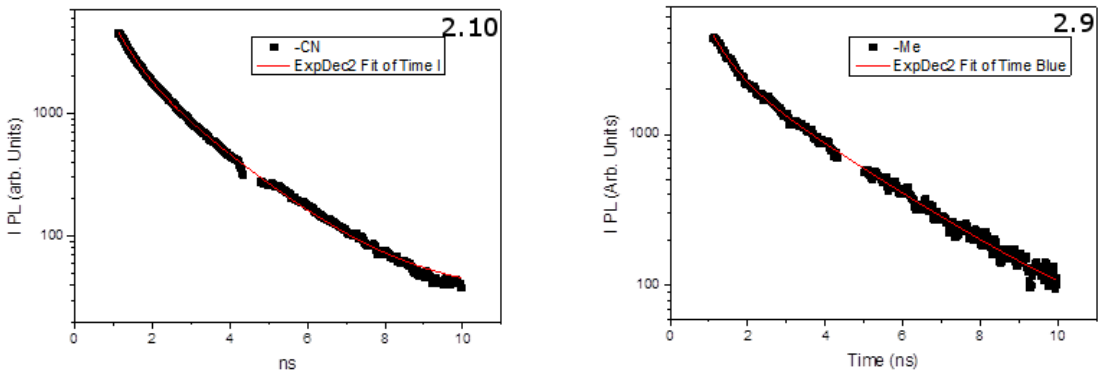


Figure 2.7

TRPL spectra of compounds **2.9** and **2.10**

The time resolved photoluminescence experiments carried out with thermally treated compounds that had been heated 200 °C show a shorter PL life by 10%, indicating a change in the crystal structure of the compounds at elevated temperatures (Figure 2.8). This change is much more evident in TRPL studies than in Raman spectra carried out at the same temperatures (Figure 2.10), and the 10% shorter PL life of the samples that have been thermally treated is a strong indicator of a structural change that takes place in these temperatures.

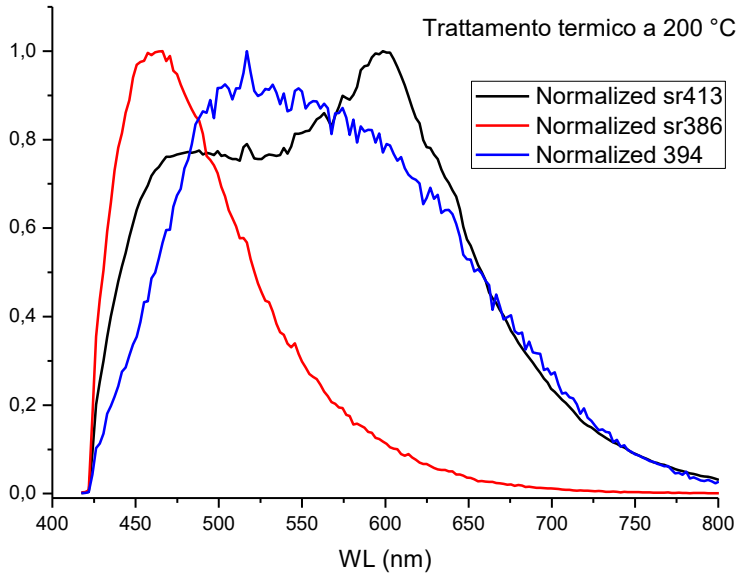


Figure 2.8

Photoluminescence experiments of **2.5** (black line), **2.9** (blue line) and **2.10** (red line).

2.3.2 Structural Studies

The Raman spectra were collected for compounds **2.5**, **2.9** and **2.10** and are reported in figure 2.9. The experimental Raman modes were compared with the theoretical frequencies computed accordingly. The experimental data was well in accordance with the calculated values (see Appendix 1).

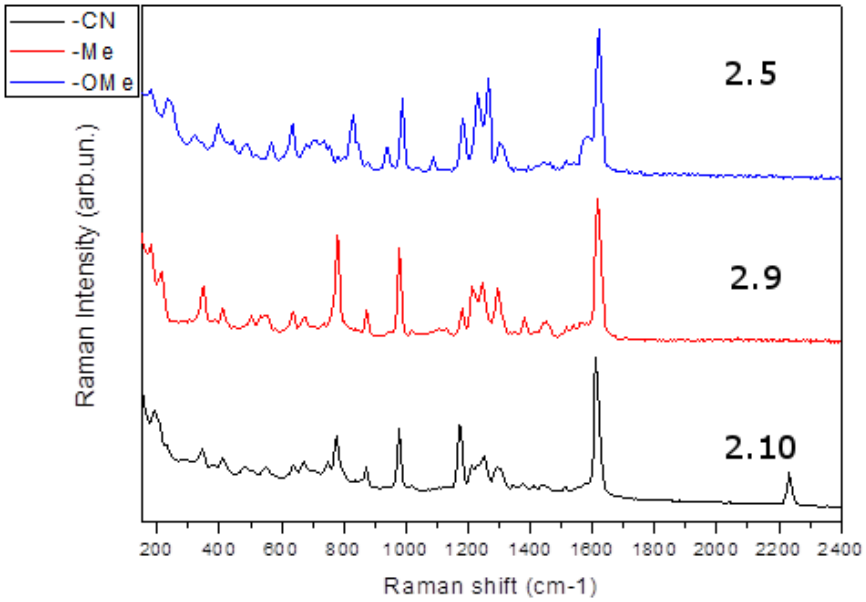


Figure 2.9

Raman spectra of compounds **2.5**, **2.9** and **2.10**.

Raman spectra of compounds **2.5**, **2.9** and **2.10** carried out at 200 °C show a lower intensity than spectra measured at 25 °C, indicating a slight change in the crystal structure of the compounds, but no other significant changes are present in the spectra (Figure 2.10).

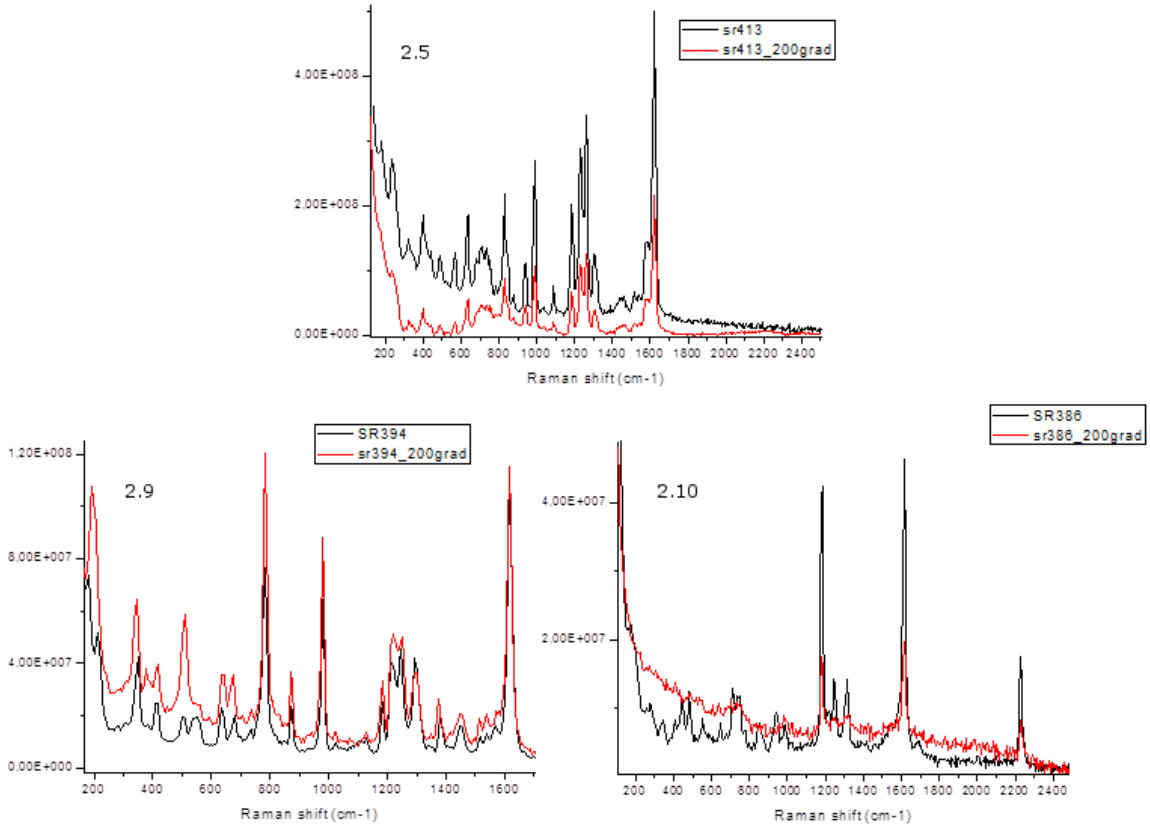


Figure 2.10

Comparison of Raman spectra of compounds **2.5**, **2.9** and **2.10** at room temperature and at 200 °C

In first photoluminescence experiments compound **2.9** exhibited a very curious and promising absorbance spectra with a double absorbance peak. The second absorbance peak, however, was not present in the successive samples when the compound was re-prepared, even though the physical characterisation remained otherwise identical presenting the same melting point, IR and NMR spectra, Raman spectra and physical aspect. The differences of the samples became evident only when XRD spectra of both the initial sample of compound **2.9** was compared with a successively prepared sample. As can be seen from figure 2.11 the XRD spectra of the two samples, although similar to some extent, present noticeable differences. This can be attributed to the different spatial arrangement of the molecules in the crystal that also affects the optical properties of the samples, creating the differences seen in the absorbance spectra.

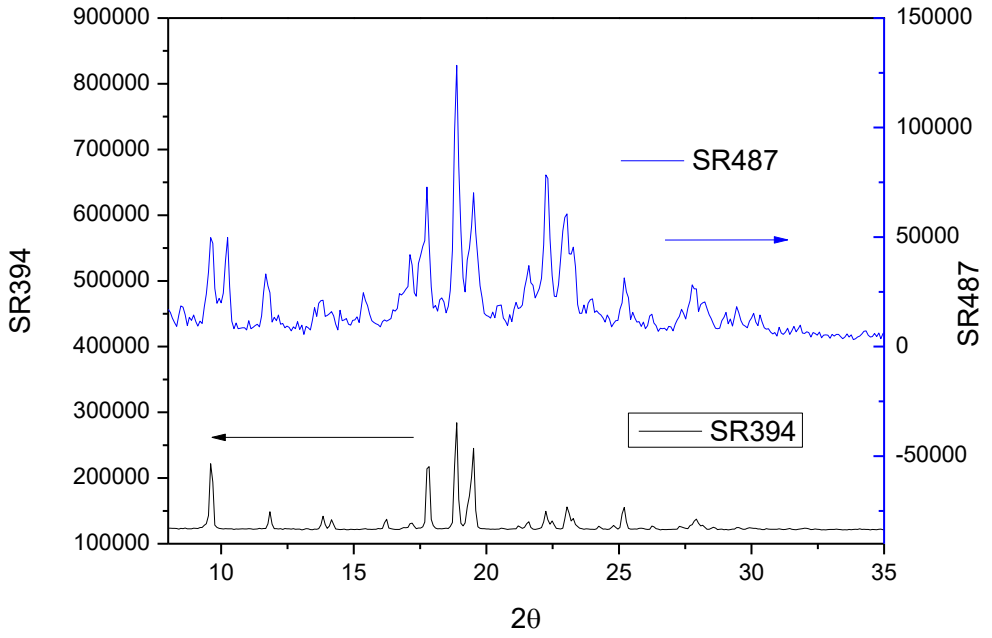


Figure 2.11

XRD spectra of the initial sample of 2.9 (in black) and a sample prepared later (in blue).

2.4 Conclusions

A group of diversely substituted triazines was synthesised and their optical and physical properties were studied. Two of the synthesised compounds – **2.9** with methyl substituents and **2.10** with nitrile substituents – showed very interesting optical properties, and the work on these compounds is still ongoing. Gold nanoparticles were also functionalised with disubstituted triazines using a sulphur bridge in order to study the combined effect of gold nanoparticles and substituted triazines on the optical properties of these compounds. Unfortunately the compounds synthesised with gold nanoparticles were not stable enough to be employed in OLED applications.

2.5 References

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3. Synthesis of Indoles

3.1. Introduction

Indole is an aromatic heterocycle that has a bicyclic structure, consisting of a benzene ring fused to a five-membered nitrogen-containing pyrrole ring (Figure 3.1). Indole is found in many natural products, and due to its importance in pharmaceutical and colour industry its synthesis has been widely studied in the past decade.

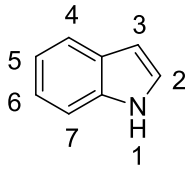


Figure 3.1

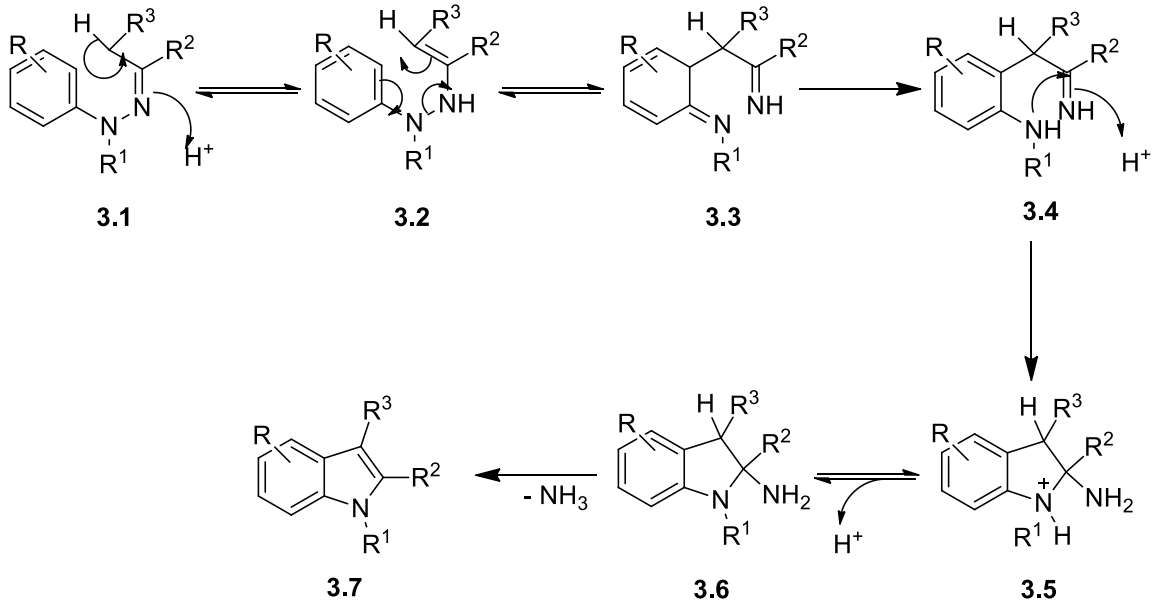
The structure of an indole ring

Indole is a stable molecule, resistant to heat and light, and many indole derivatives are characteristically coloured due to their conjugated structure. These properties, together with the fact that inserting a nitrogen heterocycle onto a compound lowers its LUMO and HOMO levels,[1] make indole an attractive substituent in OLED applications. In fact, there are some examples where the indole moiety has been used in constructing blue emitters for OLEDs.[2-4]

Current existing syntheses for indoles allow the introduction of substituents and linkers onto the indole ring in various positions, including the NH group, and one of the most versatile is the Fischer synthesis.[5,6] Although there are several valid synthetic protocols for the Fischer indole synthesis, other possible synthetic strategies for indoles were explored, mostly to enlarge the pool of possible starting materials, and to find conditions compatible with the functional groups on the indole ring. It was decided to explore three possible variations of the Fischer indole synthesis that will be discussed in this chapter.

The Fischer indole synthesis was first described in 1883 by Emil Fischer.[5,6] Despite being old, the Fischer indole synthesis is anything but outdated. Many pharmaceutical companies use it for the commercial synthesis of their compounds, and due to its operational simplicity it remains one of the

most versatile and common approaches to indoles to this day.[7,8] In Fischer indole synthesis indole is obtained by heating an enolisable phenylhydrazone in acidic conditions (Scheme 3.1).



Scheme 3.1

Mechanism of Fischer cyclisation

In acidic conditions, phenylhydrazone **3.1** isomerises to enamine or ene-hydrazine **3.2**, followed by protonation and a cyclic [3,3]-sigmatropic rearrangement, giving imine **3.3** that, after aromatisation, gives imine **3.4**. Imine **3.4** goes on to form cyclic aminal **3.5**, which under acid catalysis eliminates NH_3, resulting in the energetically favorable aromatic indole **3.7**.[9,10] Isotopic labelling studies showed that the aryl nitrogen of the starting phenylhydrazine is incorporated into the resulting indole (Scheme 3.1).[11] Tautomerisation of a phenylhydrazone derived from an unsymmetrical ketone can take place on both alpha positions respect to the carbonyl, leading to the formation of a mixture of isomers.

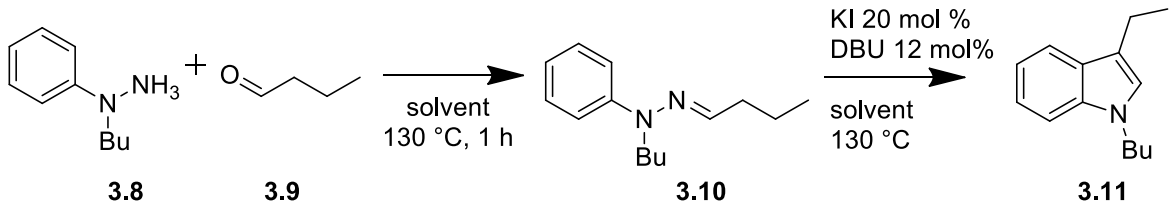
3.2. Synthesis of Indoles for OLED applications

Today, the Fischer synthesis remains the most powerful and widely employed approach ever developed for preparing indole derivatives due to its versatility and operational simplicity.[7,8,12,13] In Fischer indole synthesis *N*-aryl hydrazones are converted into the corresponding indoles *via* an acid-

catalysed [3+3] sigmatropic rearrangement, and subsequent elimination of ammonia. Through the decades, Fischer indole synthesis has been modified by various research groups that have improved it, providing several advantages and applications compared to the original procedure. The most obvious improvement has been the discovery of efficient catalysts to promote the cyclisation of arylhydrazones under milder conditions, and various protocols have been developed using Lewis acids,[14-16] Brønsted acids,[17-19] solid acids,[20,21] and acidic ionic liquids.[22-24]

3.2.1. Synthesis of Indoles *via* a Catalytic Cyclisation of Hydrazones using KI/DBU

The Fischer indole synthesis needs an acidic medium to proceed. However, during other studies of our group, it was noted that heating a phenylhydrazone with KI and DBU in dichloroethane (DCE) also gave an indole as main product (Scheme 3.2). This rather curious finding instigated further studies into the possibilities of applying this novel technique to the synthesis of indoles to be used in OLED structures. Phenylhydrazones can be easily prepared by reacting phenylhydrazines with enolisable aldehydes or ketones, and the synthesis of hydrazones from substituted hydrazines and aldehydes is well documented.[25-27] Heating hydrazine and an aldehyde in DCE in a sealed tube for one hour gave the hydrazone in quantitative yield.



Scheme 3.2

The pilot reaction for the optimisation of reaction conditions.

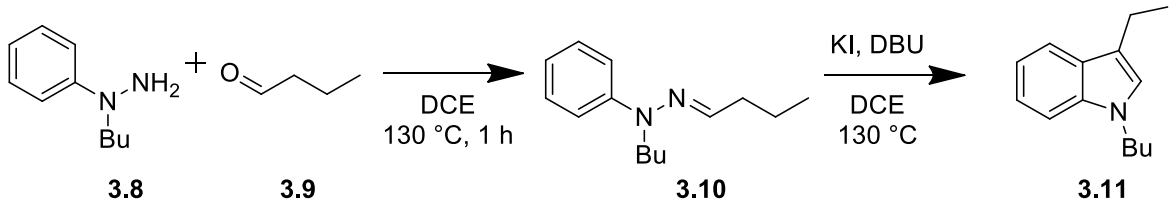
The formation of a hydrazone proceeded smoothly and in quantitative yields in a range of solvents, and so cyclisation of hydrazone **x** was studied in the same solvents (Table 3.1) surprisingly, the cyclisation reaction only proceeded in DCE, whereas in the other solvents either the starting material was recovered, or with prolonged heating only decomposition of the starting material was observed.

Table 3.1 Optimisation of reaction conditions for the indole synthesis

Entry	Solvent	Yield (%)[a]
1	DCE	45
2	CPME	-
3	Toluene	-
4	Toluene/DCE	-
5	1,3-dioxolane	sm
6	1,4-dioxane	-
7	EtOH	sm

Reactions were carried out with 1 mol 1-butyl-1-phenylhydrazine, 1 mol butyraldehyde and 2 mol solvent, in a sealed tube.

As the reaction proceeded only in DCE, the reaction conditions were then optimised in this solvent (Table 3.2). In order for the reaction to proceed the hydrazone needed to be formed previously (table 3.2, entry 4), and also in the case of forming the hydrazone from an alcohol via hydrogen transfer pathway[28] no product was observed (table 3.2, entry 2).



Scheme 3.3

Optimisation of the reaction conditions for the indole synthesis using KI and DBU as catalysts in DCE.

Rather surprisingly, the addition of an inorganic base, $CsCO_3$, inhibited the reaction almost completely, needing considerably longer reaction times (table 3.2, entry 5), whereas although the reaction did proceed in the presence of a Lewis acid such as $FeCl_3$, the yields were lower than without the catalyst (table 3.2, entry 11). Also, leaving out DBU altogether and replacing it with $CsCO_3$ resulted only in the recovery of the starting hydrazine (table 3.2, entry 14). The optimal quantities of DBU and KI were 24 mol% and 20 mol%, respectively (table 3.2, entry 13). Halving the catalyst quantities resulted in a drastic decrease in the yields (table 3.2 entry 3). Just halving DBU lowered the yields considerably as well (table 3.2, entry 3).

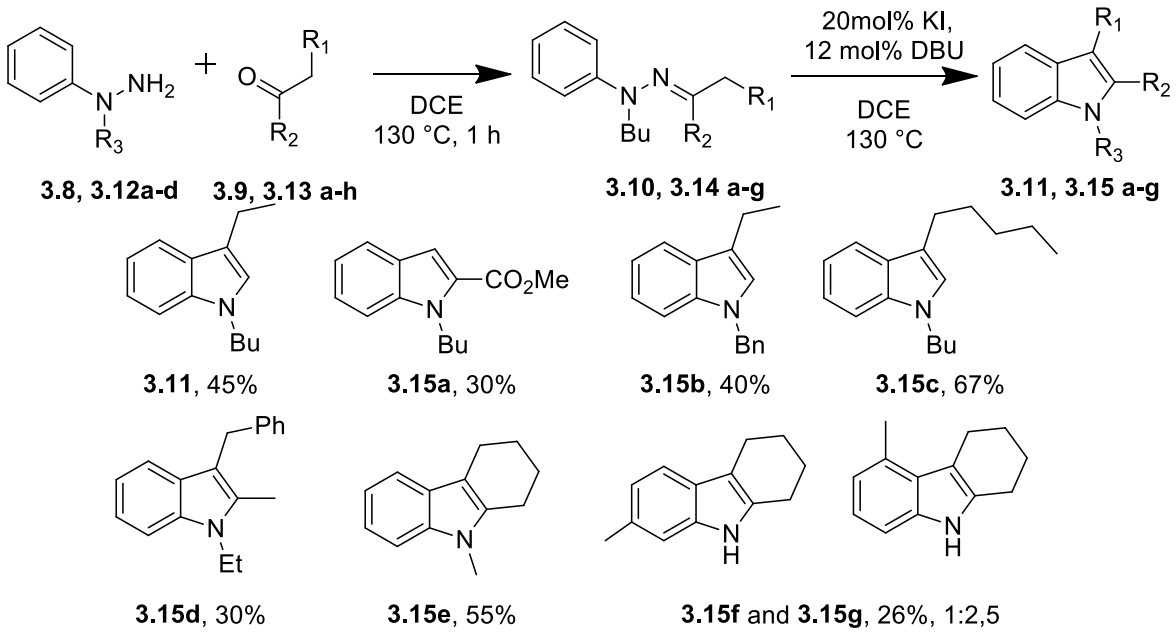
Table 3.2 Optimisation of reaction conditions for the indole synthesis.

Entry	KI (mol %)	DBU (mol %)	t (h)	Temp. (°C)	Yield (%)
1	10	6	3	130	25
2	10	6	1	130[a]	-[a]
3	20	12	3	130	45
4	10	6	3	130	-[b]
5	20	12	3	130	-[c]
6	20	12	5	130	20[c]
7	20	12	48	25	-[c]
8	20	12	48	25	-
9	20	12	72	60	30
10	20	6	4	110	50
11	20	12	3	130	40[d]
12	20	12	3	130	46[e]
13	20	24	3	130	61
14	20	12	3	130	-[f]

a) Starting with 1-butanol with 3% $Ru(CO)_{12}$ and 6% Cy_3P, MW heating. b) One pot reaction without preforming hydrazone. c) With 1 eq. $CsCO_3$. d) With 10 mol% FeCl3. e) With 2 equivalents of1-butyl-1-phenylhydrazine. f) Without DBU and with 1 equivalent of $CsCO_3$.

Lowering the reaction temperature to room temperature gave only starting material even after prolonged reaction times (table 3.2, entry 8), and at 60 °C the reaction proceeded very sluggishly and, even after days, still gave very low yields of indole (table 3.2, entry 9). At 110 °C the reaction proceeded smoothly but needed slightly longer reaction times (table 3.2, entry 10), and the optimal reaction temperature and time were found to be 130 °C and 3h (table 3.2, entry 13).

A small library of indoles was synthesised using 20 mol% KI and 12 mol% DBU. The reaction proceeded well with substituted hydrazones. Reaction with N-benzyl-hydrazone gave benzylated indole **3.15b** in good yields. This can be easily deprotected in a successive step, giving a free NH group that can be used to link the indole onto a triazine or a heptazine core. Also hydrazine derived from methyl pyruvate afforded indole **3.15a** in a reasonable yield. **3.15a** would give access to an indole with a free acid moiety by saponification, and with further manipulation this functional group can be used to attach the indole onto a triazine or a heptazine.



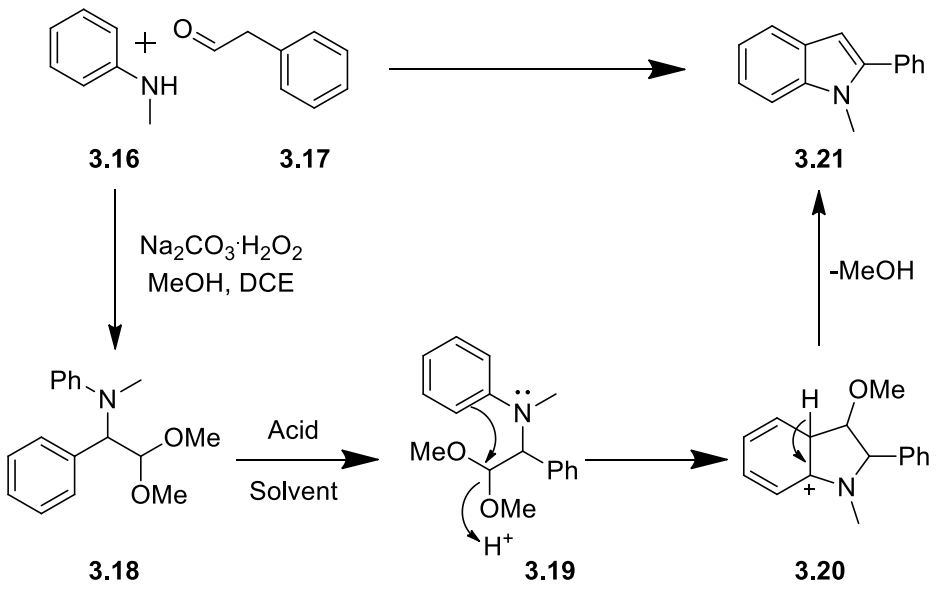
Scheme 3.4

Synthesis of a small library of Indoles using KI and DBU as catalysts.

The reaction mechanism of this reaction is still unclear. The fact that the reaction mixture remains basic throughout the reaction rules out the traditional Fischer indole synthesis mechanism, and further studies would be necessary to elucidate the reaction pathway. However, in this case the end product in itself is more important than the reaction, and these studies were not carried any further.

3.2.2 Synthesis of Indoles from α-Amino acetals *via* Acid catalysis

In 2012 Loh[29] reported an elegant synthesis for the *in situ* hypoiodite-catalysed α-amination of aldehydes. This method gives a facile access to α-aminoacetals that can then be deprotected by treatment with acid. We hypothesised that – together with deprotecting the aldehyde – with the right reaction conditions the acid may also be able to catalyse the cyclisation of the α-aminoaldehyde onto the aromatic ring, and to give an indole substituted in position 2 *via* subsequent dehydration (Scheme 3.5).

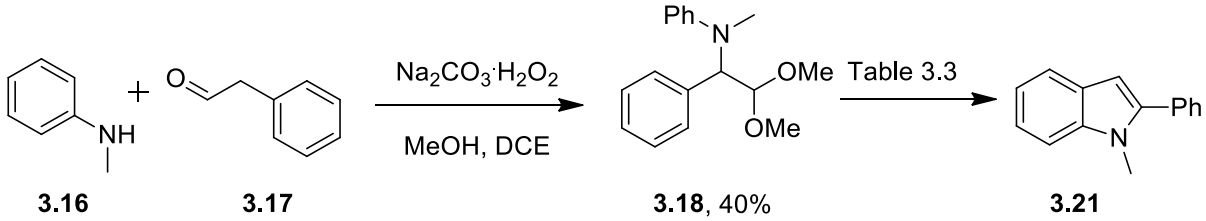


Scheme 3.5

Possible reaction pathway from α-aminoacetals to substituted indoles.

Many indole syntheses use aldehydes as starting materials. Aldehydes are, however, susceptible to oxidation, aldol reactions and polymerisation, and these side reactions severely limit their conversion into indoles.[30,31] Use of acetals in indole synthesis circumvents some of these problems that the synthesis of indoles starting from aldehydes has to face by inhibiting homocoupling and also oxidation to some extent. Combining the synthesis of an α-aminoacetal to a cyclisation reaction would give an efficient synthesis of a substituted indole in only two steps.

The synthesis of the aminoacetal **3.18** proceeded smoothly following the procedure of Loh[29] and the α-aminoacetal was isolated in decent yields. To study the cyclisation of the α-aminoacetal to indole both Lewis acids and protic acids were selected. The reaction was carried out in a selection of polar and non-polar organic solvents as well as in water to study the effect of solvent on the reaction.



Scheme 3.6

Optimisation of reaction conditions for the indole synthesis from acetals.

Table 3.3 Optimisation of reaction conditions for the indole synthesis from acetals.

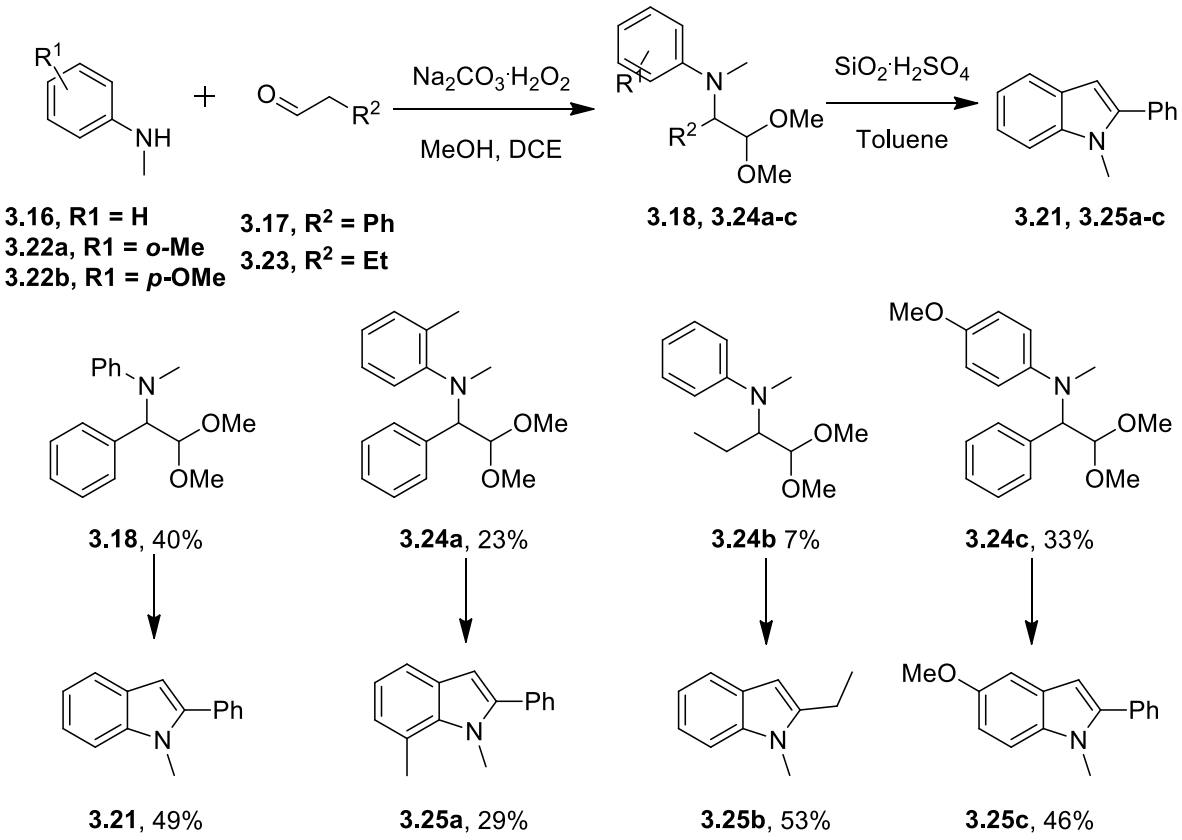
Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	HCl (3M), 3 eq	THF	80	24	10
2	$TiCl_4$, 1eq.	DCM	0	0.5	-
3	TFA/H_2O	DCM	25	16	-
4	Dowex, 2g/mmol	Toluene	110	2	18
5	Dowex, 2g/mmol	Toluene	60-80	16	-
6	pTsOH, 1.5 eq.	Toluene	110	3	37
7	pTsOH, 1.5 eq	Toluene	90	3	30
8	AcOH, 1.5 eq.	Toluene	110	6	-
9	pTsOH, 1.5 eq	Water	100	3	19
10	pTsOH, 1.5 eq	EtOH	90	3	10
11	pTsOH, 1.5 eq	EtOH	50	24	-
12	SiO_2·H_2SO_4, 500mg/1 mmol	toluene	110	3	35
13	SiO_2·H_2SO_4, 100mg/1 mmol	Toluene	110	3	37
14	SiO_2·H_2SO_4, 20mg/1 mmol	Toluene	110	3	-
15	SiO_2·H_2SO_4, 40 mg/ mmol	Toluene	110	3	49

First a group of acids were studied carrying out the reaction in toluene. Toluene was chosen as the first solvent as in previous studies it had given good yields of indole.[28] For reactions conducted in low temperatures the solvent chosen was DCM. Ethanol and water were also studied as solvents, but the best results by far were in each case obtained with toluene, as can be seen from table 3.3. The reactions were carried out in a sealed tube, except in the case of $TiCl_4$, where the reaction was carried out in an ice bath under Ar.

Lewis acids in DCM, acetic acid in toluene and trifluoroacetic acid in DCM did not afford the product, and only degradation of the starting material was observed. In the case of hydrochloric acid the indole formed very slowly and in poor yields, with the main product of the reaction being the aldehyde derived from deprotection of the acetal and its degradation products. Supported acids fared slightly better, Dowex-resin giving the indole in 18% yield upon heating (Table 3.3 entry 4). In this case, the reaction proceeded smoothly, and the low yields were attributed to either the product or the starting material being trapped in the gel. Dowex degrades slowly at high temperatures, and therefore, although the yields were promising, the idea of carrying out the reaction using this gel as the acid catalyst was not considered feasible. *Para*-toluenesulfonic acid gave good yields of the product upon heating, with a clean reaction (Table 3.3 entry 6). Lowering the temperature had a significant effect on the yields (table 3.2, compare entries 6 and 7), and as in the case of Dowex (Table 3.3 entry 5), the best results were obtained with toluene at reflux. The best results were obtained with sulphuric acid supported on silica gel. When

the reaction was carried out in toluene at 110 °C with 40mg of the supported acid per mmol of acetal, the product indole **3.21** was isolated in 40% yield in only 3 hours (table 3.3 entry 15).

A small library of substituted indoles were synthesised using this method (Scheme 3.7). However, the synthesis of the α-aminoacetals using the method described by Loh[29] resulted less general than expected. The synthesis only worked well with methylaniline as a substrate, giving no product with benzylic amines. Also unbranched aliphatic aldehydes did not give reproducibile results, with butyraldehyde affording only 4-7% yield of a product, and heptanal yielding no product at all. Thus the scope of this method remains very limited, and with the limitations of this method outweighing its advantages, it was decided not to pursue the optimisation of the synthesis of indoles from acetals any further but to concentrate on other possible methodologies.

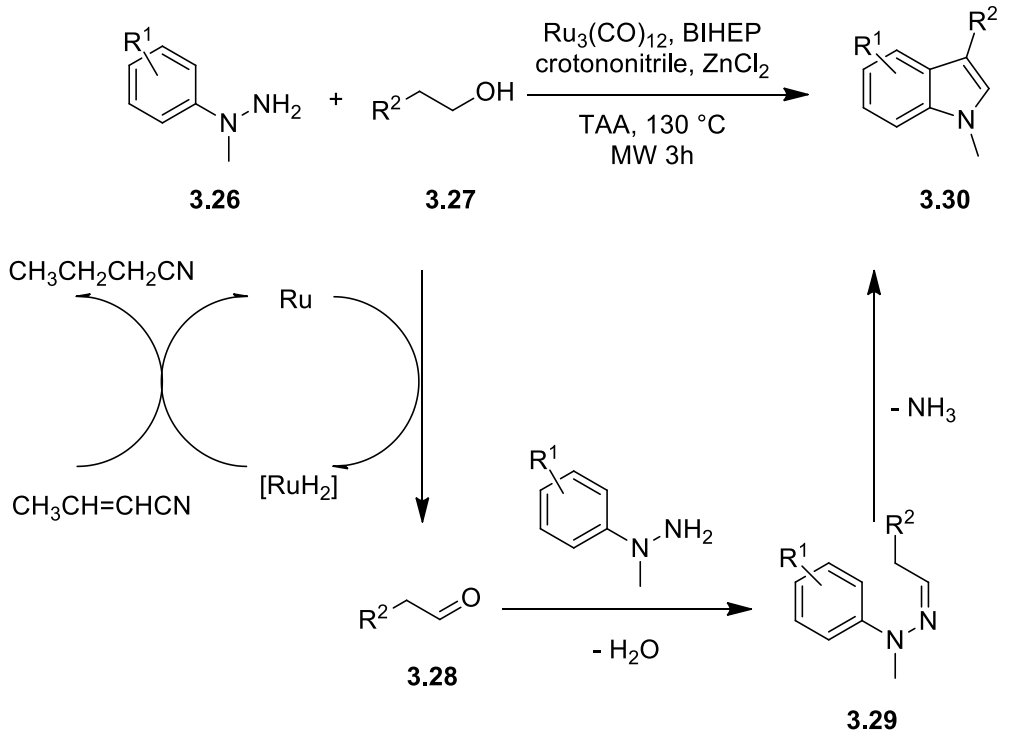


Scheme 3.7

The synthesis of indoles from α-aminoacetals.

3.2.3 Synthesis of Indoles *via* Cross-Dehydrogenative Coupling of Amines with Arylhydrazines

Lately Porcheddu *et al.*[28] reported an elegant synthesis of indoles using alcohols as starting material. By generating the aldehyde *in situ* from the alcohol they avoided autocondensation of the alcohol and were able to perform the reaction in one pot, although in two steps.



Scheme 3.8

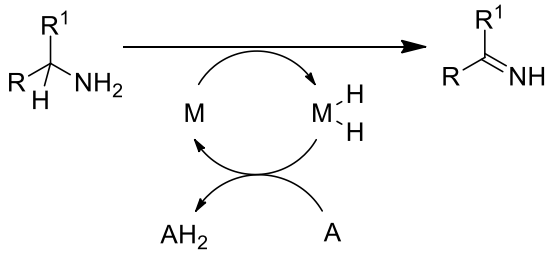
Synthesis of indoles from alcohols and hydrazines.[28]

According to Porcheddu et *al.*[28] the reaction proceeds *via* an initial oxidation of alcohol **3.27** into the corresponding carbonyl compound **3.28** by transfer of a hydrogen onto the hydrogen acceptor resulting in the regeneration of the catalyst. The *in situ* generated aldehyde or ketone **3.28** reactis immediately with the arylhydrazine, which is then converted into the corresponding hydrazone **3.29**. The subsequent acid catalysed aromatic [3 + 3] sigmatropic rearrangement gives the desired indole ring **3.30** (Scheme 3.8).

Hydrazones are traditionally synthesised much in the same way as imines. Although several methods are available for the synthesis of imines, the traditional acid-catalysed condensation of amines with aldehydes or ketones is still the simplest way to prepare them.[32,33] Imines can also be prepared by a temporary oxidation of alcohols to aldehydes or ketones in the presence of amines *via* a dehydrogenative process, as in the indole synthesis of Porcheddu.[34-43] The most direct approach to imines, however, is amine dehydrogenation that transforms primary and secondary amines into the corresponding imines.[44-47] Although common in nature, this process has been rarely applied in organic synthesis.

Imine formation by amine dehydrogenation with Pd black was first performed by Murahashi[48-50]. Afterwards, the research regarding the oxidation of amines has concentrated on alkylation of arylamines with aliphatic amines using homogeneous catalysis with ligand-stabilised Ru, Rh and Ir complexes.[51-55] More recently, Porcheddu *et al.*[55,56] reported a dehydrogenative method for using amines in alkylation of anilines and benzimidazole synthesis under hydrogen transfer conditions.

In theory, imines can act as electrophiles in a coupling with phenylhydrazines giving phenylhydrazones, allowing a new approach to the construction of the indole skeleton using amines as starting materials. The most attractive route for converting amines into imines is the selective removal of one hydrogen molecule from the amine by a transition metal catalyst, followed by hydrogen transfer to an acceptor that acts as a terminal oxidant (Scheme 3.9).

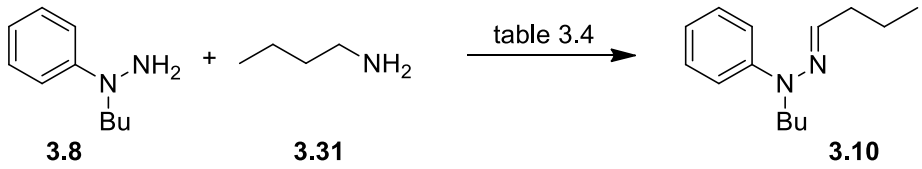


Scheme 3.9

Metal catalysed dehydrogenation of an amine to imine (A = hydrogen acceptor).

First a selection of possible catalysts were screened to see if butylamine and phenylhydrazone could be coupled to form a hydrazine as hypothesised The reactions were carried out in a sealed tube, in toluene at 170 °C for 12 h using crotononitrile as hydrogen acceptor (Table 3.4). Most ruthenium complexes did not facilitate the reaction, with the exception of the Shvo catalyst (Table 3.4, entries 1-6). Palladium- and iridium-based catalysts showed good catalytic activity (Table 3.4, entries 8-14) giving hydrazone **3.33** in decent yields. The best results - in terms of both yield and purity – were obtained using palladium catalysts. These were also preferred to iridium because of their higher stability and

relatively low cost. Palladium on charcoal (10% wt, 5 % mol) (Table 3.4 entry 14), $Pd(OH)_2$ and palladium black (Table 3.4, entries 12 and 13) proved to be the best catalysts for this reaction.



3.8 **3.31** **3.10**

Table 3.4 Catalyst screening for the cross-dehydrogenative coupling of **3.8** with **3.31**

Entry	Catalyst	3.31/3.8 Ratio	Temp. (°C)	Yield (%)[a]
1	$Ru_3(CO)_{12}$	1/3	170	-
2	$RuCl_3$	1/3	170	-
3	$RuCl_2(PPh_3)_3$	1/3	170	-
4	$[Ru(p\text{-cymene})Cl_2]_2$	1/3	170	-
5	$RuH_2(PPh_3)_4$	1/3	170	-
6	Ru/C	1/3	170	-
7	Shvo	1/3	170	41
8	$[Cp^*IrCl_2]_2$	1/3	170	57
9	$Pd(PPh_3)_4$	1/3	170	21
10	$Pd(OAc)_2$	1/3	170	85
11	Pd NPc	1/3	170	39
12	Pd black	1/3	170	95
13	$Pd(OH)_2/C$	1/3	170	96
14	Pd/C	1/3	170	98

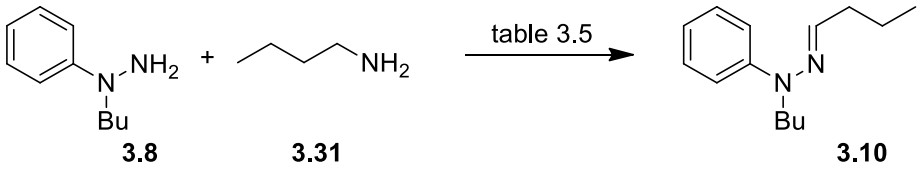
Reactions were carried out in a sealed tube inserted in a preheated heater block at the stated temperature: 1-butyl-1-phenylhydrazine (3 mmol), 1-butylamine (1 mmol), crotononitrile (1 mmol), catalyst (5 mol%), toluene (2.5 mL), under Ar, at 170 °C, 12 h. [a]Yield of isolated product.

The optimal catalyst loading was 5 mol%, as increasing catalyst concentration only slightly shortened reaction times without influencing the yields (Table 3.5 entry 2), whereas catalyst loadings lower than 5 mol% decreased reaction yields (Table 3.5 entry 1).

Unfortunately, lowering the arylhydrazine/amine ratio resulted in significantly lower yields if indole. Dibutylamine, derived from homocoupling of butylamine, was the major by-product. Excess hydrazine may in fact be required to suppress the homocoupling of amine, allowing an almost quantitative conversion of amine into arylhydrazone. Toluene as solvent gave the highest yields, whereas with more polar solvents, such as water or *tert*-amyl alcohol, yields decreased (Table 3.5, entries 6-8). The

reaction could also be conducted neat, giving hydrazine **3.10** in a remarkably high yield (90 %, Table 3.5, entry 9).

High temperatures required in this reaction may be a serious limiting factor. Luckily the temperature could be lowered down to 150 °C without affecting the conversion or yield (Table 3.5 entry 12). Unfortunately, the temperature could not be lowered further, as at 130 °C already the indole was isolated in significantly lower yields (Table 3.5, entries 11-12).



3.8 **3.31** **3.10**

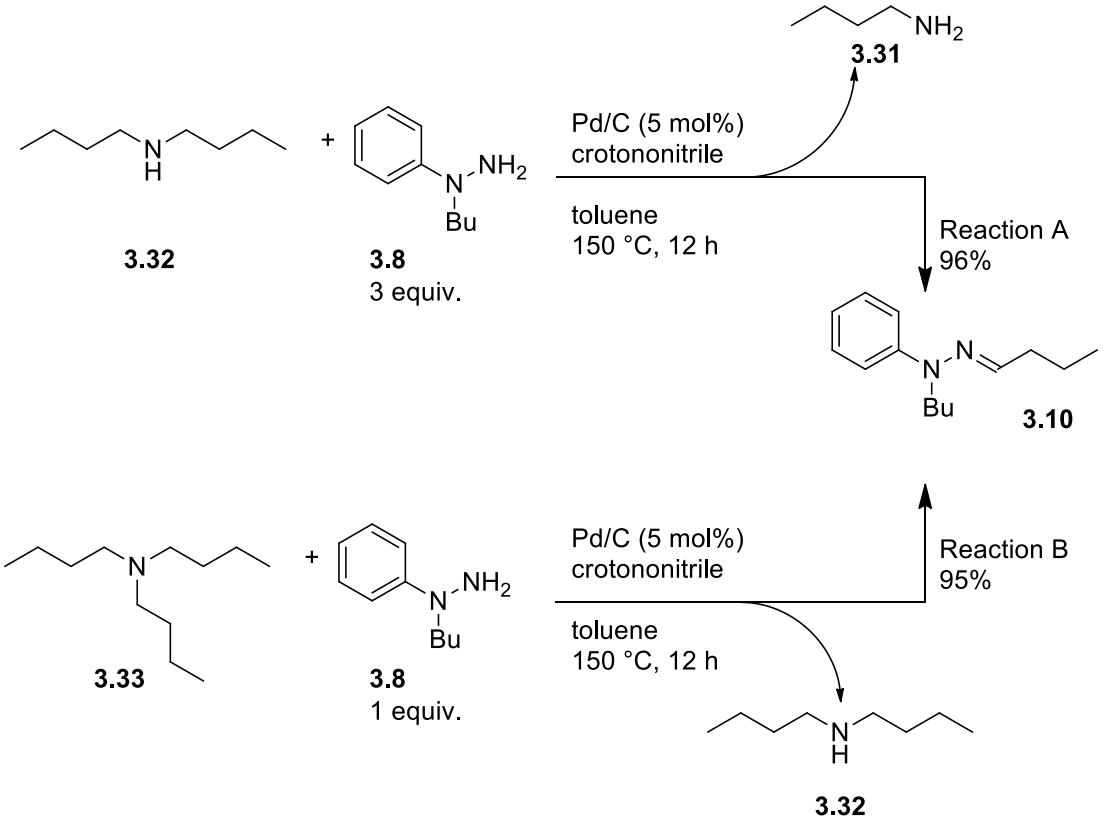
Table 3.5 Optimisation of reaction conditions for the coupling of **3.8** with **3.31**

Entry	Catalyst (mol%)	3.31/3.8 Ratio	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	Pd/C (2)	1/3	Toluene	170	12	78
2	Pd/C (50)	1/3	Toluene	170	3	91
3	Pd/C (5)	1/2	Toluene	170	12	78
4	Pd/C (5)	1/1	Toluene	170	12	45
5	Pd/C (5)	2/1	Toluene	170	12	35
6	Pd/C (5)	1/3	H_2O	170	12	70
7	Pd/C (5)	1/3	TAA[b]	170	12	63
8	Pd/C (5)	1/3	CPME[c]	170	12	59
9	Pd/C (5)	1/3	neat	170	12	90
10	Pd/C (5)	1/3	Toluene[d]	170	12	60
11	Pd/C (5)	1/3	Toluene	130	12	75
12	Pd/C (5)	1/3	Toluene	150	12	98

Reactions were carried out in a sealed tube inserted in a preheated heating block at the stated temperature: 1-butyl-1-phenylhydrazine (3 mmol), 1-butylamine (1 mmol), crotononitrile (1 mmol), catalyst (5 mol%), toluene (2.5 mL), under Ar, at 170 °C, 12 h. [a]Yield of isolated product. [b]TAA = 2-methyl-2-butanol (tert-amyl alcohol). [c]CPME = cyclopentyl methyl ether. [d]Reaction performed without hydrogen acceptor.

The possibility of using secondary and tertiary amines as well would significantly broaden the range of starting materials. To study the reaction with secondary and tertiary amines 1-butyl-1-phenylhydrazine **3.8** was reacted with both tributylamine **3.32** and dibutylamine **3.33** (Scheme 3.10). When dibutylamine was used instead of butylamine, the formation of hydrazone **3.10** was achieved under the same reaction conditions (Scheme 3.10, Reaction A). The reaction proceeded smoothly also with tributylamine, and in this case only one equivalent of hydrazine was required to get complete conversion

of hydrazine to hydrazone (Scheme 3.10, Reaction B). The formation of the reactive iminium ion intermediate and the absence of auto condensation when working with a tertiary amine could explain this result.

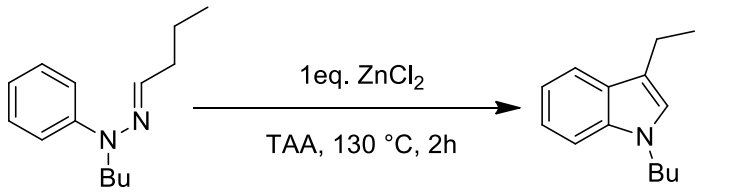


Scheme 3.10

Synthesis of phenylhydrazone **3.11** using dibutylamine **3.32** and tributylamine **3.33**

Although the overall atom economy of the process based on the tertiary amine is comparable with the reaction using primary amines (one molecule of secondary amine *vs* two molecules of hydrazine lost), primary amines were chosen as starting material for the cross-coupling reaction due to their larger availability.

With the synthesis of hydrazones now optimised the next step was the cyclisation of the synthesised hydrazones to indoles. The Fischer indole synthesis was a natural choice for this step, due to its versatility and ease. A previously prepared 1-butyl-1-phenylhydrazone **3.8** was treated with $ZnCl_2$ to promote a [3,3]-sigmatropic rearrangement. After just two hours, with 1 equivalent of $ZnCl_2$ in TAA at 130 °C, the corresponding 1-butyl-3-ethyl-1*H*-indole **3.11** was obtained in 95 % yield (Scheme 3.11).

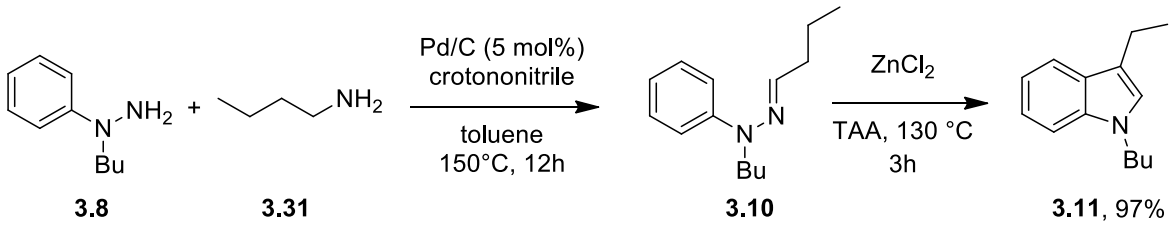


3.8 **3.11**, 95%

Scheme 3.11

Cyclisation of arylhydrazone **3.8** to indole **3.11** under acidic conditions.

The next logical step was to attempt the synthesis of indole **3.11** through a one-pot two-step procedure, by combining a Pd/C catalysed synthesis of arylhydrazone **3.8** to a subsequent Fischer cyclisation to obtain the desired product **3.11**. Pd/C could be be easily removed by filtration after the first step, and phenylhydrazone **3.8** was directly subjected to Fischer-indolisation reaction by addition of the acid catalyst, which triggers the 3,3-sigmatropic rearrangement. Combination of the two steps worked well, giving indole **3.11** in very high yield (Scheme 3.12).

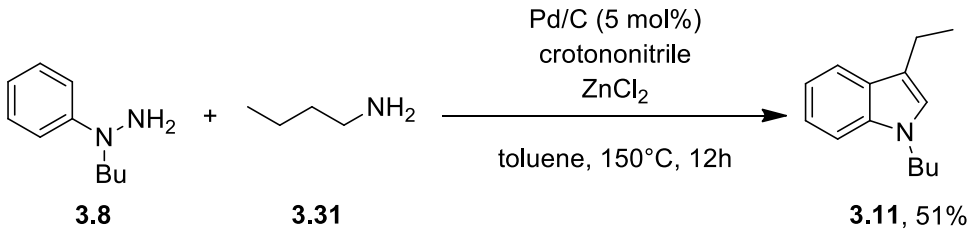


3.8 **3.31** **3.10** **3.11**, 97%

Scheme 3.12

Synthesis of indole **3.11** via a one-pot two-step procedure.

Unfortunately when both transformations were performed in one step by adding $ZnCl_2$ right at the beginning (Scheme 3.13) the yield of indole **3.11** dropped to almost half. The importance of both palladium catalyst and $ZnCl_2$ in the reaction mixture was confirmed by the fact that no hydrazine was formed in the absence of Pd/C, and no cyclisation occurred without $ZnCl_2$.



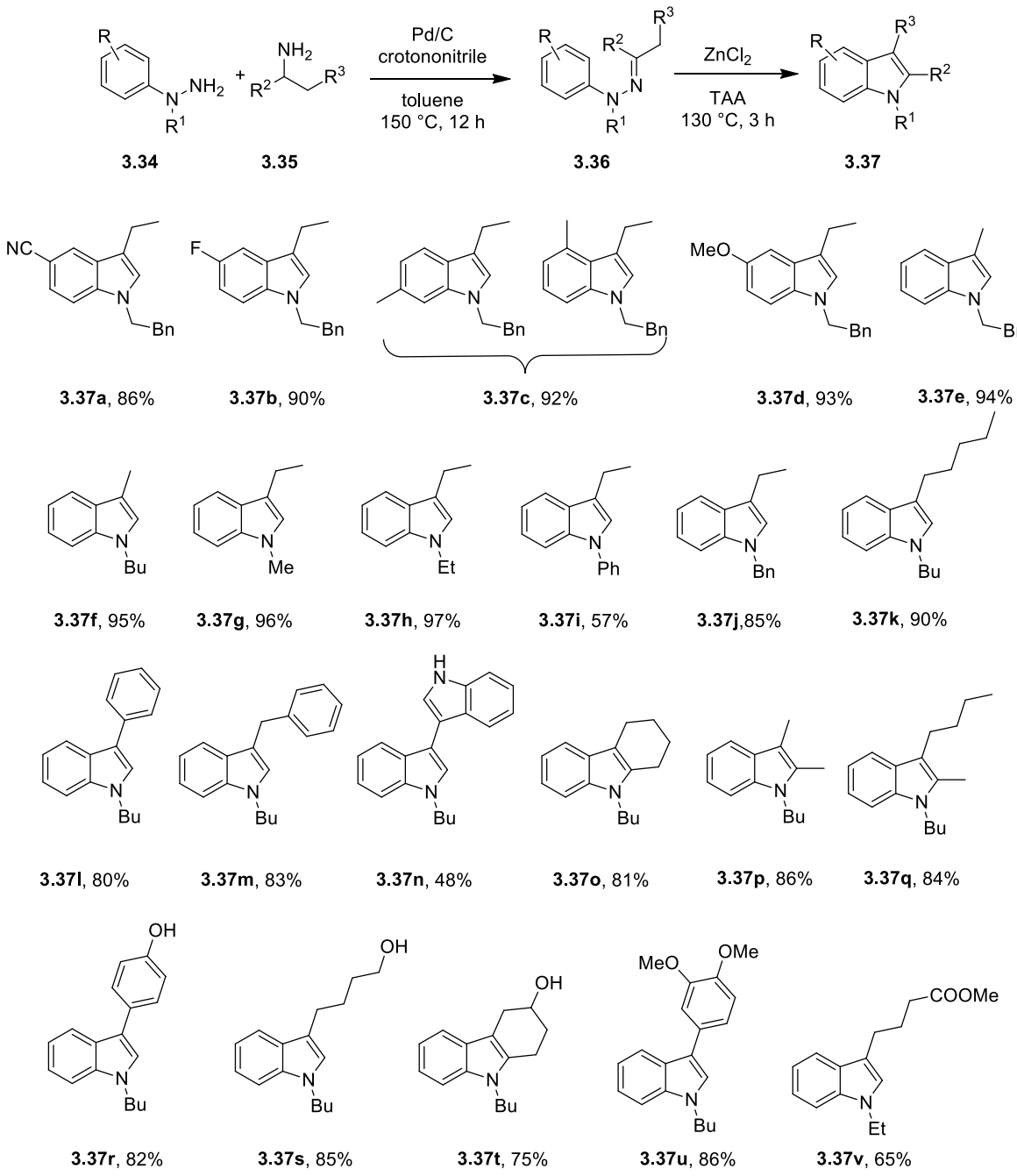
Scheme 3.13

Synthesis of indole **3.11** via a one-step procedure.

With the two-step protocol giving significantly higher yields than the one-step approach, the two-step method was used for the synthesis of a small library of indoles (Scheme 3.13). The cyclisation reaction was generally complete in less than 3 hours. A variety of both electron-withdrawing and electron-donating substituents on the aryl moiety are well tolerated, suggesting that electronic effects do not affect the reaction (Scheme 3.14, indoles **3.37a-d**). As expected, with a *meta*-substituted phenylhydrazine a mixture of the corresponding 4- and 6-substituted indole was obtained (Scheme 3.14, indoles **3.37c**).

The [3+3] sigmatropic rearrangement was also studied by combining a set of commercially available phenylhydrazines with an array of different amines. The developed reaction showed wide applicability across a range of structurally different amines, providing the corresponding indoles in good to excellent yields (Scheme 3.14, compounds **3.37k-v**). Long-chain aliphatic amines worked well (Scheme 3.14, compounds **3.37k),** as did a mines bearing either an aromatic or an aliphatic ring (Scheme 3.14, compounds **3.37l-n** and **2.48t**). Cross-coupling between tryptamine and 1-butyl-1-phenylhydrazine occurred under standard conditions, allowing the preparation of an unsymmetrical 3,3'-bis-indole **3.37n** (Scheme 3.14), that can be selectively functionalised on the NH group.

The reaction worked equally well also with a branched primary amine, giving the corresponding 2,3-dialkylindoles **3.37p** and **3.37q** in good yields as single regioisomers. Several different functional groups on the amine skeleton were also well supported (-OH, -OMe, -CO_2Me), affording compounds **3.37r-v** in 65–86 % yield. These additional functional groups provide further opportunities for subsequent chemical manipulations, and can be used as handles to attach the indoles onto more complex structures such as triazines and heptazines.

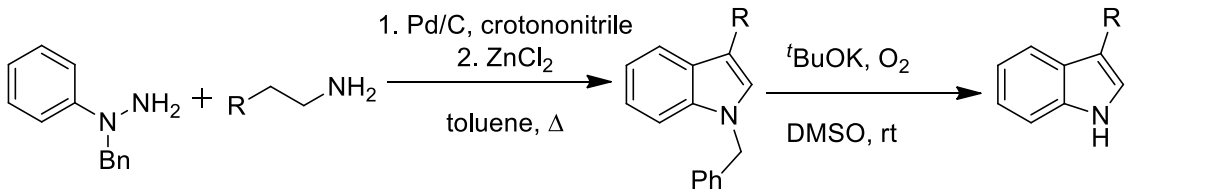


Scheme 3.14

Synthesis of indoles by reaction of arylhydrazines with amines.

Although this method seems generally applicable, indoles with a free NH group cannot be synthesised using this route. Classical NH protecting groups (Cbz, Boc, Ac, etc) on arylhydrazines have been found incompatible with the reaction conditions.[57] However, when 1-benzyl-1-phenylhydrazine was reacted with propyl amine, butylamine or phenethylamine, the corresponding 1-benzyl indoles were obtained in good yields. Indoles with a free NH group (Scheme 3.15, indoles **3.45-3.47**) were then easily

obtained in good yields by debenzylation,[58,59] by treatment with *t*BuOK/DMSO and oxygen at room temperature for 20 min. (Scheme 3.15).

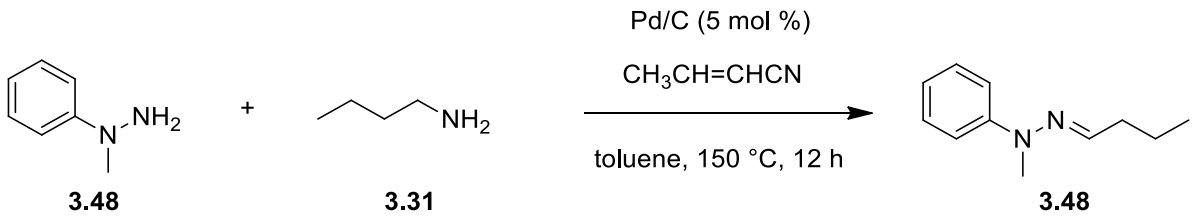


3.38 **3.39**, R = Me; **3.40**, R = Et; **3.41**, R = Ph; **3.42**, R = Me; **3.43**, R = Et; **3.44**, R = Ph; **3.45**, R = Me, 65%; **3.46**, R = Et, 66%; **3.47**, R = Ph, 69%

Scheme 3.15

Debenzylation of Indoles.

The possibility of effective recycling of the Pd/C catalyst was evaluated on the reaction of 1-methyl-1-phenylhydrazine with butylamine. The catalyst was separated by filtration from the reaction mixture after the formation of the hydrazone intermediate. The Pd catalyst was washed several times with 1M HCl, water and finally THF to remove water, and dried before using it in the next run. The recycling experiments showed that the reaction could be carried out with recycling the catalyst at least five times without noticeable decrease in activity (Scheme 3.16). To verify the heterogeneous nature of the catalytic process, several leaching studies were also carried out.[60-64] "Sheldon's hot-filtration test", ICP-MS analysis of the filtrate, and three-phase test (also called Rebeck-Collman test) determined unambiguously the heterogeneous nature of the catalytic process, as only a negligible amount of Pd was detected in solution.



cycles	Yield (%)[a]
1	98
2	96
3	97
4	96
5	95

[a] isolated yield

Scheme 3.16

Catalyst recycling experiments.

3.3 Conclusions

An intriguing new synthetic pathway to indoles from hydrazones was discovered, using a basic catalyst instead of and acidic one in the cyclisation step. A small library of indoles was synthesised using this method. Some functional groups were also well tolerated, although unfortunately the free NH group was not among these and the study of this method was therefore not carried out further. The reaction mechanism of this reaction is still unclear, and further studies would be necessary to elucidate the reaction pathway.

The possibility of using α-aminoacetals as starting materials for indoles was also studied. The cyclisation of α-aminoacetals to give indoles proceeded smoothly, but unfortunately the synthesis of the starting α-aminoacetals proved to be difficult and not very general, and therefore this strategy was not studied further.

A novel synthetic approach to indoles with amines and hydrazines was also designed and studied. The process consists in the direct transformation of primary amines into arylhydrazones by reaction with arylhydrazines under transfer hydrogenation conditions, followed by cyclisation to give the indole ring. A palladium-catalysed coupling procedure to prepare *N*-arylhydrazones, and their use as general precursors in the classical Fischer indole synthesis were central to this strategy.

3.4. References

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4. Synthesis of Quinolines

4.1 Introduction

Applications of quinoline derivatives in both pharmaceutical chemistry and industrial applications have increased interest in developing new methodologies for the preparation of quinoline-based structures.[1-14] Although there are many elegant syntheses of substituted quinolines, harsh reaction conditions and limits in the nature of starting materials and reagents still make the development of more efficient and general synthetic strategies for quinolines and their derivatives important.[15-17]

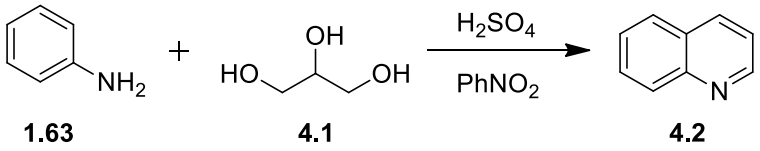
The applications of quinolines in OLEDs are less known. Although quinoline in an interesting heterocycle with high electron mobility, good thermal stability, high photoluminescence efficiency and good film forming properties that make it suitable for use in electroluminescence, the examples of OLEDs that take advantage of these traits do not abound in the literature.[18-20] There is therefore ample room for further studies in quinoline and its derivatives in OLED applications.

One of the first quinoline syntheses reported was the Skraup reaction. This synthesis[21] is named after Czech chemist Zdenko Hans Skraup (1850-1910), who synthesised quinoline by heating a mixture of nitroethane, aniline and glycerol with concentrated sulphuric acid in the 1880's. The original the Skraup synthesis gave very low yields of quinoline,[22-27] but over the years various modifications have rendered Skraup synthesis viable. A recent modification of the original Skraup synthesis – an acid-catalysed reaction between imines and enolisable aldehydes – is one of the emerging versatile approaches for preparation of functionalised quinolines.[10,28-31] Although this procedure provides a straightforward and practical access to quinolines, the starting materials can be very expensive or difficult to prepare, leaving room for further improvement.

4.1.1 Skraup Quinoline Synthesis

The Skraup[21] synthesis, as described above, was first carried out by heating a mixture of nitroethane, aniline and glycerol with concentrated sulphuric acid, affording very low yields of quinoline.[22-27] When the reaction was performed for the first time, As_2O_3 was used as an oxidising agent and the reaction was known for being violent. In the modern Skraup synthesis nitrobenzene functions both as an oxidising agent and as a solvent (Scheme 4.1). Various moderators such as acetic or boric acids, ferrous sulfate, thorium, or vanadium or iron oxides have been used to accelerate the reaction and make it higher yielding.[32-35] The direct use of acrolein is not recommended since it easily undergoes

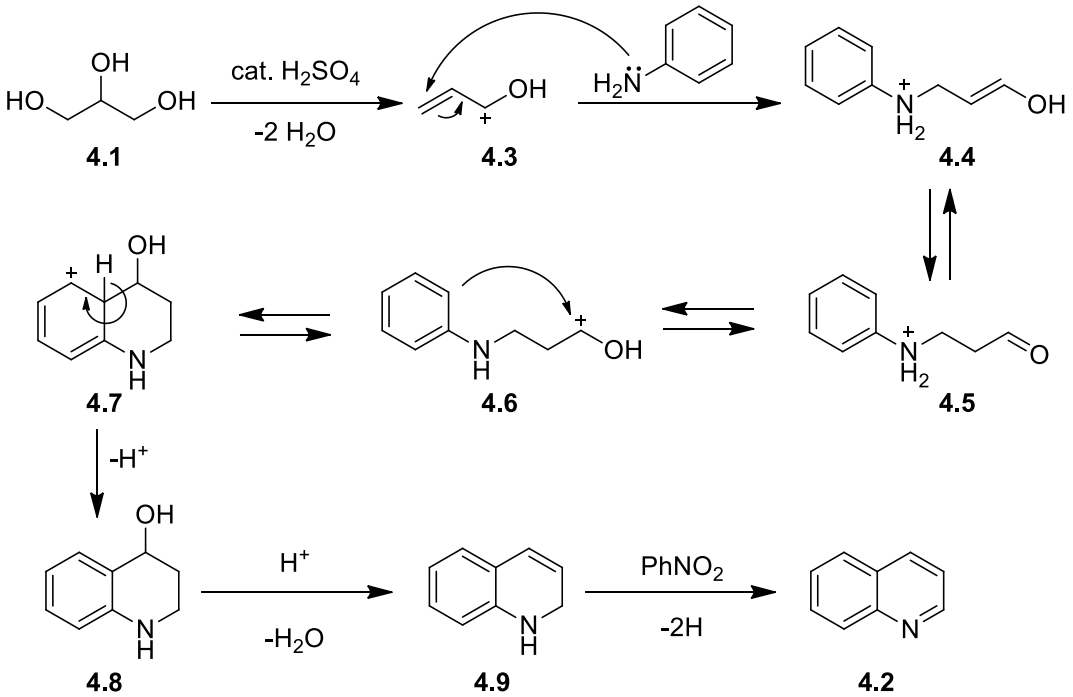
polymerisation under acid reaction conditions, and therefore acrolein is often released in the reaction from its precursors.



Scheme 4.1

Skraup quinoline synthesis

The reaction mechanism remains unclear. Acrolein, generated by dehydration of glycerol in the presence of concentrated sulfuric acid, is believed to first undergo a 1,4-addition reaction followed by an intramolecular electrophilic aromatic substitution, resulting in the corresponding dehydroquinoline **4.9** after dehydration. In the last step, nitrobenzene promotes the oxidation/aromatisation process of **4.9** to the final quinoline (Scheme 4.2).



Scheme 4.2

Reaction mechanism of Skraup reaction.

4.1.2 Döbner-Miller Reaction

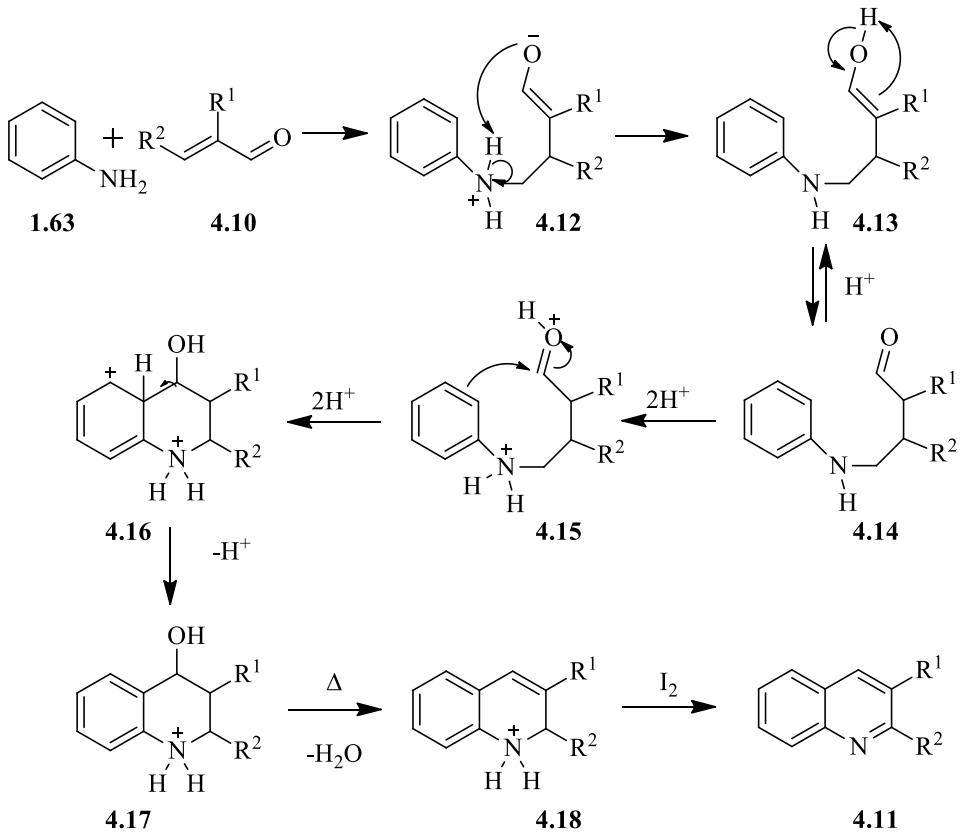
Oscar Döbner and Wilhelm Von Miller modified the original Skraup synthesis by replacing glycerol with an α,β-unsaturated aldehyde or ketone.[36-40] The method was further improved by Beyer, who used α,β-unsaturated carbonyl derivatives prepared *in situ* from two carbonyl compounds *via* an aldol condensation.[41]

1.63 **4.10** **4.11**

Scheme 4.3

Döbner-Miller Reaction

The mechanism of Döbner-Miller reaction is still subject to debate as well. A plausible hypothesis involves an initial attack of an aniline to the polarised C=C double bond of an unsaturated aldehyde, to generate the enolate **4.12**, which *via* 1,5-proton transfer gives the corresponding ketone **4.14**. Subsequently **4.14** is protonated on the carbonyl and amino groups and the following electrophilic aromatic substitution gives intermediate **4.16**. Quinoline **4.11** is then formed by subsequent dehydration and oxidation (Scheme 4.4).

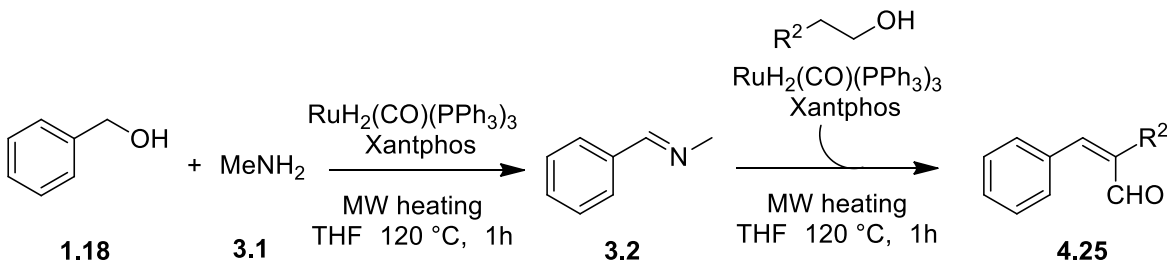


Scheme 4.4

A possible mechanism for the Döbner-Miller reaction with iodine as oxidant.

4.2 Synthesis of Indoles for OLED applications

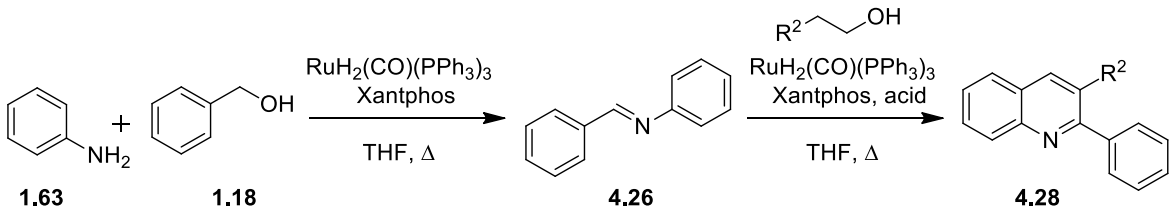
Porcheddu *et al.*[42] have described a cross-dehydrogenative coupling (CDC) of two different primary alcohols in the presence of methylamine to obtain α-β-unsaturated aldehydes using a Ru-based catalyst.[42] In this reaction methylamine and benzyl alcohol react to form the corresponding imine **3.2** through oxidation of the alcohol *in* situ. The subsequent Mannich-type addition of an aliphatic alcohol (behaving as a masked aldehyde) to imine **3.2** gives the desired cinnamaldehyde derivative **4.25** (Scheme 4.8).



Scheme 4.8

Synthesis of α-β-unsaturated aldehydes from alcohols.

When using arylamines instead of methylamine in the imine formation step, it may be possible to extend this method also to the preparation of substituted quinolines as well, also improving the efficacy of the Skraup synthesis by using *hydrogen-transfer* methodology.[12,43-59] In the first step benzyl alcohol reacts with aniline leading to imine **4.26** (Scheme 4.9). When **4.26** is submitted to a Mannich-type reaction with an aliphatic alcohol under acidic conditions, instead of an elimination reaction an acid-mediated cyclocondensation can take place, leading to quinoline **4.28** (Scheme 4.9). In this way it may be possible to perform the quinoline synthesis with simple and stable alcohols instead of aldehydes as starting materials.

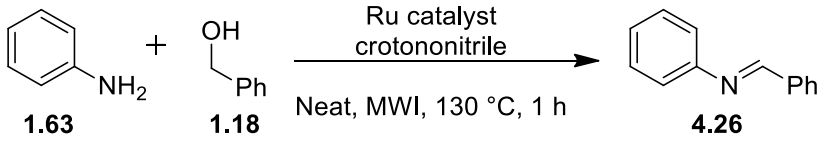


Scheme 4.9

A hypothetical strategy for the synthesis of quinolines from alcohols.

4.2.1 Optimisation of the Schiff-Base Synthesis

To test the feasibility of the method described above, first the synthesis of arylimines using a hydrogen-transfer protocol was studied. Aniline **1.63** and benzyl alcohol **1.18** were used as model substrates for establishing the optimal reaction conditions for formation of the imine intermediate (Scheme 4.10).



Scheme 4.10

Optimisation of imine synthesis.

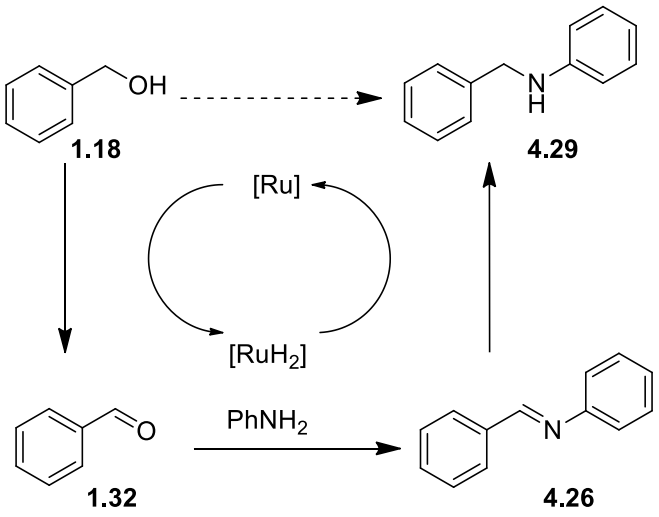
The performance of several Ru-based catalysts was evaluated. The chosen catalysts were known to be particularly active in hydrogen transfer reactions. All of the ruthenium complexes studied afforded reasonable yields of quinoline (Table 4.1, entries 1-5), with best results obtained when using $RuH_2CO(PPh_3)_3$ (Table 4.1, entry 5). Catalyst loading could be lowered to 4 mol% without decrease in yield, whereas already with 3 mol% of catalyst the yields were somewhat lower (Table 4.1, entry 13). The catalyst performance was further enhanced by addition of a catalytic amount of Xantphos as a ligand. Use of a ligand improved the catalyst efficiency (Table 4.1, entries 5 and 6), and a slight excess of benzylalcohol further improved the Schiff base formation (Table 4.1, entries 7-10).

Table 4.1 Catalyst screening for synthesis of imine from **4.1** with **4.30**

Entry	4.1 (mmol)	4.31 (mmol)	Catalyst [a]	Ligand[a]	Temp. (°C)	Time (h)	Yield (%)[b]
1	1.0	5.0	$Ru_3(CO)_{12}$	-	130	1	60
2	1.0	5.0	$RuH_2(PPh_3)_4$	-	130	1	43
3	1.0	5.0	$[Ru(p\text{-cymene})Cl_2]_2$	-	130	1	57
4	1.0	5.0	$RuHCl\ (PPh_3)_3$	-	130	1	48
5	1.0	5.0	$RuH_2(CO)(PPh_3)_3$	-	130	1	63
6	1.0	5.0	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	97
7	1.0	3.0	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	98
8	1.0	1.5	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	98
9	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	98
10	1.0	1.0	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	97
11	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	18[c]
12	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	24	95[c]
13	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	86[d]
14	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	1	36[e]
15	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	130	0.5	83
16	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	120	1	90
17	1.0	1.2	$RuH_2(CO)(PPh_3)_3$	Xantphos	110	3	79

Unless otherwise specified all reactions were carried out under MW. [a] 4 mol %. [b] Conversion into imine was determined by ^1H NMR spectroscopic analysis. [c]Reaction conducted under thermal heating. [d]Reaction performed using 3 mol% of catalyst and 3 mol% of ligand. [e] Reaction performed without crotononitrile.

Imine formation proceeded smoothly both with traditional heating and under MW conditions. With MW the reaction was complete in 1 h, whereas with traditional heating the imine formation required 24 h (Table 4.1, entries 9 and 12). In both cases the yields were almost quantitative as shown by ^{1}HNMR analysis of the reaction mixture. Both halving the reaction time and lowering the temperature caused the imine conversion to drop significantly even after prolonged reaction times (Table 4.1, entries 15-17). When the reaction is performed without crotononitrile, benzyl alcohol is still oxidised quantitatively. However, the hydrogen acceptor is needed to inhibit reduction of the imine to amine **4.29** *via* a borrowing hydrogen pathway. Indeed, without crotononitrile it was found that the imine was present in low quantities in the reaction mixture, the main product of the reaction being amine **4.29 (**Scheme 4.11). This underlines the importance of the presence of a hydrogen acceptor in the reaction mixture, not only to promote the formal oxidation of the benzyl alcohol, but also to prevent the reduction of the imine. (Table 4.1, entry 14). In the optimal reaction conditions, aniline **1.63** (1 mmol) with 1.2 equivalents of alcohol **1.18** in the presence of catalytic amounts of $RuH_2CO(PPh_3)$ (4 mol%), Xantphos (4 mol%) and crotononitrile (1.5 mmol) under solvent-free MW heating at 130 °C for 1 h resulted in a quantitative conversion of the starting materials into imine **4.26** (Table 4.1, entry 9).



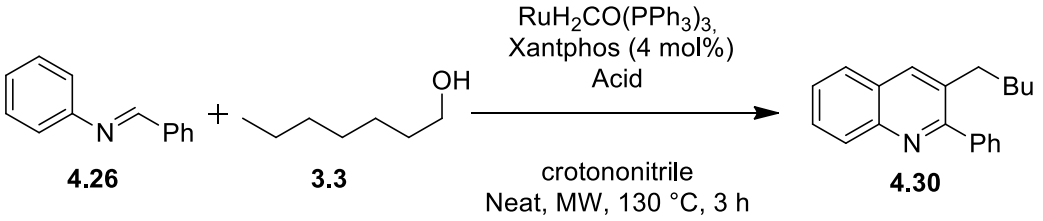
Scheme 4.11

In the absence of crotononitrile imine **4.26** is reduced to amine.

Unfortunately all attempts to prepare imines by reacting arylamines with aliphatic primary alcohols failed. This is due to the fact that the resulting alkyl imines (ArNH=CHR) are better hydrogen acceptors than crotononitrile, and only product observed was alkylated amine that is formed when the imine is reduced through hydrogen borrowing pathway.

4.2.2 Cyclisation of Imine with an Aldehyde, Optimisation of the Quinoline synthesis

Once the imine synthesis was optimised, the application of the catalytic system was extended to the reaction between imine **4.26** and heptanol **3.3** for the synthesis of quinolines. The reaction of imine **4.26** (3 mmol) with 1-heptanol **3.3** (1 mmol) in the presence of catalytic amounts of $RuH_2CO(PPh_3)$ (4 mol%), Xantphos (4 mol%), a suitable acid catalyst and crotononitrile (3 mmol) worked well, affording quinoline **4.30** in good yields (Scheme 4.12).



4.26 **3.3** **4.30**

Scheme 4.12

Synthesis of quinoline **4.30** from imine and alcohol.

To find the best catalyst for the cyclocondensation test reaction various acids were examined. When HCl was used heptanol did not oxidise quantitatively, thus giving low yield of quinoline (Table 4.2, entries 1-2). HCl may in fact inhibit the ruthenium catalyst used in the oxidation, and to avoid this heterogeneous acid were next studied (Table 4.2, entries 3-5). Heterogeneous acids have an added advantage in that they can be easily recycled and reused. The acid chosen was silica gel functionalised with sulphuric acid but, unfortunately, 1-heptanol was not converted quantitatively, and hence the yield of the quinoline resulted low.

The best results were obtained with organic acids of moderate strength. Among the screened acids, trifluoroacetic acid (TFA) gave the best results in the cyclisation reaction (Table 4.2, compare entries 1-7 with entry 9). Unsurprisingly, no product was formed in the absence of an acid catalyst (Table 4.2, entry 11). The amount of TFA could be lowered down to 0.3 equivalents with no decrease in the yields (Table 4.2, compare entries 8 and 9), whereas lower amounts of TFA resulted in diminished yields (Table 4.2, entry 10).

Varying the molar alcohol **3.3** to imine **4.26** ratio under the optimised conditions also proved to have a significant impact on the reaction. (Table 4.2 entries 12-14). The best results were achieved with a 1.5:1 molar ratio (Table 4.2, entry 13).

Table 4.2 Optimisation of the cyclisation step

Entry	Acid Catalyst	**4.34** (mmol)	**4.35** (mmol)	Yield (%)[a]
1	HCl (0.5 mmol)[b]	3.0	1.0	10
2	HCl (0.5 mmol)[c]	3.0	1.0	12
3	SiO_2-OSO_3H (100 mg)	3.0	1.0	20
4	SiO_2-OSO_3H (250 mg)	3.0	1.0	20
5	SiO_2-OSO_3H (500 mg)	3.0	1.0	20
6	TsOH[d]	3.0	1.0	51
7	MsOH[e]	3.0	1.0	53
8	TFA (0.5 mmol)[f]	3.0	1.0	58
9	TFA (0.3 mmol)	3.0	1.0	60
10	TFA (0.15 mmol)	3.0	1.0	51
11	-	3.0	1.0	-
12	TFA (0.3 mmol)	2.0	1.0	65
13	TFA (0.3 mmol)	1.5	1.0	70
14	TFA (0.3 mmol)	1.0	1.0	49
15	TFA (0.3 mmol)[g]	1.5	1.0	51
16	TFA (0.3 mmol)[h]	1.5	1.0	55

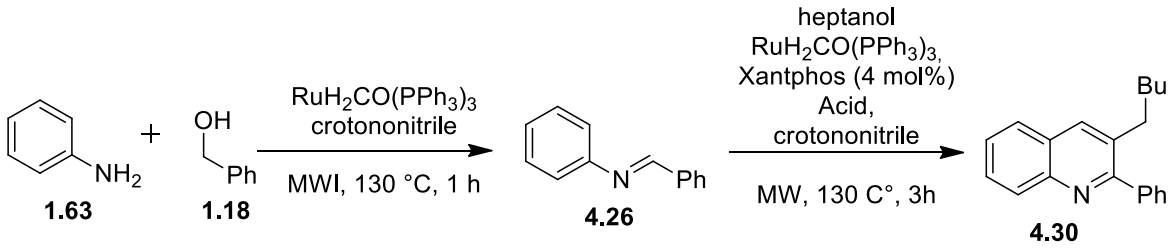
[a] Isolated yields. [b] 4 M in Dioxane. [c] 4 M in CPME. [d] TsOH = p-toluenesulfonic acid. [e] MsOH = methanesulfonic acid. [f] TFA = trifluoroacetic acid. [g] Reaction preformed at 120 °C (MWI) for 3 h. [h] Reaction preformed at 130 °C (MWI) for 1 h.

The optimal reaction temperature proved to be 130 °C. Higher temperatures did not provide better yields, and decrease of the reaction temperature by as little as 10 °C, from 130 °C to 120 °C, already resulted in slightly lower yields (Table 4.2, entries 15 and 16).

4.2.3 Optimisation of the One Pot Procedure for Synthesis of Quinolines

After both the imine formation and the cyclisation step were optimised separately, a direct one-pot conversion of benzyl alcohol **1.18**, aniline **1.63**, and 1-heptanol **3.3** into quinoline **4.30** was studied. Performing both transformations in a one-pot fashion resulted in a complex reaction mixture with the main products being *N*-alkylated anilines instead of a quinoline. This was not altogether unsurprising, considering the complexity of the reaction sequence and the possible side reactions in all of the transformations. Performing the imine formation first, followed by addition of the aliphatic alcohol in a following step should circumvent this problem. The synthesis of quinoline **4.30** was therefore performed

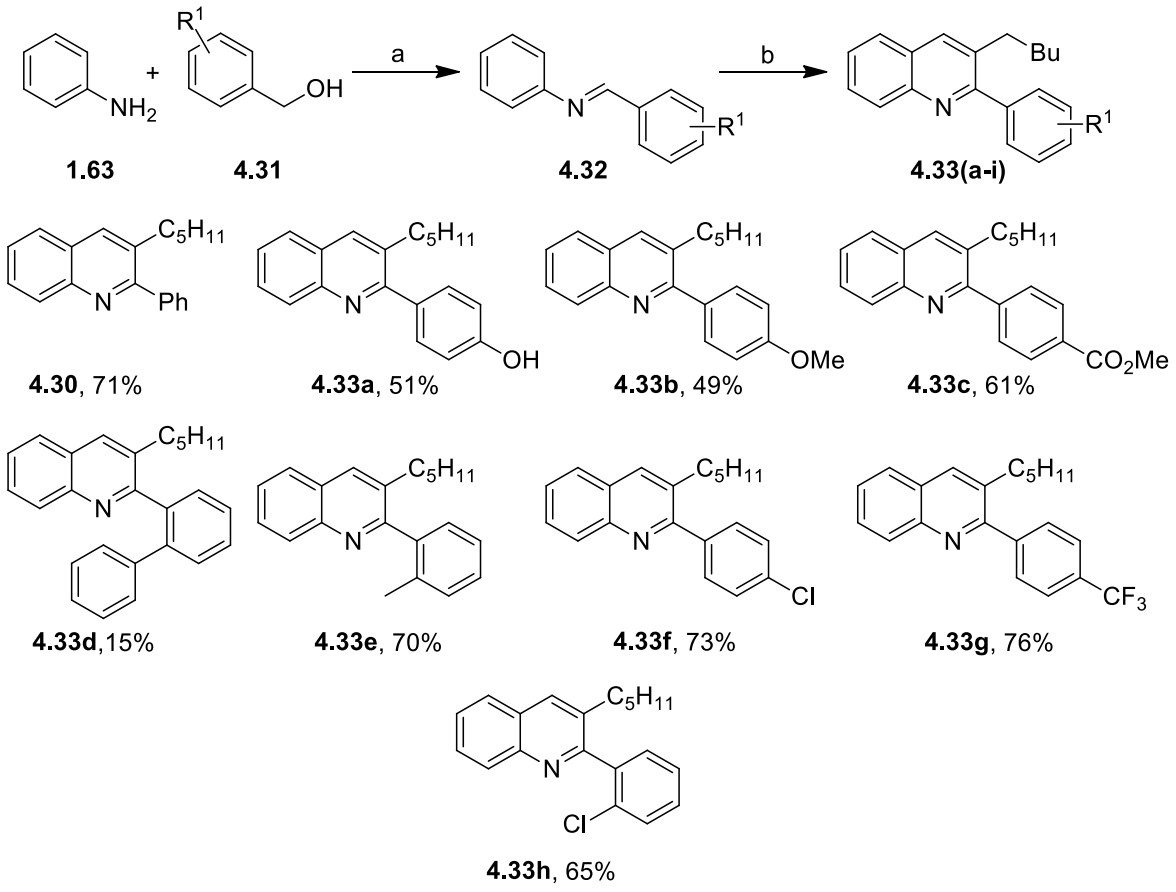
using a one-pot two-steps approach, where the benzyl alcohol and aniline were allowed to react first, and then, in the second step, 1-heptanol was added into the reaction mixture (Scheme 4.13). The Ru-based catalyst was added during the first step, and it promotes the hydrogen transfer reactions in both steps of the process, while TFA was only added in the second step to catalyse the intra-molecular annulation reaction. Crotononitrile plays a dual role by promoting both the "formal" *in-situ* oxidation of alcohols to aldehydes and the final aromatisation of the intermediate hydroquinoline ring system.



Scheme 4.13

Synthesis of quinoline by one pot two step approach.

In a standard reaction procedure, benzyl alcohol (1.8 mmol) and aniline (1.5 mmol) were reacted in the presence of $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%) and crotononitrile (2 mmol) under MW at 130 °C for 1 h. After the imine formation was complete 1-heptanol (1 mmol) was added, along with crotononitrile (2.2 mmol) and a catalytic amount of TFA (0.3 mmol). The resulting reaction mixture was heated (MW) at 130 °C for further 3 h, affording the expected quinoline **4.30** in 71 % isolated yield. These optimised reaction conditions were used to study the scope and limitations of this synthesis, by combining a broad range of anilines with benzylic and aliphatic alcohols.



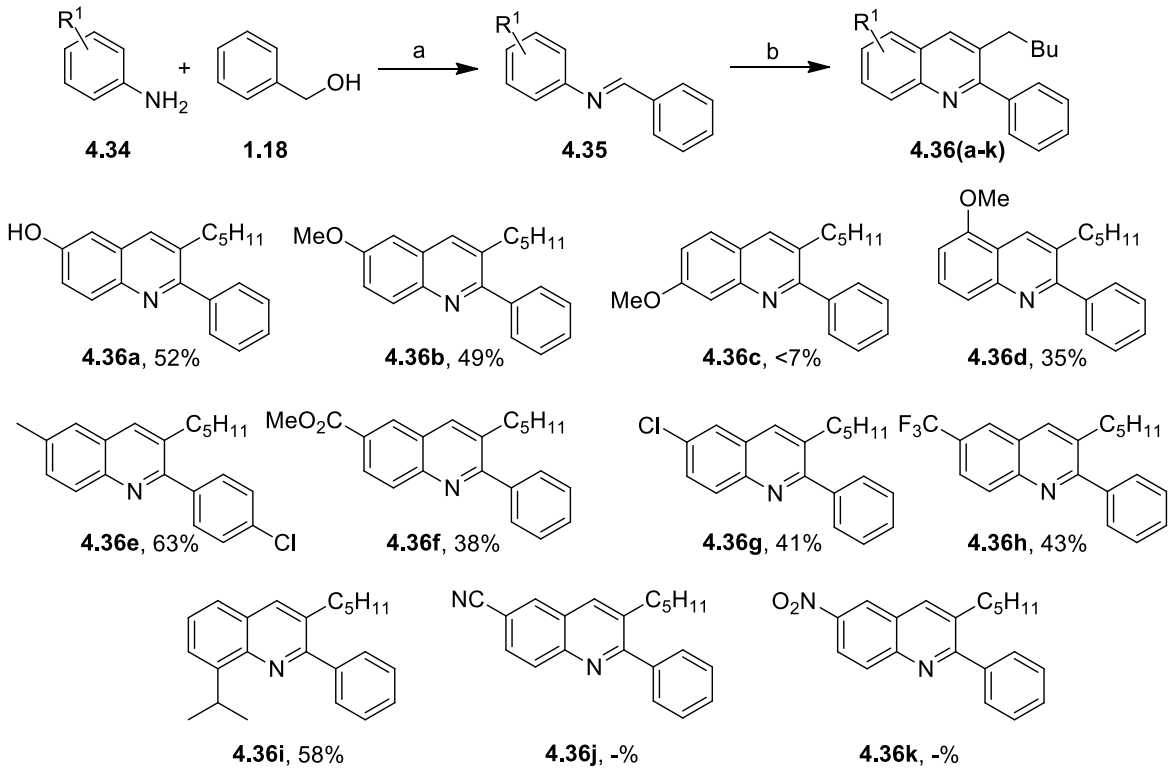
Scheme 4.14

Synthesis of quinolines from substituted benzylic alcohols. a) $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%) , crotononitrile , Neat, MW at 130 °C for 1 h. b) TFA, crotononitrile, neat, MW, 130 °C, 3 h.

First, the benzylic alcohol used in the imine formation was varied. Alcohols with electron withdrawing groups on the aromatic system showed better activity than those with electron donating groups, indicating that the reaction is sensitive to electronic effects (Scheme 4.14, **4.33c, 4.33f**-**g** and **4.33a**-**b**). Although electron rich benzylic alcohols were less reactive and gave slightly lower yields, the corresponding quinolines were still obtained in reasonable quantities. The effect of steric hindrance was also studied (Scheme 4.14, **4.33d** and **4.33e**). When a bulky substituent was introduced at the *ortho*-position of the aromatic ring, the yields suffered a considerable decrease (Scheme 4.14, quinoline **4.33d**). The reaction tolerates a wide range of functional groups such as halogen, carboxymethyl, alkoxy, and hydroxyl substituents on the aromatic alcohol moiety (Scheme 4.14, quinolines **4.33a**, **c**, **d**, **f**).

Next a variety of arylamines (Scheme 4.15) were studied. A range of substituents were chosen to assess the feasibility of the reaction, and both electron withdrawing and electron donating substituents

were included, as well as substituents in *meta* position to determine the regioselectivity of the reaction, and substituents in the *ortho* position to study the steric effect on the yields.

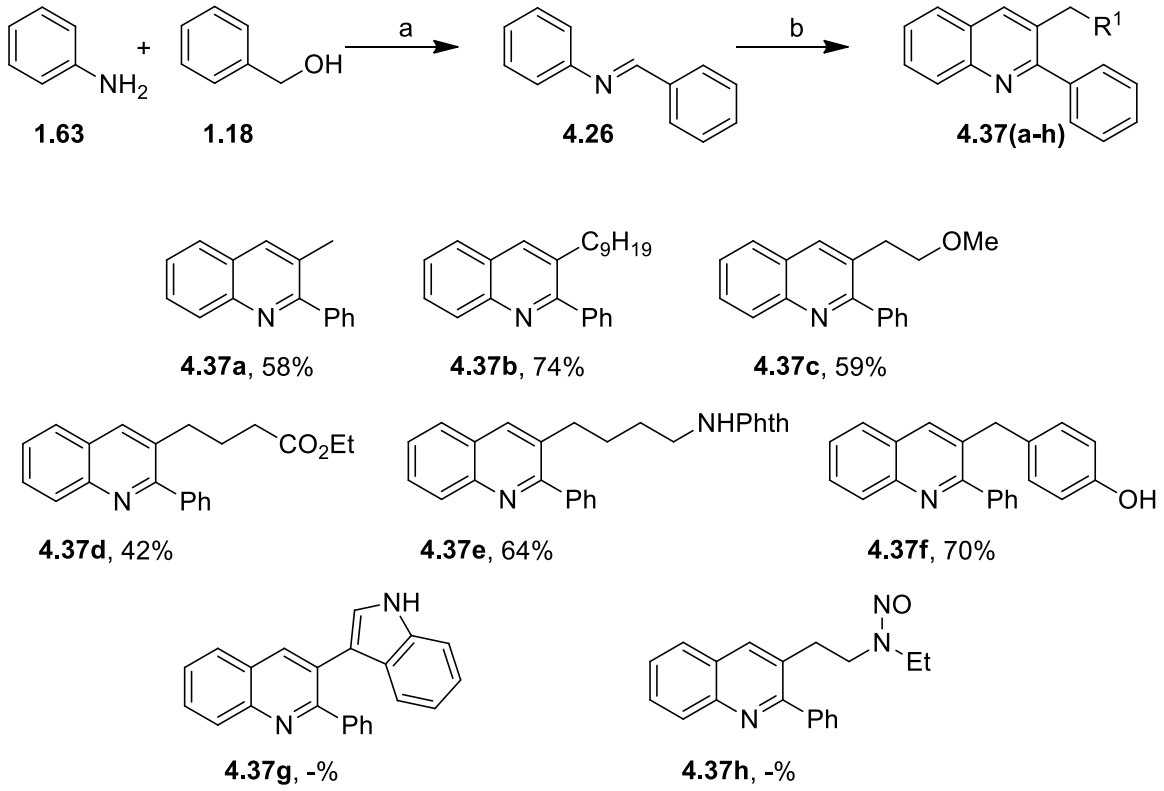


Scheme 4.15

Synthesis of quinolines with substituted anilines. a) $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%), crotononitrile , Neat, MWI at 130 °C for 1 h. b) TFA, crotonitrile, Neat, MWI, 130 °C, 3 h.

Most aniline derivatives studied worked satisfactorily, with anilines containing electron withdrawing groups on the aromatic ring proving only slightly less reactive, giving somewhat lower yields than the others. Both 4-nitroaniline and 4-cyanoaniline reacted very sluggishly in the imine formation step, and also failed to afford intended quinolines **4.36k** and **4.36j**, respectively. When 3-methoxyaniline was used, the reaction gave a 85/15 mixture of two regioisomers **4.36c** and **4.36d** as determined by ^{1}HNMR analysis.

Last, quinolines with different aliphatic alcohols were prepared in order to vary the substituents in the C-3 position. We chose primarily alcohols with easily modifiable functional groups such as ester, protected amine and phenol. The possibility of further manipulation of these groups opens a route to an easy synthesis of diversely-substituted quinolines.



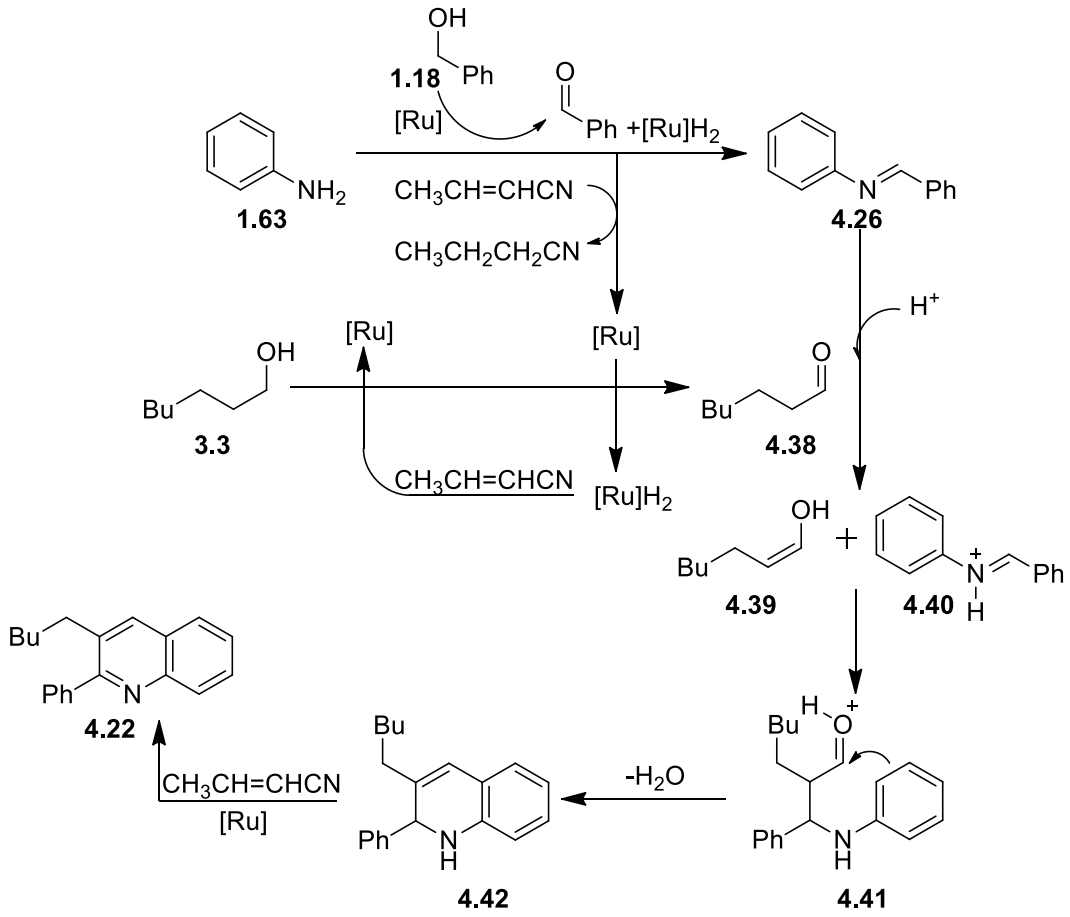
Scheme 4.16

Synthesis of quinolines with functionalised aliphatic alcohols. a) $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%), crotononitrile, MW at 130 °C for 1 h. b) R^1CH_2OH, TFA, crotonitrile, MW, 130 °C, 3h.

Changing the length of the aliphatic alcohol had little effect on the outcome of the reaction, as did the fuctional groups on the aliphatic alcohol. Primary alcohols with different chain-end functionalities worked satisfactorily (Scheme 4.16, quinolines **4.37a**-**f**), and all of the above mentioned functional groups gave satisfactory yields. Only in the cases of **4.37g** and **4.37h** no product formation was observed (Scheme 4.16).

A proposed reaction mechanism involves an initial hydrogen transfer from the benzyl alcohol **1.18** to the ruthenium catalyst, generating the corresponding aromatic aldehyde along with the reduce form of the catalyst, $[Ru]H_2$ (Scheme 4.17). Crotononitrile acts as a sacrificial hydrogen acceptor, oxidising $[Ru]H_2$ back to the active catalytic species. In the second step the aliphatic alcohol **3.3** undergoes a ruthenium-assisted oxidative dehydrogenation reaction in a similar way, giving the reactive aliphatic

aldehyde. Nucleophilic attack of enol **4.39** to protonated imine **4.40** gives intermediate **4.41**, which in the subsequent heteroannulation reaction forms the 1,2-dihydroquinoline **4.42**.



Scheme 4.17

Reaction mechanism

The aromatisation process is accompanied by the generation of one equivalent of hydrogen, which is trapped by crotononitrile, with concomitant formation of quinoline **4.22**. In the absence of crotononitrile, it is the imine intermediate **4.26** that works as hydrogen acceptor, leading to very low reaction yields of quinoline.

In order to validate the proposed reaction mechanism, the model reaction was reinvestigated using benzaldehyde (first step) and heptanal (second step) instead of the corresponding alcohols. Under the same experimental conditions, indeed quinoline **4.22** was obtained, albeit with a lower yield (51%). A proposed hypothesis was that the use of alcohols as *in-situ* source of aldehydes might avoid or at least limit several side reactions that are typical of aldehydes.

4.3 Conclusions

It was demonstrated that a set of aliphatic and aromatic alcohols can be oxidatively cyclised with an array of anilines under acidic conditions and in the presence of a ruthenium catalyst to afford quinolines in moderate to good yields. Alcohols (attractive, readily available and easily handled starting materials) play a key role in this reaction as aldehyde precursors. The simple experimental procedure combined with the wide availability of cheap building blocks makes this method reasonably general. The reaction proceeds, in most cases, in good yields. It tolerates microwave heating conditions, which considerably reduced reaction times. The possibility to carry out the reaction neat and without stoichiometric amounts of oxidants makes this reaction environmentally benign and no cumbersome purification techniques are necessary. Many of the compounds synthesised using this procedure were previously unknown (78%), suggesting that this methodology may provide a direct route to quinoline derivatives inaccessible using a conventional approach.

4.4 References

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5. Synthesis of β-Lactams

5.1 Introduction

β-Lactams are four-membered cyclic amides, that are most widely known for their applications in pharmaceutical chemistry. They can be found in antibiotics such as penicillin and its derivatives, cephalosporins and carbapenems (Figure 4.1). Lately β-lactams have also been applied in other fields of pharmaceutical chemistry. They have proven to have activity also as HIV-protease inhibitors in vitro[1,2] and some penicillin derivatives have even been found to have antitumoral properties.[3] They are also valuable intermediates in the synthesis of non-natural β-amino acids and peptidomimetic compounds[4,5], have also been used in polymerisation reactions,[6] for example to produce bio-functional nylon-3-polymers that have peptide-like backbone.[6-9]

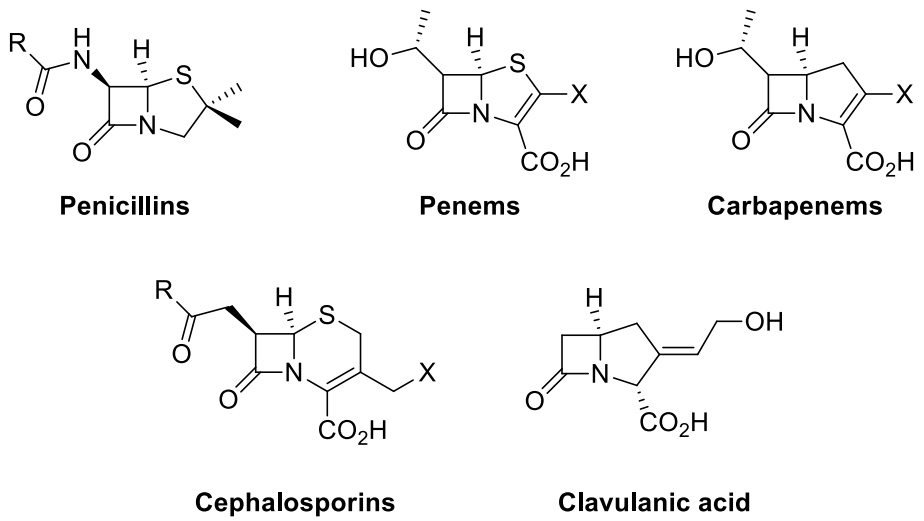


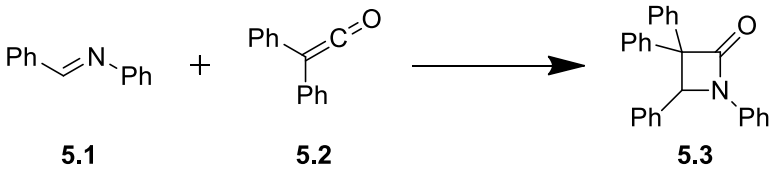
Figure 5.1

Common classes ofantibiotics with a bicyclic β-lactam core, and Clavulanic acid that is used as a β-lactamase inhibitor, thus prolonging the half-life of antibiotics.

Most existing synthetic strategies for β-lactams are still based on a [2,2] cycloaddition of an imine and a ketene. The ketene can be formed in various ways; from a terminal alkyne via a metallovinylidene,[10] from a carboxylic acid,[11] or by the most commonly adopted way, via elimination from an acid chloride.[12-14] Both imines and ketenes are very labile molecules, and especially ketenes need to be synthesised only just before their use.

5.2 Staudinger β-lactam Synthesis and its Variations

There are various existing syntheses for β-lactams, mostly by a [2,2] cycloaddition of a ketene with an imine.[15-17] The first synthesis of a β-lactam was achieved by Hermann Staudinger[18] in 1907. He reacted a Schiff base of an aniline and benzaldehyde with diphenylketene, and a [2,2] cycloaddition of the imine and the ketene gave β-lactam **x** (Scheme 4.1). Up until 1970 the synthesis and research on β-lactams concentrated mostly on penicillin and cephalosporin analogs (Figure 4.1), but in the recent decades the research has gone beyond antibiotics and β-lactams have found new applications both in pharmaceutical chemistry, and as building blocks in polymer synthesis.

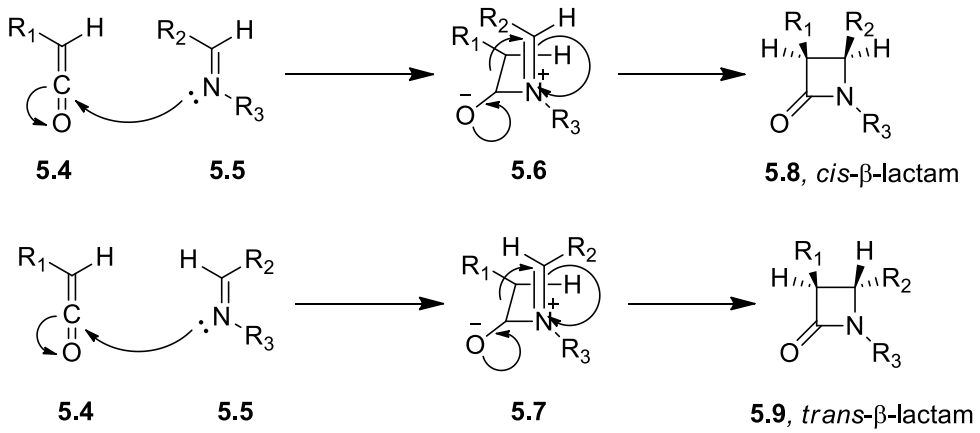


5.1 **5.2** **5.3**

Scheme 5.1

Staudinger beta lactam synthesis

The Staudinger synthesis is a [2,2] cycloaddition reaction.[19] In the first step the nucleophilic nitrogen attacks the electrophilic carbonyl carbon, generating a zwitterionic intermediate. This step is facilitated by electron donating groups on the imine, whereas in the presence of electron withdrawing group the reaction does not usually take place. The second step can be either an intermolecular nucleophilic ring closure, or alternatively a conrotatory electronic ring closure.



Scheme 5.2

The reaction mechanism of the Staudinger synthesis. E-enolate gives the cis-product **5.8**, whereas a Z-enolate gives the trans product **5.9**.

The stereochemistry of the product is difficult to predict, as it depends on which of the two steps is rate determining, and on other factors that affect the initial stereochemistry of the imine. Generally it can be agreed that (E)-imines give *cis*- β-lactams, and (Z)-imines form *trans*- β-lactams. The ketene substituent affects the transition state by either speeding up or slowing down the progress towards the β-lactam. A slower reaction allows time for the isomerisation of the imine, and generally results in a *trans* product, whereas a faster reaction is obviously more likely to give a *cis* β-lactam (Scheme 5.2).[19-23] The outcome of the reaction can also be guided by addition of catalysts[20,24-26], chiral ligands[27,28], directing groups[29] or chiral auxiliaries[27,28,30-32].

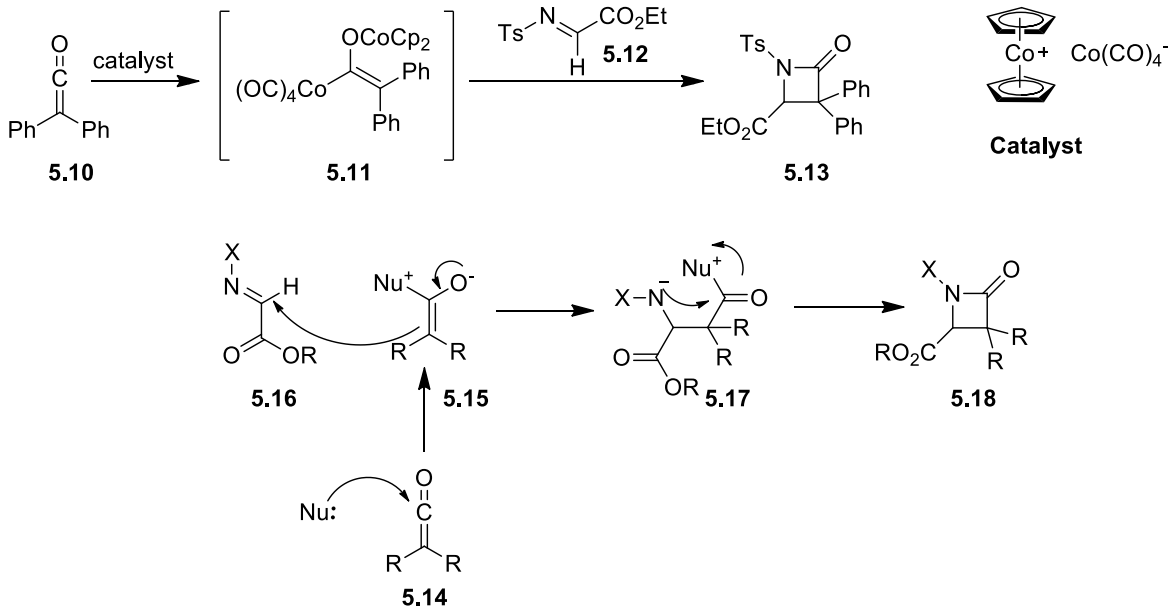
Most Staudinger syntheses use acid chlorides or carboxylic acids as ketene precursors. Acid chlorides are readily available, easy to handle even in large quantities and often stable enough to store for prolonged periods in the right conditions. Acid chloride synthesis is also very straightforward and gives access to a variety of starting materials. There are some synthetic methods where the ketene is synthesised from other precursors, but as a rule acid chlorides are the reagent of excellence in ketene synthesis.

5.2.1 Catalytical Staudinger Syntheses with Acid Chlorides and Imines as Starting Materials

Traditional Staudinger synthesis proceeds without a catalyst, and among the reactions using acyl chloride as starting material is still often the method of choice for the synthesis of beta lactams. In recent

years major advances in developing the Staudinger synthesis have been in catalytic Staudinger reactions using acyl chlorides as starting materials, and these reactions are represented by some examples below.

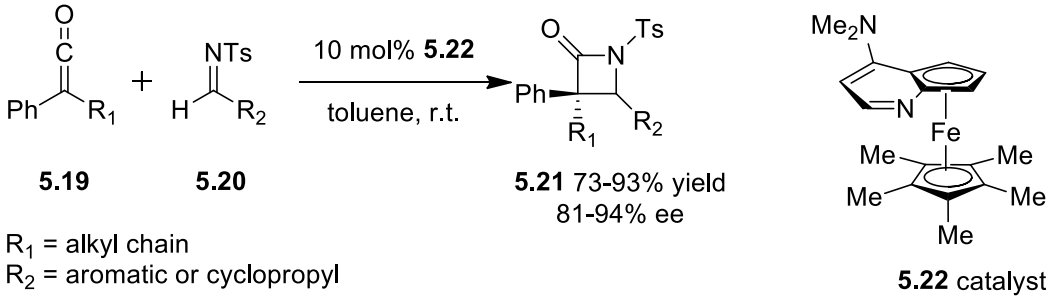
In order to render the reaction catalytic the classical reaction pathway needs to be modified. This can be achieved by reversing the electronic properties by altering the substituents on the reagents so that the imine reacts as an electrophile, and the ketene becomes a nucleophile (classical umpolung). The first catalytic Staudinger reaction was reported by Lectka[26] in 1999. They used the umpolung method by using a cobalt catalyst that adds to the ketene forming a metalloenolate, thus umpoling the reaction (Scheme 4.3).



Scheme 5.3

The first catalytic synthesis of beta lactams, performed by Lectka[26] and the mechanism of the Staudinger synthesis in catalysed reactions.

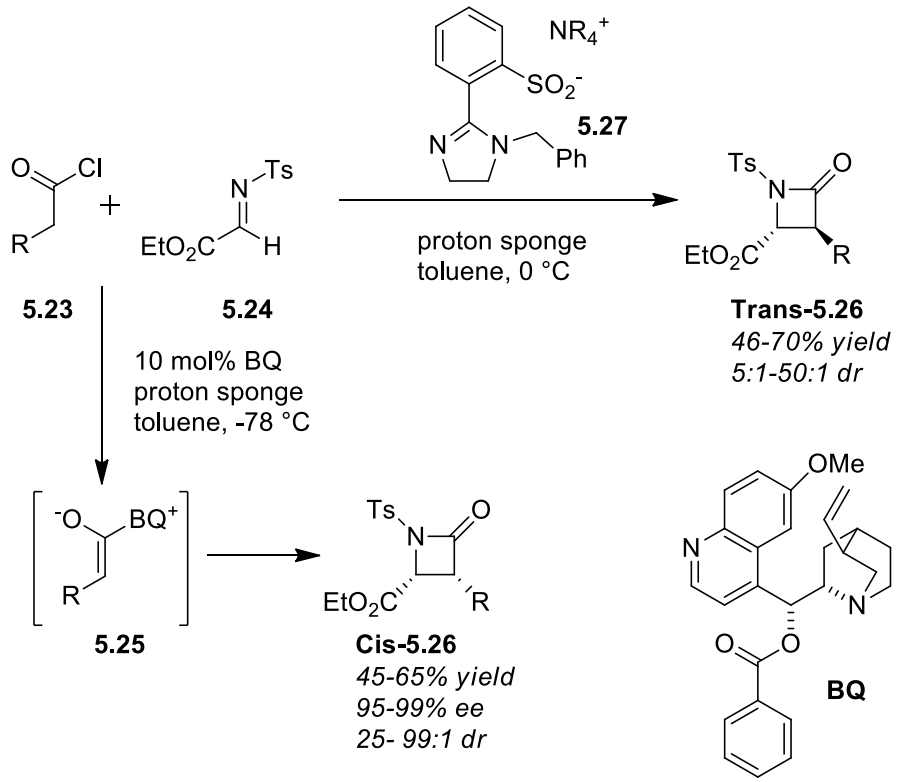
A few years later Hodous *et al.*[28] reported a similar reaction, using a planar chiral catalysts such as azaferrocene and its derivatives. The best stereoselectivity was achieved with pyrrolidino derivative **5.22** that gave cis-β-lactams in good enantiomeric excess (Scheme 5.4).



Scheme 5.4.

Stereoselective synthesis of N-Tosyl- β-lactams using a ferrocene catalyst **5.22**.[28]

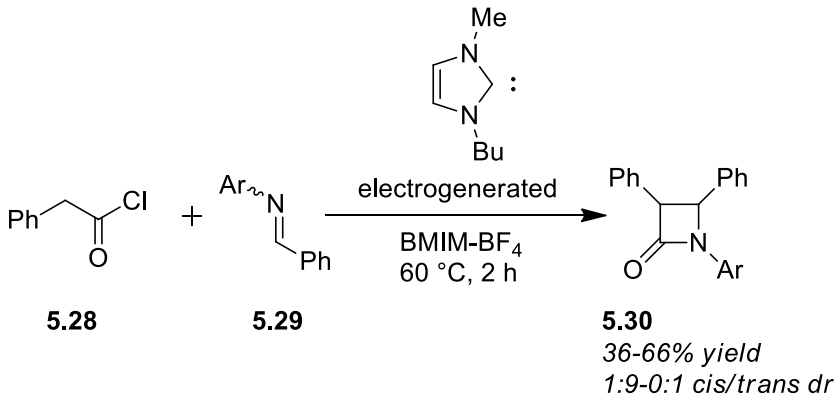
Lectka also used the umpolung methodology later on, moving from metal catalysts to organocatalysis, to synthesise a range of beta lactams from electron deficient ketenes and tosyl imines with high enantioselectivity, albeit with only moderate yields.[26,33-35] He optimised a synthesis using an anionic catalyst based on a 2-aryl-2-imidazoline scaffold, where the same starting materials -changing the reaction conditions- gave either *cis*- or *trans*- β-lactams as the product with excellent diastereoselectivity (Scheme 5.5). Trans- β-lactams were obtained at 0 °C with **5.27** as catalyst, whereas when the reaction temperature was lowered to -78°C and benzoylquinine (BQ) was used as catalyst the major product was the cis- β-lactam.



Scheme 5.5

Selective synthesis of cis- and trans- beta lactams from same starting materials by changing the catalyst.[33,34]

Another type of anionic catalyst that has been used in the synthesis of β-lactams are *N*-heterocyclic carbenes (NHC). These can be generate either by using bases,[29] or electronically as done by Feroci *et al.*[16] They used electrogenerated NHCs as organocatalysts in Staudinger synthesis, using the ionic liquid as both catalyst and solvent (Scheme 5.6). This is one of very few Staudinger syntheses that have been reported where ionic liquids have been used.[16,29,36,37] Instead of using a base to deprotonate the imidazolium, triazolium or thiazolium salts, the anion was generated using an electrochemical one-electron process. They chose to use less electrophilic imines, as the reaction of an electronegative imine with NHC is normally not reversible. The reaction proceeded smoothly with good yields, giving mainly the trans- diastereomer (Scheme 5.6). Also in this case the reaction seems to proceed via the alternative pathway described for organicatalytic Staudinger syntheses (Scheme 5.3).



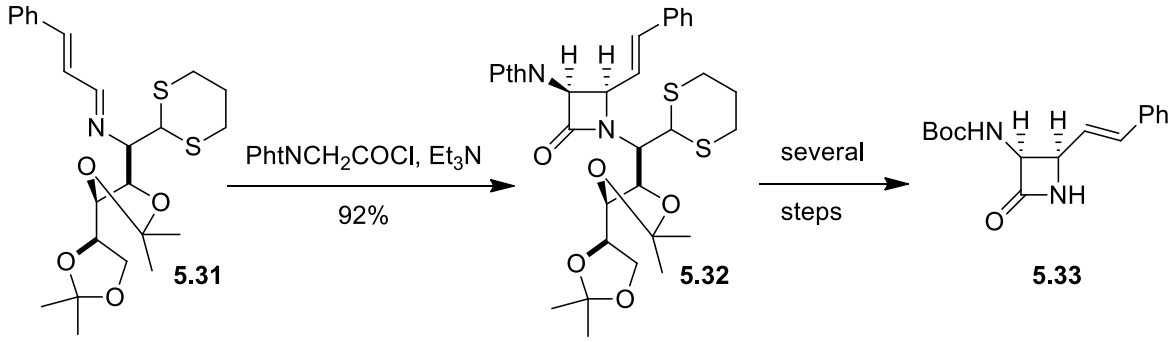
Scheme 5.6

NHC-Catalysed Staudinger synthesis in BMIM-BF_4

In 2007 Tao[37] and co-workers applied ionic liquids into the synthesis of β-lactams on solid support, using an imine grafted onto solid support and using acid chloride as ketene precursor. They synthesised a small library of compounds using this methodology, in high yields and with good diastereoselectivity. All reactions gave almost exclusively the *cis*- β-lactam as a product.

5.2.2 Use of Chiral auxiliaries in the Staudinger reaction

One of the possible strategies in asymmetric β-lactam synthesis is the use of chiral auxiliaries, most commonly on the imine nitrogen. These auxiliaries guide the reaction towards the desired diastereoselectivity –most commonly the cis- β-lactam- and can then be removed to give the final product.



Scheme 5.7

Synthesis of a β-lactam with chiral auxiliary.

One of the first examples of asymmetric induction using chiral auxiliaries dates back to 1990 when Barton *et al.* used an imine derived from D-glucosamine and cinnamaldehyde, with phthalimidoyl acetyl chloride to synthesise β-lactam **5.33**.[38-40] This compound was then transformed into β-lactam **5.33** in several steps (Scheme 5.7).[38] In this case, the chiral auxiliary is derived from the amine, and indeed when the chiral moiety is derived from the aldehyde, the reactions often give very poor yields.[27,41]

5.3 Synthesis of β-lactams for OLED Applications

Although β-lactams have so far been most useful in pharmaceutical chemistry, this does not exclude their possible applications in other fields of chemistry and material science. Like quinoline derivatives, β-lactam structure, especially if fused onto another ring or as a part of a bigger system, could open new possibilities for the development of efficient OLEDs. They could be used to tweak the molecules, shifting the emission spectra, and also to provide greater solubility and decrease the stacking of planar molecules. The ring structure is stable in the manufacturing and operating temperatures of OLEDs, so introducing a β-lactam moiety onto a scaffold should not decrease the stability of the molecule.

As can be seen from the examples above, the synthesis of β-lactams and the improvements of the Staudinger synthesis are mostly concerned on improving the stereoselectivity and yields of the compounds, without giving as much concern to the ease of performing the reaction, the starting materials needed and their costs, the purification of the product and its intermediates, as well as the general scope of the reactions. Often the improvements made in obtaining the desired product are shaded by the general cost of the reaction and the time consumed in performing it. When the needed β-lactam is not the end product but rather a building block in a synthesis of a larger molecule (like in the case of OLEDs), these considerations can become limiting in the choice of synthetic approach, and a more facile and economic route is often preferred. One can of course always opt for the classical Staudinger synthesis, preforming and imine and a ketene separately and then reacting them together, but the obvious optimal solution, both time- and cost wise, would be to perform all the steps - imine formation, ketene formation and the cycloaddition reaction- all in one pot.

Most existing synthetic strategies for the synthesis of β-lactams are still based on a [2,2] cycloaddition of an imine and a ketene. The ketene can be formed in various ways; from a terminal alkyne via a metallo vinylidene,[10] from a carboxylic acid,[11] or by the most commonly adopted way, via elimination from an acid chloride.[12-14] Both imines and ketenes are very labile molecules, and therefore a method with which they can be generated *in situ* should facilitate the synthesis. The synthesis of β-

lactams without the need of catalysts or other expensive reagents is industrially more convenient, and reducing the synthetic and purification steps in the process would make it even more appealing.

A modification of a traditional Staudinger synthesis, where both imine and ketene are formed in situ from cheap starting materials using no additives apart from a base would reduce both the cost and the purification to minimum. Recent advances in the Staudinger synthesis often rely on expensive catalysts and reagents, labile starting materials, and pose problems in purification and versatility. Although we now have methods for synthesising selectively the desired product with even quite exotic substituents, the reactions in themselves have become more complex and demanding to perform. There is therefore still room for improvement, and a facile and yet versatile synthetic route to β-lactams would definitely find its uses.

For initial studies on how a β-lactam substituent would affect the optic properties of a bigger molecule, such as substituted triazine or heptazine, a simple β-lactam with no special substituents should suffice. The aim in the β-lactam synthesis was therefore not so much to synthesise a myriad of compounds with a vast array of properties, but rather to put together a facile and efficient synthesis that would give a series of β-lactams with aromatic substituents, and with hopefully either a free NH group or another functional group that would allow to link the β-lactam onto the triazine or heptazine core.

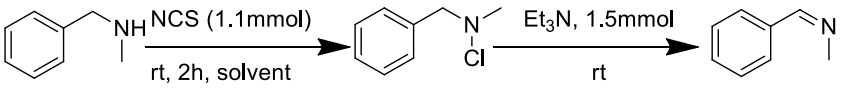
The traditional Staudinger synthesis was chosen due to its versatility and the diversity of the available starting materials. To limit the purification steps, cost and the time consumed in synthesising the β-lactams all the steps, from imine formation to the final cycloaddition, were performed in one pot.

5.3.1 Formation of Imine *in Situ*

Formation of chloroamines from secondary amines is widely described in the literature,[42-48] as is also the conversion of chloroamines to imines.[48-53] It was therefore decided that a good approach to the synthesis of imines in situ would be first the formation of a secondary chloroamine, followed by the conversion of this into the corresponding imine. This would subsequently react with either a preformed ketene, or a ketene also synthesised *in situ* in the same reaction mixture, hopefully giving a β-lactam as a product.

The pilot reactions on chloroamine and imine formation were carried out with *N*-methylbenzylamine, and the chloroamine formed smoothly and in quantitative yields either in diethyl ether, dichloromethane or in acetonitrile. For the formation of the imine from the chloroamine a group of bases were studied, and the best results were obtained by performing the formation of chloroamine and elimination to give the imine in acetonitrile, using triethylamine as a base (Table 5.1). The synthesis of a chloroamine from methylbenzylamine with *N*-chlorosuccinimide proceeded smoothly and in

quantitative yields, as did the generation of the corresponding imine with trimethylamine as a base, and the imine formation was complete in a few hours at room temperature.



5.34 **5.35** **5.36**

Table 5.1 Screening of bases and solvents for imine formation

Entry	Base	Solvent	Yield (%)
1	DBU	DCM	49
2	DBU	MeCN	54
3	Et_3N	MeCN	quant.
4	Et_3N	DCM	85
5	DABCO	MeCN	-
6	TMG	MeCN	-
7	Et_3N/DMAP	MeCN	61

Reactions were carried out at room temperature under Ar. yields were determined by NMR from crude reaction mixture.

5.3.2 Formation of Ketene *in Situ* and Cycloaddition Reaction

At this point, the formation of a ketene in situ in the reaction mixture was studied. Another equivalent of triethylamine was added, followed by phenoxyacetyl chloride. The ketene formed from phenoxyacetyl chloride with triethylamine then reacted smoothly with the imine already present in the reaction, resulting in a cis β-lactam as a product.

A number of solvents were screened, as well as different quantities of the base and phenoxyacetyl chloride for ketene formation. The results are summarised in table 5.2. The best results were achieved with acetonitrile as solvent, and 2 equivalents of both phenoxyacetyl chloride and triethylamine for ketene formation, although lowering the amount of acid chloride to 1.5 equivalent and triethyl amine to 1 equivalent did not lower the yields significantly. As the ketene formation in situ and the subsequent 2+2 rearrangement proceeded smoothly, preforming the ketene separately was not necessary.

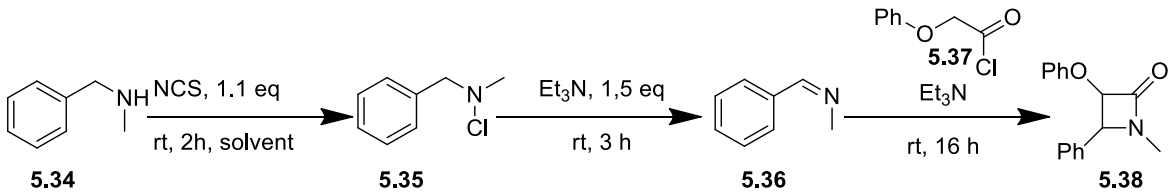


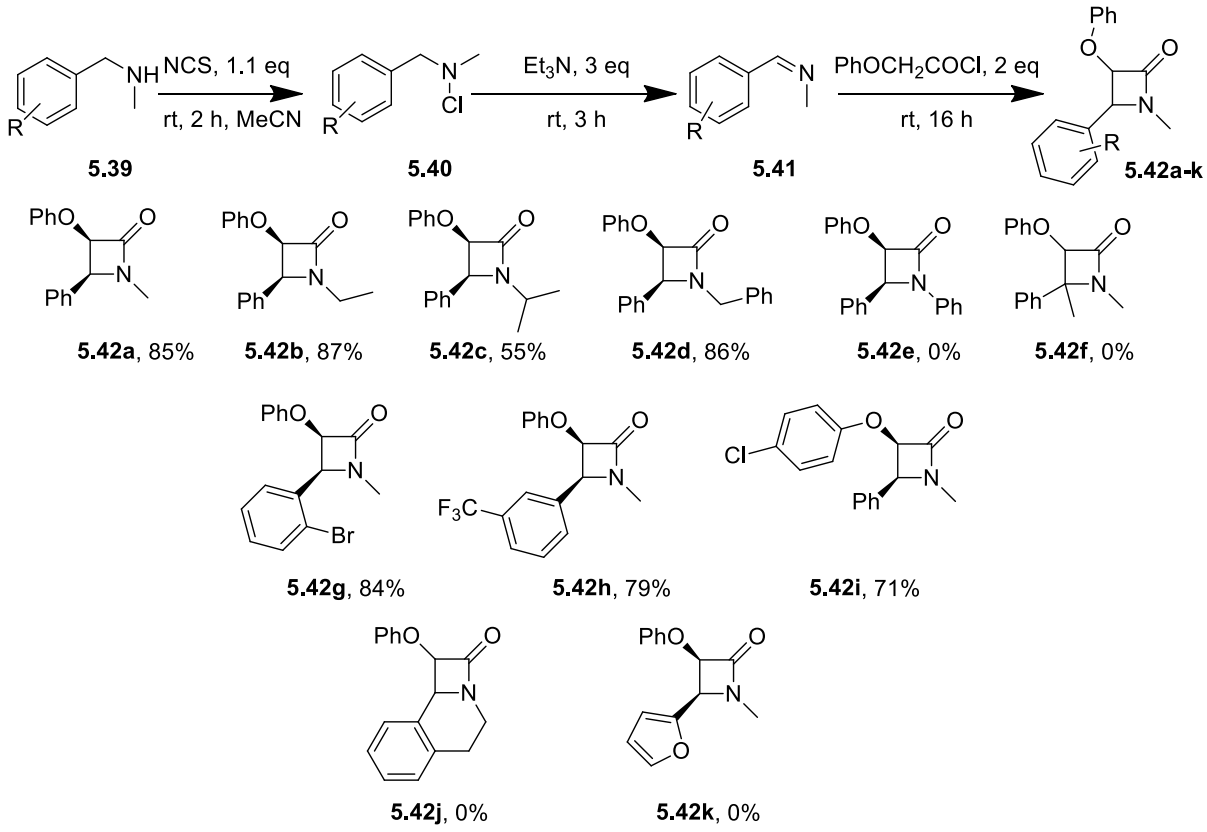
Table 5.2 Screening of solvents and reagent quantities for final step

Entry	5.34 (eq)	5.37 (eq)	Solvent	Yield (%)[a]
1	1	2	toluene	16
2	1	2	CH_2Cl_2	69
3	1	2	THF	22
4	1	2	MeCN	85
5	1	1	MeCN	42
6	1	1.5	MeCN	71
7	1.5	1	MeCN	60

Reactions were carried out at room temperature under Ar. a) Isolated yields.

5.3.3 Synthesis of β-lactams from Phenoxyacetyl Chloride and Methoxyacetyl Chloride

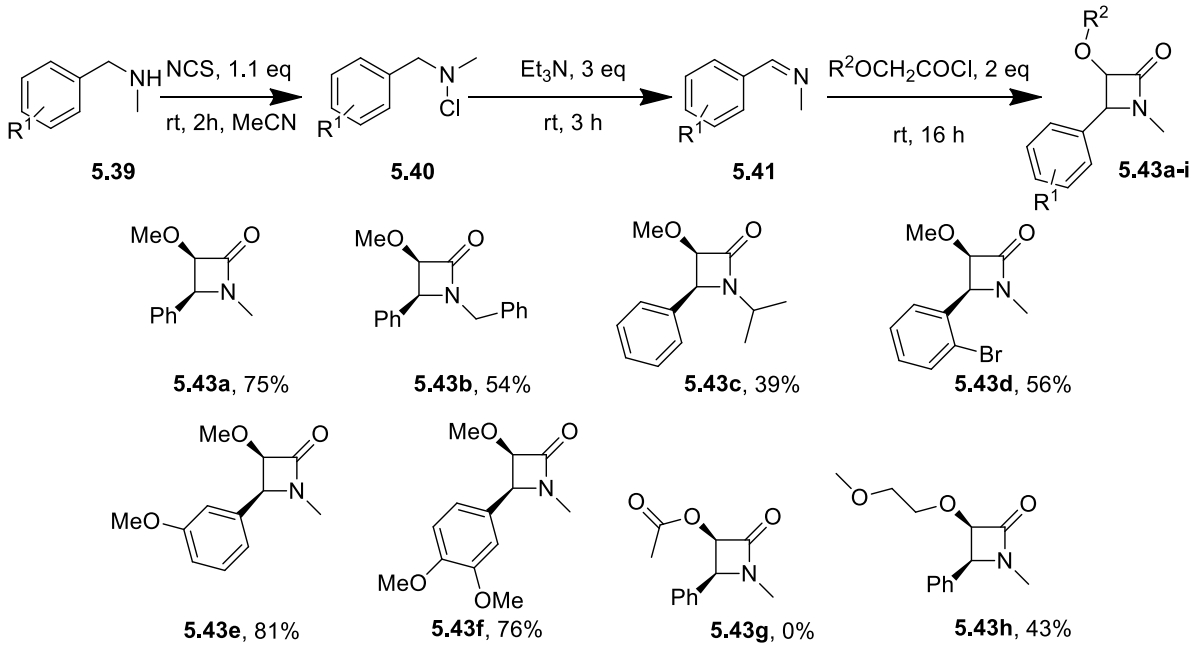
The developed methodology was now tested on a variety of amines. The reaction works well with a variety of substituted benzylic amines with little change in yields. Dibenzylamine gave **5.42d** in very good yields, and debenzylating the β-lactam should give a free NH group that can then be used to attach the molecule onto a triazine or a heptazine core. Unfortunately when the reaction was carried out with a cyclic aromatic amine –although the chloroamine formation and the elimination step to give the imine worked well- a reaction with a ketene did not afford the desired product. This may be due to the additional ring strain in the forming of a fused β-lactam ring. Even when the reaction with tetrahydroisoquinoline was carried out with stronger bases and elevated reaction temperatures no product was observed. (Scheme 5.8) Also reactions with branched amines and amines with other aromatic rings were problematic and only traces of product were observed. In the case of **5.42k**, the product was formed in good yield as could be seen from the crude NMR, but unfortunately the reaction was very messy and separating the product from the side products proved to be impossible.



Scheme 5.8

Synthesis of beta lactams with phenoxyacetyl chloride.

The next step was to vary the acid chloride. The reaction worked well also with methoxyacetyl chloride. The yields were somewhat lower than with phenoxyacetyl chloride, but still acceptable. The reaction was also performed with acetoxyacetyl chloride. Successive deacetylation would afford a free OH group that could be used as a handle to attach the β-lactam onto a triazine or a heptazine core. Unsurprisingly, acetoxyacetyl chloride did not yield the desired product. It chloride most likely deacetylates already at some point in the reaction giving rise to a series of side products, and although lowering the reaction temperature does avoid this to some extent, it also slows down the reaction allowing time for the ketene to decompose before reacting with the imine.



Scheme 5.9

Synthesis of beta lactams with methoxyacetyl chloride.

5.3.4 Studies with Aliphatic Amines

Reactions with aliphatic amines afforded no product. The reaction was tested with N-methylbutylamine and phenoxyacetyl chloride, varying the base used in imine formation, as well as solvent and temperature of the reaction. Synthesis of the chloroamine proceeded smoothly, but imine formation and reaction with ketene to give a β-lactam proved to be more problematic. With triethylamine the the imine did not form even in high temperatures, nor with ^{t}BuOK or DBA-DBU, either in room temperature or at reflux in toluene or acetonitrile. We also attempted the formation of an aliphatic imine with KO_2 in diethyl ether, but also in this case the imine formation was problematic, and ketene formation in situ failed.

The problems encountered with forming aliphatic imines from chloroamines were not unexpected, but it was nevertheless decided to persevere on studying this reaction as there are indeed very few literature precedents of forming the imine from an aliphatic amine. Unfortunately even though we did in the end succeed in forming the imine in situ, the reaction conditions were not compatible with forming the ketene in situ and performing the cycloaddition reaction.

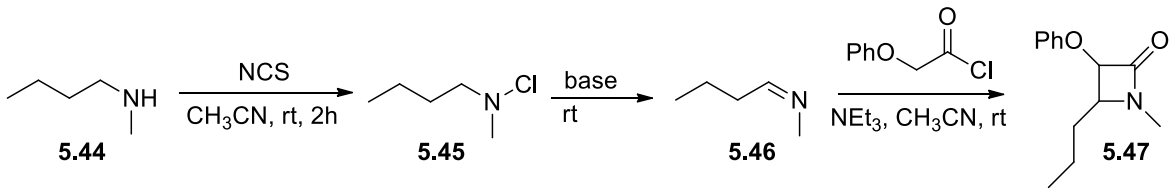


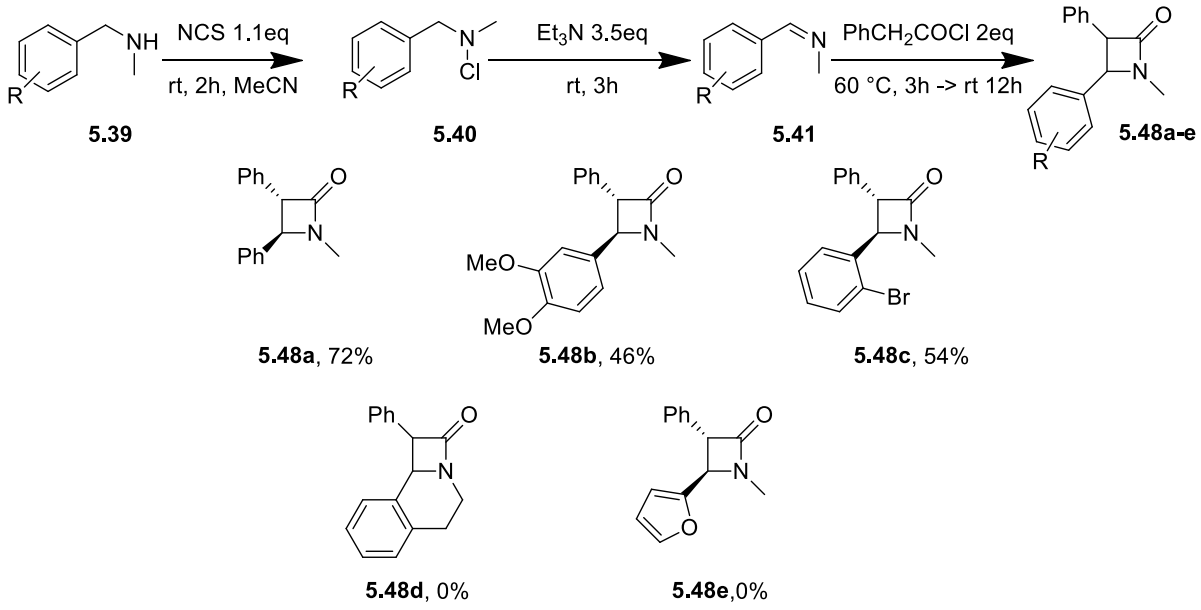
Table 4.3

Entry	Amine (eq)	Solvent	result
1	NEt_3 (1.5)	MeCN	The imine does not form even when heated
2	^tBuOK (1.1)	MeCN	An open amide forms instead of a cyclic one.
3	KO_2 (2,2)	MeCN	An open amide forms instead of a cyclic one.
4	KO_2 (2,2)	Et_2O	Chloroamine does not form well.
5	KO_2 (2,2)	DCM	Both chloroamine and imine are formed, but not the final product.
6	DBA-DBU	-	trace s of product with large excess of DBA-DBU
7	NBS/pyridine	MeCN	Imine does not form

5.3.5 Optimisation of the Reaction Conditions with Phenylacetylchlorides and aliphatic Acid Chlorides

Surprisingly, when the phenoxyacetyl chloride was replaced with phenylacetyl chloride the reaction did not proceed as before and no product was obtained. Phenoxy substituent on the ketene obviously makes it more reactive and the reaction with phenylacetyl chloride was not expected to be as fast or to give equally good yields, but not obtaining any product at all came as a surprise. However, with a few small changes to the reaction procedure – heating the reaction mixture in the ketene formation step to 60 °C– the reaction proceeded as smoothly as before, giving the products in reasonable yields (Scheme 5.10).

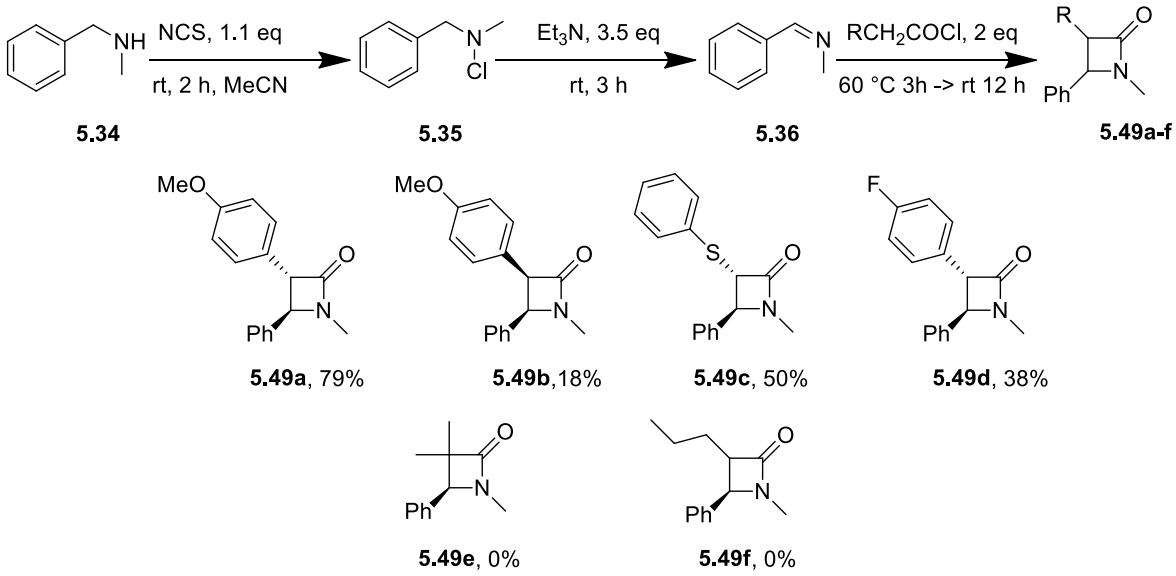
Again, substituents on the benzylamine had little effect on the reaction outcome (**5.48a-c**), and as before cyclic amine gave no product (**5.48d**). It is possible that forming such a constrained fused ring system requires even more energy than what heating to 60°C provides, and the ketenes are not stable in the reaction temperatures required for this ring formation for long enough to allow the reaction to take place. In the case of **5.48e** the product was identified in the crude NMR, but as in the case of β-lactam **5.42k**, isolation and purification proved to be very difficult and the product was not isolated in reasonable purity.



Scheme 5.10

Synthesis of beta lactams with phenylacetyl chloride.

With substituted phenylacetyl chlorides electron withdrawing groups decrease the yield very slightly, whereas electron donating groups increase the yield significantly, giving an overall quantitative yield of *cis* and *trans* isomers (scheme 5.11, compounds **5.49a** and **5.49b**). The reaction with (phenylthio)acetyl chloride failed to give the desired product at room temperature, but with the procedure used for phenylacetyl chlorides the reaction proceeded smoothly and in good yield giving the trans isomer **5.49c** as the only isolated product.



Scheme 5.11

Synthesis of beta lactams with substituted phenylacetyl chlorides.

Unsurprisingly aliphatic acyl chlorides did not afford the desired products. Aliphatic ketenes are most likely not stable enough in these reaction conditions, and the reaction of the ketene with an imine does not take place in the low temperatures where alkyl ketenes would be stable. Indeed there are no literature precedents using aliphatic ketenes in reactions with imines.

Curiously enough, in the case of phenoxy- and methoxyacetylchlorides all the products obtained have the *cis* conformation, and no *trans* beta lactams were observed. Instead, with phenylacetyl chlorides the major, and in most cases only, product was the *trans* beta lactam. This was first thought to be due to different reaction temperatures, since there are several literature precedents where heating gives the trans isomer, whereas carrying out the reaction at colder temperatures results in the cis isomer. However, even when heated phenoxyacetyl chloride still gives the cis isomer **5.42a** as the only product. Also, reacting benzylidenemethylamine with 2 equivalents of phenylacetyl chloride and triethylamine at room temperature gives the *trans* isomer **5.48a** as the only product, although in only 13% yield. It is therefore more likely that the electronic properties of the starting materials play a greater role in the outcome of the reaction, with the more electronegative phenoxy-substituent favouring the *trans*- conformation in the final product.

5.4 Conclusions

A facile synthetic approach to substituted β-lactams was designed, starting from a secondary benzylic amine and an acid chloride. The reactions proceeded smoothly in the case of phenoxy- methoxy- and phenylacetyl chlorides, and with all benzylic amines. The substituents on the aromatic rings had little effect on the outcome of the reactions, and the products were obtained in good yields. The reactions with aliphatic amines proved challenging, and the work on resolving the problems encountered in the synthesis of β-lactams using aliphatic amines is still ongoing.

5.5. References

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6. Experimental

6.1 General Experimental

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware. Reagents used were of commercial grade and, when necessary, were purified prior to use as described by Perrin and Armarego.[1] Solvents used were distilled before use: THF was distilled from sodium and benzophenone under Ar, DCM and triethylamine were was distilled from calcium hydride. Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or Fluka in sure/sealedTM bottles over molecular sieves.

Thin layer chromatography was performed on glass backed sheets coated with silica gel (0.25 mm) containing the fluorescent indicator UV_{254}. Flash chromatography was performed following the procedure outlined by Still,[2] on Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh).

^{1}H NMR spectra were obtained at 400 MHz on a Bruker Bruker Avance III NMR spectrometer at 25 °C. Peak positions are quoted against the δ scale relative to the residual chloroform (δ 7.27) or DMSO (δ 2.54) signal, using the following abbreviations; singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quint), multiplet (m). ^{13}C NMR spectra were obtained at on a Bruker Bruker Avance III NMR spectrometer at 25 °C. The multiplicities of the signals were determined by DEPT experiment at 135° and are quoted within the brackets using the following notation; quaternary (0), tertiary (1), secondary (2) and primary (3). Coupling constants are are reported in hertz (Hz).

All infrared spectra were obtained on a Bio-Rad Golden Gate A FT-IR spectrometer. The relative intensity of the peaks are quoted within the brackets using the following abbreviations; broad (br), strong (s), medium (m), weak (w).

High resolution CI and EI mass spectra were obtained on a VG 70SE normal geometry double focusing mass spectrometer. High resolution ES mass spectra were obtained on a Bruker Apex III FT-ICR mass spectrometer, or on a Micromass Q-Tof 1 mass spectrometer.

All the reactions involving microwave dielectric heating were performed with a microwave oven (Discover from CEM) under mono-mode irradiation in a 10-mL glass tube sealed with a CEM's proprietary "snap-on" cap, or in open vessel mode. The reaction mixtures were stirred with a magnetic stirrer bar during the irradiation. During the course of reactions in sealed tube, the internal temperature was monitored through an IR sensor (standard infrared temperature sensor). The maximal internal pressure was monitored and maintained under the value of 300 psi using the provided software. At the end of the reaction, the tube was cooled to room temperature with air-compressed jet cooling.

Raman scattering measurements were carried out in back scattering geometry with the 1064 nm line of an Nd:YAG laser. Measurements were performed in air at room temperature with a compact spectrometer BWTEK i-Raman Ex integrated system with a spectral resolution of about 9 cm−1. The spectra were collected with very low power (5 mW) concentrate in a spot of 1 mm2 of dimension in order to avoid any degradation and/or modification of the organic compounds during the measurements.

UV−vis absorption measurements were carried out by means of a spectrophotometer Perkin-Elmer Lambda 15 (spectral bandwidth 2 nm) in the 250−700 nm range.

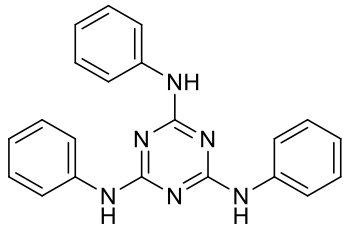
Steady state photoluminescence (SSPL) measurements were performed using the filtered light from a laser driven Xenon lamp (EQ-99-X) with a final bandwidth of about 1 nm. The excitation wavelength for each sample was in correspondence of the relative absorption maximum.

Calculations of Vibrational modes were carried out using Gaussian 09 code.[3] Raman spectra calculations for the optimized structures were performed in density functional theory (DFT) with the Becke's 3 parameters and the Lee–Yang–Parr's nonlocal correlation functional (B3LYP).[4,5] The basis sets for C, N, H were 6-31G (d,p). Analysis of frequencies confirms that optimized structures are at minimum of potential surface and no imaginary frequencies are obtained. Calculated frequencies were compared to experimental data after a scaling by a factor 0.96 due to the correction of the harmonic approximation and the incomplete DFT approaches. The intensities of the Raman bands were estimated by calculating the differential Raman scattering cross-section.

Time-resolved photoluminescence (TRPL) measurements were performed by means of a streak camera (Hamamatsu C5680) coupled to grating spectrograph (Arc-Spectra-Pro 275i). Pulsed laser excitation source at λexc = 355 nm was provided by a Coherent PS laser module with a pulse duration of 300ps and repletion rate of 1 KHz. The laser spot was focused on a 500 μm spot with a power of 0.2 mW. PL measurements were obtained in different time range: temporal resolution was 100 ps with a 20 ns time range and better than 40 ps in the range lower than 10 ns.

6.2. Experimental for Chapter 2

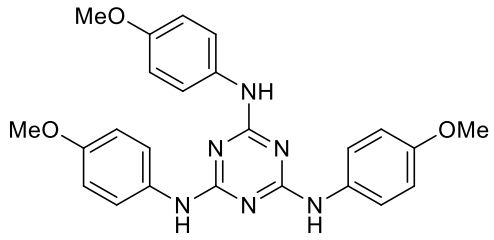
N^2,N^4,N^6-triphenyl-1,3,5-triazine-2,4,6-triamine (2.4)



Cyanogen chloride (184 mg, 1 mmol) was dissolved in THF (8 ml), DIPEA (600 µl, 3.5 mmol) was added followed by aniline(320 µl, 3.5 mmol) and the reaction mixture was heated to reflux for 48h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with water and brine, dried over Na2SO4 and concentrated to give the crude product. Purification by column chromatography gave the product as a pale yellow solid, 235 mg, 66%. M.p. 210-213 °C.

R_f = 0.42 (4:1 Hexane/EtOAc)
ν (nujol) 3258, 1578, 1520, 1449, 1378, 1231, 993, 755.
δ_H (400MHz; DMSO-d^6) 7.74-7.56(6H, m, NH, Ar), 7.34(6H, t, *J* = 7.3, Ar), 7.09(6H, t, *J* = 7.4Hz, Ar).
δ_C (100MHz; DMSO-d^6) 163.8(0), 138.3(0), 128.5(1), 128.5(1), 121.1(1).
HRMS (EI) Calcd. for $C_{21}H_{18}N_6$: 354.1593. Found: 354.1601.

N2,N4,N6-tris(4-methoxyphenyl)-1,3,5-triazine-2,4,6-triamine (2.5)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in THF (10 ml). DIPEA (0.60 ml, 3.5 mmol) and a solution of p-anisidine (430 mg, 3.5 mmol) in THF (5 ml) were added and the reaction mixture was heated to reflux for 72 h. The reaction mixture was concentrated on silica and column chromatography (40% EtOAc in hexane) gave the product as a palebrown solid, 100 mg, 22%. M.p. 212-214 °C, lit.[6] 214-216 °C.

R_f = 0.41 (1:1 Hexane/EtOAc)
ν (nujol) 3330, 3251, 1576, 1530, 1505, 1380, 1227, 1036, 987, 827, 794.

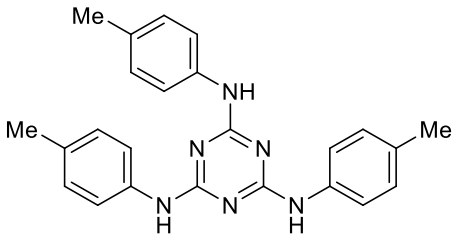
δ_H (400MHz; DMSO-d^6) 10.1(3H, m, NH), 7.67-7.49(6H, m, Ar), 6.90(6H, d, *J* = 7.7Hz, Ar), 3.75(9H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 163.7(0), 155.6(0), 131.2(0), 122.7(1), 113.7(1), 55.2(3).

HRMS (EI) Calcd. for $C_{24}H_{24}N_6O_3$: 444.1910. Found: 444.1916.

Spectroscopic data agrees with Kolmakov.[6]

N2,N4,N6-tri-p-tolyl-1,3,5-triazine-2,4,6-triamine (2.9)



Method A; Cyanuric chloride (1 mmol, 184 mg) was dissolved in dioxane (20 ml), and p-toluidine (642 mg, 6 mmol) was added, followed by potassium carbonate (830 mg, 6 mmol). The reaction mixture was heated to reflux overnight, concentrated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The obtained off-white solid was suspended in hot ethanol (75ml) and filtered. The product precipitated from ethanol as a white solid, 114 mg, 29%. m.p. 238-240°C. lit.[7] 238-239 °C

Method B; Following a method described by Sha[7] Cyanogen chloride (3,33 mmol, 600 mg) was dissolved in a mixture of dioxane (15ml)and DMF (1,5 ml), and p-toluidine (1,07 g, 10 mmol) was added followed by $NaHCO_3$. The reaction mixture was then refluxed under microwave heating, 300 W, for 20 min. Solvent was concentrated under reduced pressure, the residue was suspended in water and filtered to give the product as a white solid, 1,27 g, 97%.

R_f = 0.45 (8:2 Hexane/EtOAc)

ν (nujol) 3431, 3407, 2360, 1516, 1496, 1456, 1424, 1377, 804.

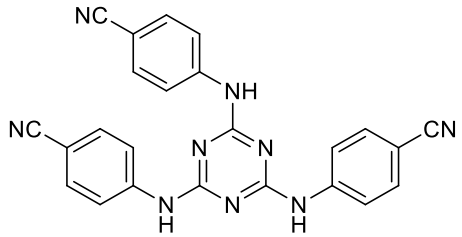
δ_H (400MHz; DMSO-d^6) 9.07(3H, s, NH), 7.67(6H, d, *J* = 7.6Hz, Ar), 7.09(6H, d, *J* = 8.0Hz, Ar), 2.28(9H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 164.0(0), 137.4(0), 130.7(0), 128.7(1),120.3(1), 20.4(3).

HRMS (EI) Calcd. for $C_{24}H_{24}N_6$: 396.2062. Found: 396.2057.

Spectroscopic data agrees with Kolmakov.[6]

4,4',4''-((1,3,5-triazine-2,4,6-triyl)tris(azanediyl))tribenzonitrile (2.10)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in toluene (4 ml) and 4-aminobenzonitrile (354 mg, 3 mmol) was added, followed by a solution of NaOH (120 mg, 3 mmol) in water (1 ml). Reaction mixture was heated to reflux for 16h, and the resulted suspension was filtered and washed with water to give the product as a white solid, 296mg, 69%. m.p. >300°C

R_f = 0.32 (1:1 Hexane/EtOAc)

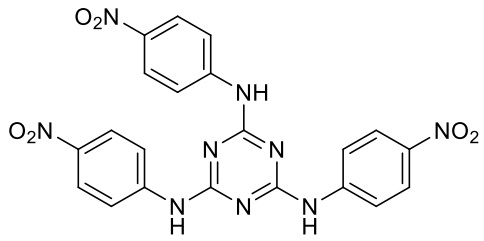
ν (nujol) 2224, 1696, 1607, 1589, 1465, 1378, 836.

δ_H (400MHz; DMSO-d^6) 7.38(6H, d, *J* = 7.9Hz, Ar), 6.60(6H, d, *J* = 7.9Hz, Ar), 6.13 (3H, s, NH).

δ_C (100MHz; DMSO-d^6) 153.0(2C, 0), 133.4(1), 120.6(1), 113.4(0), 95.5(0).

HRMS (EI) Calcd for $C_{24}H_{15}N_9$: 429.1450. Found: 429.1455.

N2,N4,N6-tris(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine (2.11)



Following a method described by Sha[7] Cyanogen chloride (3,33 mmol, 600 mg) was dissolved in a mixture of dioxane (15ml)and DMF (1,5 ml), and *p*-Nitroaniline (1.38 g, 10 mmol) was added, followed by $NaHCO_3$ (10 mmol). The reaction mixture was then refluxed under microwave heating, 300 W, for 20 min. Solvent was concentrated under reduced pressure, the residue was suspended in water and filtered to give the product as a yellow solid, 1,55 g, 95%.

R_f = 0.40 (8:2 Hexane/EtOAc)

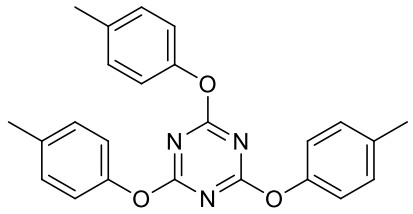
ν (nujol) 3340, 2924, 2853, 1624, 1591, 1521, 1506, 1483, 1465, 1326, 1302, 1250, 1111, 847, 750.

δ_H (400MHz; DMSO-d^6) 10.32(3H, s, NH), 8.25(6H, d, *J* = 8.5Hz, Ar), 8.12(6H, d, *J* = 8.8Hz, Ar).

δ_C (100MHz; DMSO-d^6) 163.9(0), 145.1(0), 141.4(0), 124.6(1),119.5(1).

HRMS (EI) Calcd. for $C_{21}H_{15}N_9O_6$: 489.1145. Found: 489.1141.

2,4,6-tris(p-tolyloxy)-1,3,5-triazine (2.14)

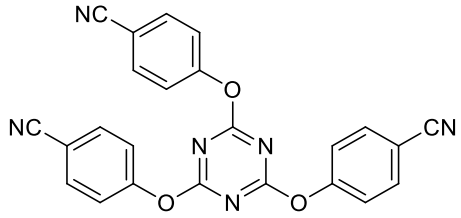


p-Cresol (811 mg, 7.5 mmol) was dissolved in acetone (3 ml) and 2M NaOH in water (3.75 ml, 7.5 mmol) was added to form solution A.

Cyanuric chloride (424 mg, 2.3 mmol) was dissolved in acetone (5 ml) and solution A was added dropwise. The reaction mixture was stirred at rt for 24 h, the formed precipitate was filtered and washed with water, ethanol and diethyl ether to give the product as a white solid, 794 mg, 86%. M.p. 222-224 °C.

R_f = 0.68 (7:3 Hexane/EtOAc)
ν (nujol) 3420, 2923, 2853, 1576, 1507, 1375, 1360, 1219, 1204, 1020, 805.
δ_H (400MHz; DMSO-d^6) 7.21(6H, d, J = 8.0Hz, Ar), 7.10(6H, d, J = 7.7Hz, Ar), 2.31(9H, s, CH_3).
δ_C (100MHz; DMSO-d^6) 173.2(0), 149.2(0), 135.1(0), 129.8(1), 121.1(1), 20.4(3).
HRMS (EI) Calcd. for $C_{24}H_{21}N_3O_3$: 399.1583. Found: 399.1587.
Spectroscopic data agrees with Iranpoor.[8]

4,4',4''-((1,3,5-triazine-2,4,6-triyl)tris(oxy))tribenzonitrile (2.15)



4-Hydroxybenzonitrile (894 mg, 7.5 mmol) was dissolved in acetone (5 ml) and a solution on NaOH (300 mg, 7.5 mmol) in water was added to form solution A.

Cyanuric chloride (424 mg, 2.3 mmol) was dissolved in acetone (3 ml) and the solution was cooled on ice. Solution A was then added dropwise. A white suspension formed immediately. The reaction mixture was stirred at room temperature overnight, the white precipitate was filtered and washed with

water, ethanol, diethyl ether and hexane to give the product as a white solid, 838 mg, 84%. M.p. 258-260 °C.

R_f = 0.50 (1:1 Hexane/EtOAc)

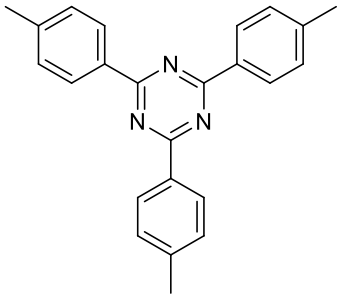
ν (nujol) 2239, 1575, 1501, 1456, 1221, 1023, 806.

δ_H (400MHz; DMSO-d^6) 77.96(6H, d, *J* = 7.6Hz), 7.48(6H, d, *J* = 7.6Hz).

δ_C (100MHz; DMSO-d^6) 172.5(0), 154.4(0), 134.1(1), 122.8(1), 118.2(0), 109.1(0).

HRMS (EI) Calcd. for $C_{24}H_{12}N_6O_3$: 432.0971. Found: 432.0968.

2,4,6-tri-p-tolyl-1,3,5-triazine (2.17)



Cyanogen chloride (92 mg, 0.5 mmol) and *p*-tolylboronic acid (340 mg, 2.5 mmol) were dissolved in a mixture of ethanol (0.75 ml) and toluene (10 ml). Cs_2CO_3 (488 mg, 1.5 mmol) and 2M K_2CO_3 (0.75 ml, 1.5 mmol) were added and the reaction was degassed. $Pd(PPh_3)_4$ (30 mg) was added and the reaction mixture was heated to reflux under Ar for 16h. The reaction mixture was allowed to cool to rt and was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (2-5% EtOAc in hexane) gave the product as a white solid, 23 mg, 13%. M.p. 278-280 °C. lit.[9] 278-280 °C.

R_f = 0.75 (9:1 Hexane/EtOAc)

ν (liq. film) 2920, 2359, 1516,1370, 1177, 797.

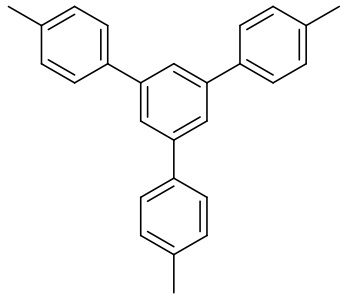
δ_H (400MHz; $CDCl_3$) 8.64(6H, d, *J* = 7.6Hz, Ar), 7.35(6H, d, *J* = 7.8Hz, Ar), 2.46(9H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 171.4(0), 142.8(0), 133.8(0), 129.3(1), 128.9(1), 21.7(3).

HRMS (EI) Calcd. for $C_{24}H_{21}N_3$: 351.1735. Found: 351.1729.

^{1}H NMR data data agrees with Zhou.[10]

4,4''-dimethyl-5'-(p-tolyl)-1,1':3',1''-terphenyl (2.19)



p-TsOH and 4-methylacetophenone were heated to 130 °C for 16h, after which the reaction was quenched with aqueous saturated $NaHCO_3$ (10 ml) and extracted with DCM (3x30 ml). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by column chromatography (5% EtOAc in hexane) gave the product as a white solid, 215 mg, 70%. M.p. 178-180 °C, lit.[11] 175-177 °C.

R_f = 0.65 (95:5 Hexane/EtOAc)

ν (liq. film) 1510, 1464, 1377, 809.

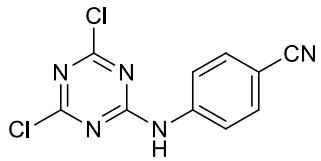
δ_H (400MHz; $CDCl_3$) 7.73(3H, s, Ar), 7.59(6H, d, *J* = 7.7Hz, Ar), 7.28(6H, d, *J* = 7.7Hz, Ar), 2.41(9H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 142.2(0), 138.4(0), 137.3(0), 129.6(1), 127.2(1),124.6(1), 21.2(3).

HRMS (EI) Calcd. for $C_{27}H_{24}$: 348.1878. Found: 348.1874.

Spectroscopic data agrees with Deng.[11]

4-((4,6-dichloro-1,3,5-triazin-2-yl)amino)benzonitrile (2.20)



Cyanuric chloride (369 mg, 2 mmol) and DIPEA (340 µl, 2 mmol) were dissolved in THF (10 ml). The reaction mixture was cooled on ice and a solution of 4-aminobenzonitrile (236 mg, 2 mmol) in THF (8 ml) was added dropwise. The reaction mixture was allowed to slowly warm to rt and was stirred at rt overnight. The reaction mixture was partitioned between EtOAc and water and the organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (10-15% EtOAc in hexane) to give the product as an off-white solid, 250 mg, 47%. M.p. 250-259 °C (dec.)

R_f = 0.32 (4:1 Hexane/EtOAc)

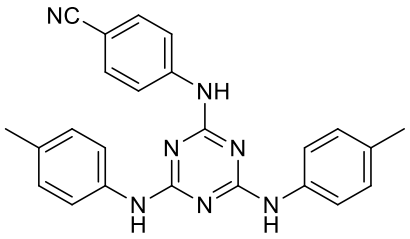
ν (nujol) 3276,2228, 1548,1461, 1377, 1227, 845, 832.

δ_H (400MHz; DMSO-d^6) 11.59(1H, s, NH), 7.95-7.86(4H, m).

δ_C (100MHz; DMSO-d^6) 154.0(0),152.7(0), 142.1(0), 133.3(1), 120.4(1), 118.9(0), 105.4(0).

HRMS (EI) Calcd. for $C_{10}H_5Cl_2N_5$: 264.9922. Found: 264.9927.

4-((4,6-bis(p-tolylamino)-1,3,5-triazin-2-yl)amino)benzonitrile (2.21)



2.20 (101 mg, 0.38 mmol), p-toluidine (163 mg, 1.516 mmol) and K2CO3 (210 mg, 1.516 mmol) were suspended in dioxane and the reaction mixture was heated to reflux for 72h. Water (2 ml) was added, the reaction mixture was heated for further 30 min and the remaining precipitate was filtered and washed with water and DCM to give the product as an off-white solid, 105 mg, 68%. M.p. 336-338 °C.

R_f = 0.50 (7:3 Hexane/EtOAc)

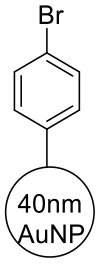
ν (nujol) 3382, 3294, 2924, 2230, 1575, 1516, 1409, 1175, 806.

δ_H (400MHz; DMSO-d^6) 9.67(1H, s,NH), 89.28(2H, s, NH), 8.07(2H,d, J = 8.1Hz, Ar), 7.71(2H, d, J = 8.0Hz, Ar), 7.65(4H,d, J = 7.2Hz), 7.13(4H,d, J = 7.9Hz, Ar), 2.29(3H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 164.0(0), 163.9(0), 144.7(0), 137.0(0), 132.7(1), 131.3(0), 128.8(1), 120.7(1), 119.5(0), 119.4(1), 102.8(0), 20.4(3).

HRMS (EI) Calcd. for $C_{24}H_{21}N_7$: 407.1858. Found: 407.1605.

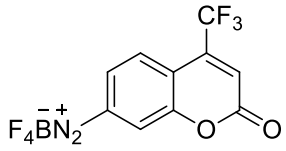
4-bromobenzene functionalised gold nanoparticles (2.30)



4-Bromobezenediazonium tetrafluoroborate solution (20 μl, 2 mM in MeCN) was added to citrate capped 40 nm gold nanoparticles in citrate buffer (2 ml). The reaction mixture was left to incubate at 24

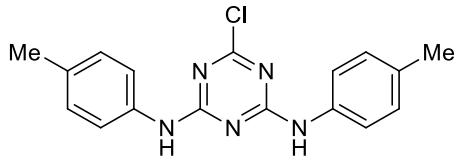
°C for 24 hours, centrifuged (4500 rpm, 20 min) to separate the supernatant and the gold nanoparticles were washed with water (2x2 ml) and stored in water (2 ml) at 4 °C.

2-oxo-4-(trifluoromethyl)-2H-chromene-7-diazonium tetrafluoroborate (2.35)



$BF_3{\cdot}Et_2O$ (190 μl, 1.5 mmol) was cooled to -15 °C and a solution of 7-amino-4-(trifluoromethyl)coumarin (229 mg, 1 mmol) in THF (3 ml) was added. The reaction mixture was stirred under Ar for 5 min and a solution of ^{t}BuONO (160 μl, 1.2 mmol) in THF (1 ml) was added dropwise over 5 min. The reaction mixture was stirred at -10 °C for 20 min and at 5 °C for 1 h. Cold hexane (20 ml) was added and the formed pale brown precipitate was quickly filtered and washed with cold Et2O to give the clean product. The product was used in the next step without further purification or characterisation.

6-chloro-N2,N4-di-p-tolyl-1,3,5-triazine-2,4-diamine (2.38a)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in THF (8 ml) and DIPEA (340 μl, 2 mmol) was added, followed by a solution of *p*-toluidine (214 mg, 2 mmol) in THF (2 ml). The reaxtion mixture was heated to 60 °C for 72h, diluted with water and extracted with ethyl acetate. he combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (40% ethyl acetate in hexane) to give the product as a white solid, 310 mg, 91%. m.p. 203-205°C, lit. 198°C[12]

R_f = 0.48 (6:4 Hexane/EtOAc)

ν (nujol) 3287, 1623, 1576, 1521, 1507, 1457, 1379, 1232, 994, 816.

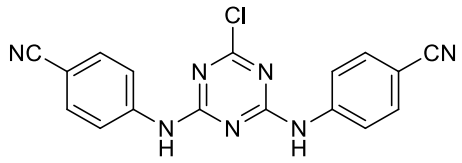
δ_H (400MHz; DMSO-d^6) 10.0(3H, br s, NH), 7.52-7.51 (6H, m, Ar), 7.13(6H, d, *J* = 7.9Hz, Ar), 2.28(9H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 163.8(0), 135.7(0), 132.6(0), 128.9(1), 121.0(1), 20.4(3).

HRMS (EI) Calcd for $C_{17}H_{16}ClN_5$: 325.1094. Found: 325.1100.

Spectroscopic data agrees with Desai.[12]

4,4'-((6-chloro-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibenzonitrile (2.38b)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in THF. DIPEA (340 μl, 2 mmol) was added and the reaction mixture was stirred at rt for 15 min. A solution of 4-aminobenzonitrile (280 mg, 2 mmol) in THF (5 ml) was added dropwise, and the reaction mixture was heated to 65 °C for 72h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in an 1:1 mixture of Ethyl Acetate and THF. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (50% ethyl acetate in hexane) to give the product as a white solid, 298 mg, 86%. M.p. 348-350 °C.

R_f = 0.45 (1:1 Hexane/EtOAc)

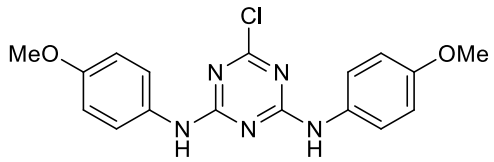
ν (nujol) 3298, 1576, 1507, 1373, 986, 795.

δ_H (400MHz; DMSO-d^6) 10.78(2H, br s, NH), 7.84-7.82(8H, m, Ar).

δ_C (100MHz; DMSO-d^6) 168.5(0), 163.7(0), 142.7(0), 133.1(1), 120.5(0), 119.0(1), 105.1(0).

HRMS (EI) Calcd. for $C_{17}H_{10}ClN_7$: 347.0686. Found: 347.0690.

6-chloro-N2,N4-bis(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (2.38c)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in THF (8 ml). DIPEA (340 μl, 2 mmol) was added,followed by a solution of p-anisidine (246 mg, 2 mmol) in THF (2 ml).The reactionmixture was stirred at rt for 3h and then heated to 65°Cfor 16h. Reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (50% EtOAc in hexane) to give the product as an off-white solid, 311 mg, 87%. M.p. 213-215 °C.

R_f = 0.48 (1:1 Hexane/EtOAc)

ν (nujol) 3252, 1577, 1528, 1506, 1464, 1379, 1227, 1036, 987, 794.

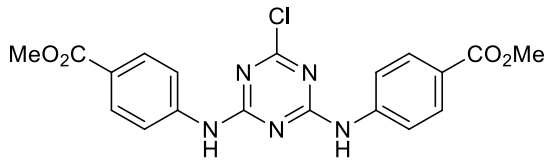
δ_H (400MHz; DMSO-d^6) 10.06-9.87(2H, m, NH), 7.51(4H, m, Ar), 6.90(4H, d, *J* = 8.0Hz, Ar), 3.75(6H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 167.8(0), 136.7(0), 155.6(0), 131.2(0), 122.7(1), 113.7(1), 55.2(3).

HRMS (EI) Calcd. for $C_{15}H_{16}ClN_5O_2$: 357.0993. Found: 357.1001.

Spectroscopic data agrees with Kolmakov.[6]

dimethyl 4,4'-((6-chloro-1,3,5-triazine-2,4-diyl)bis(azanediyl)) dibenzoate (2.38d)



Cyanuric chloride (184 mg, 1 mmol) was dissolved in THF (10 ml).DIPEA (340 µl, 2 mmol) was added, followed by a solution of methyl-4-aminobenzoate (302 mg, 2 mmol) in THF (5 ml). The resulting suspension was heated to 65 °C overnight, concentrated onto silica and column chromatography (50-90% EtOAc in hexane) gave the product as an off-white solid, 226 mg, 55%. M.p. 286-289 °C.

R_f = 0.25 (1:1 Hexane/EtOAc)

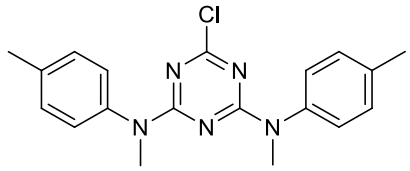
ν (nujol) 3298, 3202, 1707, 1616, 1576, 1508, 1464, 1377, 988, 766.

δ_H (400MHz; DMSO-d^6) 10.68(2H, s, NH), 7.94(4H, d, *J* = 8.0Hz, Ar), 7.85(4H), 3.85(9H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 168.4(0), 165.8(1), 142.9(0), 130.0(1), 124.0(0), 120.0(0), 51.9(3).

HRMS (EI) Calcd. for $C_{19}H_{16}ClN_5O_4$: 413.0891. Found: 413.0898.

6-chloro-N2,N4-dimethyl-N2,N4-di-p-tolyl-1,3,5-triazine-2,4-diamine (2.38e)



Cyanuric chloride (185 mg, 1 mmol) was dissolved in THF (6 ml), and a solution of DIPEA (340 µl, 2 mmol) and N-methyl-p-toluidine (260 µl, 2 mmol) in THF (3 ml) was added dropwise. The reaction mixture was stirred at rt for 2 h and at 65 °C for 5 h and then concentrated onto silica. Column chromatography (20-40% EtOAc in hexane) gave the product as a dense viscous oil, 327 mg, 93%.

R_f = 0.71 (3:7 Hexane/EtOAc)

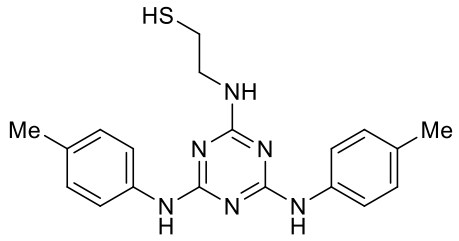
ν (liq. film) 1564, 1511, 1490, 1390, 1237, 1096, 972, 800.

δ_H (400MHz; $CDCl_3$) 7.12(8H, m, Ar), 3.39(6H, s, CH_3), 2.33(6H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 169.4(0), 165.0(0), 141.1(0),135.9(0), 129.4(1), 129.4(1), 126.1(1), 38.1(br s, 3), 21.1(3).

HRMS (EI) Calcd. for $C_{19}H_{20}ClN_5$: 353.1047. Found: 353.1052.

2-((4,6-bis(p-tolylamino)-1,3,5-triazin-2-yl)amino)ethanethiol (2.39a)



2 (163 mg, 0.5 mmol) was dissolved in THF (15 ml) and DIPEA (103 μl, 0.6 mmol) and cysteamine (46.3 mg, 0.6 mmol) were added. The reaction mixture was heated to reflux under Ar for 48 h, concentrated onto silica gel and purification by column chromatography (40% EtOAc in hexane) gave the product as a clear viscous solid, 172 mg, 94%. M.p. 72-75 °C.

R_f = 0.45 (1:1 Hexane/EtOAc)

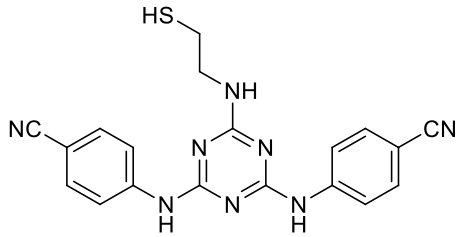
ν (liq. film) 3401, 3276, 2921, 1576, 1496, 1418, 1236, 809.

δ_H (400MHz; $CDCl_3$) 9.00(1H, s, NH), 8.86(1H, s, NH),7.65(4H, d, *J* = 6.5Hz, Ar), 7.15(1H, s, NH), 7.15(4H, d, *J* = 7.5Hz, Ar), 3.44(2H, q, *J* = 7Hz, CH_2), 2.68(2H, d, *J* = 7.5Hz, CH_2), 2.32(1H, t, *J* = 8Hz, SH), 2.26(6H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.1(0),164.4(0), 136.2(0), 132.7(0), 129.3(1), 120.9(1), 120.5(1), 44.1(2), 24.6(2), 20.8(3).

HRMS (EI) Calcd. for $C_{19}H_{22}N_6S$: 366.1627. Found: 366.1624.

4,4'-((6-((2-mercaptoethyl)amino)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibenzonitrile (2.39b)



4 (104.3 mg, 0.3 mmol) was dissolved in THF (15 ml). DIPEA (62 μl, 0.36 mmol) and cysteamine (28 mg, 0.36 mmol) were added. The reaction mixture was heated to reflux under Ar for 48h, after which the reaction mixture was concentrated directly onto silica and purified by column chromatography (50% EtOAc in hexane) to give the product as a white solid, 108 mg, 93%. M.p. 243-245 °C.

R_f = 0.30 (1:1 Hexane/EtOAc)

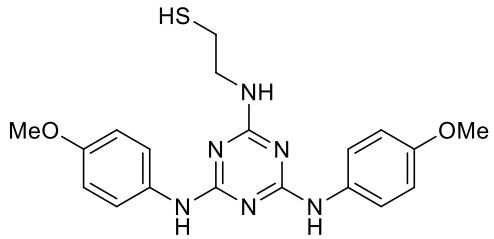
ν (nujol) 3306, 2220, 1621, 1577, 1507, 1176, 807.

δ_H (400MHz; DMSO-d^6) 9.81(1H, s, NH), 9.72(1H, s, NH), 8.04-8.01(4H, m, Ar), 7.75-7.71(4H, m, Ar), 7.63(1H, s, NH), 3.49(2H, q, *J* =6.3Hz, CH_2), 2.70(2H, d, *J* = 7.4Hz, CH_2), 2.41(1H, t, *J* = 8.0Hz, SH).

δ_C (100MHz; DMSO-d^6) 165.5(0), 164.0(0), 163.7(0), 144.6(0), 132.8(1), 119.4(1), 103.0(0), 43.7(2), 23.3.

HRMS (EI) Calcd. for $C_{19}H_{16}N_8S$: 388.1219. Found: 388.1223.

2-((4,6-bis((4-methoxyphenyl)amino)-1,3,5-triazin-2-yl)amino)ethanethiol (2.39c)



5 (107.3 mg, 0.3 mmol) was dissolved in THF (15 ml), DIPEA (62 μl, 0.36 mmol) and cysteamine (28 mg, 0.36 mmol) were added and the reaction mixture was heated to reflux under Ar for 48 h.The reaction mixture was concentrated on silica and column chromatography (60% EtOAc in hexane) gave the product as a white solid, 59 mg, 49%. M.p. 243-244 °C.

R_f = 0.30 (1:1 Hexane/EtOAc)

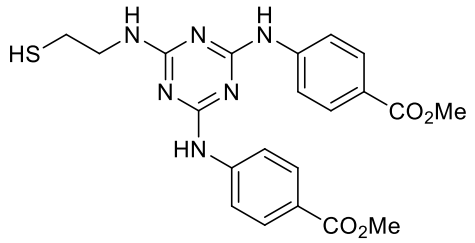
ν (nujol) 3390, 3280, 2930,1576, 1506, 1419, 1243, 1033, 827, 809.

δ_H (400MHz; $CDCl_3$) 7.38-7.25(6H, m, Ar, 2NH), 6.82(4H, d, *J*= 8.0Hz, Ar), 3.77(6H, s, $2CH_3$), 3.52 (2H, q, *J* = 6.3Hz, CH_2), 2.70(2H, q, *J* = 7.0Hz, CH_2), 1.39(1H, t, *J* = 8.4Hz, SH).

δ_C (100MHz; $CDCl_3$) 166.1(0), 164.5(1), 155.8(0), 131.9(0), 123.0(0), 122.3(0), 114.0(1), 55.5(3), 44.0(2), 24.6(2).

HRMS (EI) Calcd. for $C_{19}H_{22}N_6O_2S$: 398.1525. Found: 398.1519.

Dimethyl 4,4'-((6-((2-mercaptoethyl)amino)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibenzoate (2.39d)



10 (133 mg, 0.32 mmol) was dissolved in THF (10 ml) and DIPEA (60 µl, 0.35 mmol) was added followed by cysteamine (27.3 mg, 0.35 mmol). The reaction mixture was heated to reflux for 48h, concentrated onto silica and purified by column chromatography (50% EtOAc in hexane) to give the product as a white glassy solid, 102 mg, 70%. M.p. 101-103 °C.

R_f = 0.54 (1:1 Hexane/EtOAc)

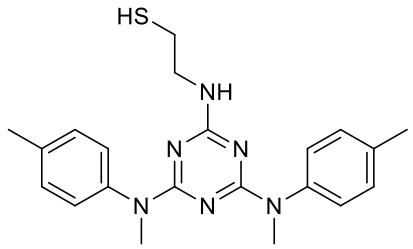
ν (nujol) 3329, 1701, 1577, 1518, 1493, 1412, 1279, 1175, 769.

δ_H (400MHz; DMSO-d^6) 9.69(1H, s, NH), 9.58(1H, s, NH), 7.98(4H, d, *J* = 8.0Hz, Ar), 7.88(4H, t, *J* = 8.0Hz, Ar), 7.53(1H,s, NH), 3.23(6H, s, CH_3), 3.50(2H, q, *J* = 6.7Hz, CH_2), 2.72(2H, q, *J* = 7.5Hz, CH_2), 2.42(1H, t, *J* = 7.5Hz, SH).

δ_C (100MHz; DMSO-d^6) 166.0(0), 165.5(0), 164.0 and 163.8(0), 144.91 and 144.86(0), 129.9 and 129.8(1), 122.2and 122.1(0), 118.8 (1), 51.7(3), 43.8(2), 23.3(2).

HRMS (EI) Calcd. for $C_{21}H_{22}N_6O_4S$: 454.1423. Found: 454.1419.

2-((4,6-bis(methyl(p-tolyl)amino)-1,3,5-triazin-2-yl)amino)ethanethiol (2.39e)

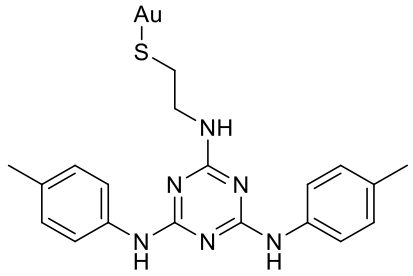


11 (150 mg, 0.425 mmol) was dissolved in THF (10 ml) and DIPEA (85 µl, 0.5 mmol) and cysteamine (38.6 mg, 0.5 mmol) were added. The reactionmixture was heated to reflux under Ar for 72h.

The reaction mixture was concentrated onto silica and column chromatography (20% EtOAc in hexane) gave the product as a colourless oil, 43 mg, 23%.

R_f = 0.48 (4:1 Hexane/EtOAc)
ν (liq. film) 3420, 3274, 2923, 1538, 1386, 1105, 820, 809, 737.
δ_H (400MHz; $CDCl_3$) 7.17(4H, d, *J* = 8.0Hz, Ar), 7.11(4H, d, *J*= 8.0Hz, Ar),5.09(1H, t, *J* = 5.6Hz, NH), 3.39-3.34(8H, m, $2CH_3$, CH_2), 2.58(2H, q, J = 7.2Hz, CH_2), 2.34(6H, $2CH_3$), 1.25(1H, t, *J* = 8.3Hz, SH).
δ_C (100MHz; $CDCl_3$) 165.9(0), 165.6(0), 142.4(1), 134.7(0), 129.0(1), 126.4(1), 44.3(2), 37.4(3), 24.5(2), 21.0(3).
HRMS (EI) Calcd. for $C_{21}H_{26}N_6S$: 394.1940. Found: 394.1934.

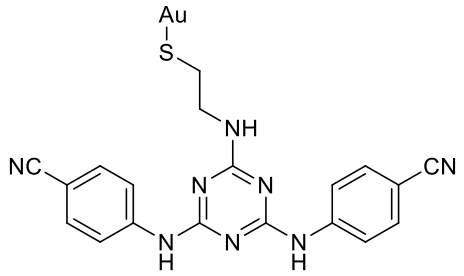
((2-((4,6-bis(p-tolylamino)-1,3,5-triazin-2-yl)amino)ethyl)thio)gold nanoparticles (2.40a)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 5 mM solution of **8** in ethanol (200 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the procedure was repeated one more time. The resulting pale pink solution was stored at 4 °C.

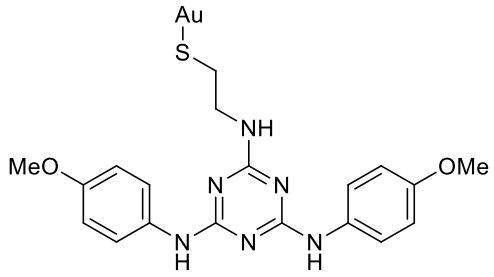
((2-((4,6-bis((4-cyanophenyl)amino)-1,3,5-triazin-2-yl)amino)ethyl)thio)gold nanoparticles (2.40b)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 10mM solution of **6** in dioxane (100 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the procedure was repeated one more time. The resulting pale pink solution was stored at 4 °C.

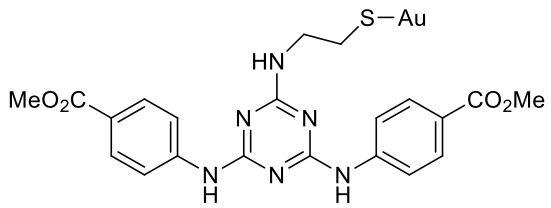
((2-((4,6-bis((4-methoxyphenyl)amino)-1,3,5-triazin-2-yl)amino)ethyl)thio) gold nanoparticles (2.40c)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 10 mM solution of **7** in ethanol (100 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the procedure was repeated one more time. The resulting pale pink solution was stored at 4 °C.

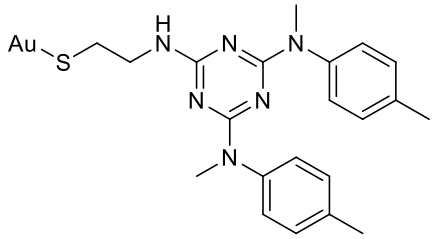
Dimethyl 4,4'-((6-((2-mercaptoethyl)amino)-1,3,5-triazine-2,4-diyl)bis(azanediyl))dibenzoate functionalised gold nanoparticles (2.40d)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 5mM solution of **14** in ethanol (200 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water and the procedure was repeated. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the resulting pale pink solution was stored at 4 °C.

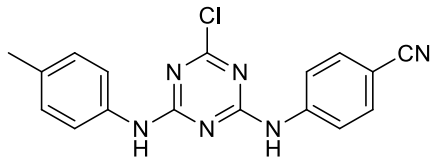
((2-((4,6-bis(methyl(p-tolyl)amino)-1,3,5-triazin-2-yl)amino)ethyl)thio)gold (2.40e)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 5mM solution of **12** in ethanol (200 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water and the procedure was repeated one more time. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the resulting pale pink solution was stored at 4 °C.

4-((4-chloro-6-(p-tolylamino)-1,3,5-triazin-2-yl)amino)benzonitrile (2.41)



Cyanogen chloride (184 mg, 1 mmol) and DIPEA (340 μl, 2 mmol) ere dissolved in THF (8 ml) and the reaction mixture was cooled on ice. *p*-Toluidine (107 mg, 1 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min and was then allowed to warm to rt. The reaction mixture was stirred at rt for 1h, 4-aminobenzonitrile (118 mg, 1 mmol) was added. The reaction mixture was stirred at rt for 1h, and was then heated to 60 °C for 72h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to give the crude product. Purification by column chromatography (30-50% EtOAc in hexane) gave the product as an off-white solid, 230 mg, 68%. M.p. 255-257 °C.

R_f = 0.57 (6:4 Hexane/EtOAc)

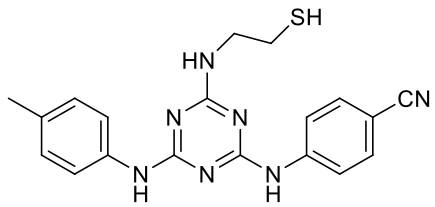
ν (nujol) 3424, 3270, 2227, 1617, 1576, 1507, 1457, 1235, 987, 794.

δ_H (400MHz; DMSO-d^6) 10.61(1H, br s, NH), 10.33(1H, br s, NH), 8.03-7.86(2H, m, Ar), 7.78(2H, m, Ar), 7.50(2H, m, Ar), 7.25(2H, m, Ar), 2.31(3H, s, CH_3).

δ_C (100MHz; DMSO-d^6) 168.1(0), 163.8(0), 143.0(0), 135.4(0), 132.9(1), 129.0(1), 121.3(1), 120.2(1), 119.1(0), 104.6(0), 20.4(3).

HRMS (EI) Calcd. for $C_{17}H_{13}ClN_6$: 336.0890. Found: 336.0897.

4-((4-((2-mercaptoethyl)amino)-6-(p-tolylamino)-1,3,5-triazin-2-yl)amino)benzonitrile (2.42)



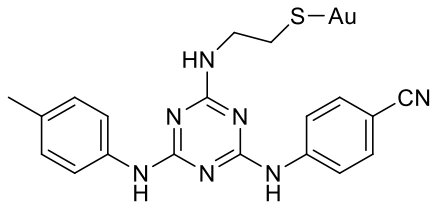
16 (100 mg, 0.297 mmol) was dissolved in THF (6 ml) and DIPEA (56 μl, 0.33 mmol) and cysteamine (25.2 mg, 0.33 mmol) were added. The reaction mixture was heated to reflux for 48 h, concentrated onto silica and purification by column chromatography (50% EtOAc in hexane) gave the product as a white solid, 80 mg, 71%. M.p. 189-191 °C.

R_f = 0.40 (1:1 Hexane/EtOAc)

ν (nujol) 3445, 3282, 2232, 1616, 1575, 1559, 1464, 1174, 809.

δ_H (400MHz; DMSO-d^6) 9.59(1H, m, NH), 9.15(1H, m, NH), 8.04(2H, d, *J* = 8.2Hz, Ar), 7.69-7.62(4H, m, Ar), 7.38(1H, s, NH), 7.10(2H, d, *J* = 7.3Hz, Ar), 3.46(2H, q, *J* = 6.5Hz, CH_2), 2.70(2H, q, *J* = 6.7Hz, CH_2), 2.36(1H, q, *J* = 8.7Hz, SH), 2.27(3H, s, CH_3).
δ_C (100MHz; DMSO-d^6) 165.5(0), 163.8(0), 145.0(0), 137.3(1), 132.7(1), 130.9(0), 128.8(1), 120.2(1), 119.5(0), 119.2(1), 102.5(0), 43.7(2), 23.3(2), 20.4(3).
HRMS (EI) Calcd. for $C_{19}H_{19}N_7S$: 377.1423. Found: 377.1427.

((2-((4-((4-cyanophenyl)amino)-6-(p-tolylamino)-1,3,5-triazin-2-yl)amino)ethyl)thio)gold nanoparticles(2.43)



Following a procedure described by Zhong.[13]

To a solution of citrate capped 40nm gold nanoparticles (2 ml) was added a 5mM solution of **18** in ethanol (200 μl). The mixture was incubated at 25 °C for 24 h and centrifuged at 4500 rpm for 40 min. The supernatant was removed and replaced with distilled water and the procedure was repeated. The solution was again centrifuged at 4500 rpm for 40 min, the supernatant was replaced with distilled water and the resulting pale pink solution was stored at 4 °C.

6.3. Experimental for Chapter 3

6.3.1. General method for the Synthesis of Indoles using KI and DBU as Catalysts in the Cyclisation Step (Method A)

A mixture of butyraldehyde (90 μl, 1 mmol), crotononitrile, 1-butyl-1-phenylhydrazine (170 μl, 1 mmol) in DCE (2.0 mL) was charged in a 12-mL Q-tube pressure reactor equipped with a high-pressure adapter. The reaction was stirred at 130 °C for 2 hours (the reaction was monitored by TLC). The reaction mixture was allowed to cool to room temperature, and KI (34 mg, 0.20 mmol) and DBU (36 μl, 0.24 mmol) were added. The reaction mixture was heated at 130 °C for further 3 h, diluted with water, and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate: 98/2 as eluent) to give compound **3.11** as pale yellow oil (135 mg, 61 %).

6.3.2 General Method for the Synthesis of α-Amino Acetals (Method B)

Following a method described by Loh *et al.*[14]

N-methylaniline (220 μl, 2 mmol) and phenylacetaldehyde 340 μl, 3 mmol) were dissolved in DCE (8 ml). MeOH (2 ml), I2 (100 mg, 0.40 mmol), $Na_2CO_3 \cdot 1.5H_2O_2$ (316 mg, 2 mmol) were added and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was concentrated onto silica gel and purified by column chromatography (a gradient of 5-10% EtOAc in PE) to give the product as a pale yellow oil, 197 mg.

6.3.3 General Method for the Synthesis of Indoles from α-Amino Acetals (Method C)

N-(2,2-dimethoxy-1-phenylethyl)-N-methylaniline (271 mg, 1 mmol) was dissolved in toluene and $SiO_2 \cdot SO_4H$ (40 mg) was added. The reaction mixture was heated to 130 for 3 h, filtered and the silica gel was washed with EtOAc. The combined organic phases were concentrated and the crude product was purified by column chromatography (a gradient of 5% to 10% EtOAc in PE) to give the indole **3.21** as a pale yellow solid, 101 mg, 49%.

6.3.4. General Method for the Preparation of Arylhydrazone Derivatives (Method D)

A mixture of *n*-butylamine (73 mg, 99 μl, 1 mmol), 10% Pd/C (53 mg, 0.05 mmol, 5 mol%), crotononitrile (67 mg, 82 μl, 1 mmol), 1-butyl-1-phenylhydrazine (493 mg, 493 μl, 3 mmol) in toluene (2.0 mL) was charged in a 12-mL Q-tube pressure reactor equipped with a high-pressure adapter. The tube was heated to 150 °C and the reaction mixture stirred vigorously at this temperature for 12 hrs (the progress of the reaction was monitored by TLC). The reaction mixture was allowed to cool to room temperature, the catalyst was filtered off and toluene was removed under reduced pressure. Finally the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate: 98/2 as eluent) to give compound **3.10** as pale yellow oil (213 mg, 98 %).

6.3.5. General Method for the Preparation of Indoles from Amines using Pd/C as Catalyst (Method E)

A mixture of n-butylamine (73 mg, 99 μl, 1 mmol), 10% Pd/C (53 mg, 0.05 mmol, 5 mol%), crotononitrile (67 mg, 82 μl, 1 mmol) and 1-butyl-1-phenylhydrazine (493 mg, 493 μl, 3 mmol) in toluene (1.0 mL) was charged in a 12-mL Q-tube pressure reactor equipped with a high pressure adapter. The tube was heated to 150 °C and the reaction mixture was stirred vigorously at this temperature for 12 hrs, then cooled with a stream of compressed air. After cooling, the catalyst was filtered off,[20] and a solution of anhydrous $ZnCl_2$ (136 mg, 1 mmol) in 2-methyl-2-butanol (2 mL) was slowly added at room temperature. The resulting reaction mixture was stirred at 130 °C for 3 hours, diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated and the crude product was purified by column chromatography (5% to 10% EtOAc in PE) to give the indole **3.11**.

6.3.6. General Method for the Deprotection of Benzyl Indoles (Method F)

Benzyl indole (1 mmol) was dissolved in DMSO (10 ml) and *t*BuOK (2 mmol) was added. The reaction mixture was stirred under O_2 at rt overnight, quenched with H_2O and concentrated. The residue was taken up in EtOAc, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% EtOAc in PE) to give the product.

6.3.7. General procedure for recycling the catalyst

After reaction, the mixture was passed through a syringe equipped with a frit and Pd/C was washed with CH_2Cl_2 (3 x 10 mL), MeOH (3 x 10 mL) and diethyl ether (2 x 10 mL). Then the bottom of the syringe was closed and 1 mM aqueous HCl (3mL) was added. After 10 min, the solvent was drained, and the residue washed with H_2O (3 x 10mL) mL, MeOH (3 x 10 mL) and dry THF (3 x 10 mL). The Pd/C was dried under vacuum and removed from the syringe. The catalyst (5% of overall weight loss) was wet with water and used a second time.

6.3.8. Palladium leaching test

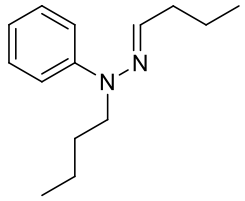
ICP-MS Analyses: prior to ICP-MS analyses, samples were subjected to a complete mineralization/dissolution process. The filtrate obtained after hot filtration of the reaction mixture was evaporated under reduced pressure. A mixture of concentrated H_2SO_4 (3 mL) and fuming HNO_3 (2 mL) was added to the residue. This mixture was heated in a fume hood until disappearance of nitric fumes. After cooling to 100 °C, fuming HNO_3 (2 mL) was then added, the mixture was heated until evaporation of HNO_3 and this process was repeated three times. Most of the H_2SO_4 was then boiled off and after cooling a solution of concentrated HCl (2 mL) and concentrated HNO_3 (2 mL) was added and heated until to complete evaporation. The residue was then dissolved in H_2O (24 mL) and the amount of Pd present in this solution was then determined by ICP-MS. Less than 2 ppm leached Pd was detected in the filtrate after catalyst removal.

Sheldon's hot-filtration test: A mixture of 1-methyl-1-phenylhydrazine (366 mg, 353 µl, 3.0 mmol), fresh distilled *n*-butylamine (73 mg, 99 µl, 1 mmol), crotononitrile (67 mg, 82 µl, 1 mmol), and 10% Pd/C (53 mg, 0.05 mmol, 5 mol% compared to *n*-butylamine) in dry toluene (2.5 mL) was charged into a 12-mL Q-tube pressure reactor equipped with a high pressure adapter. The tube was heated under vigorous stirring at 150 °C. After 6 hrs, the reaction was stopped and the filtrate, obtained after the removal of the solid catalyst, was heated at 150 °C for a further 6 hrs. It was observed that after separation of the heterogeneous catalyst no conversion takes place in the filtrate part.

Rebeck-Collman three-phase tests: Three-phase test was performed by reacting 3 mmol of polymer-supported *N*-butyl-*N*-phenyhydrazine [21] (0.75 mmol/g) with 1 mmol of 3-phenylpropylamine (135 mg, 142 µl) in the presence of Pd/C (53 mg, 0.05 mmol, 5 mol%) and crotononitrile (67 mg, 82 µl, 1 mmol), following the general procedure for the synthesis of phenylhydrazones. No conversion was observed (TLC) with immobilized phenylhydrazines, and the 3-phenylpropylamine was almost quantitatively recovered at the end of reaction.

6.3.9. Characterisation Data for Indoles

1-Butyl-2-butylidene-1-phenylhydrazine (3.10)



Method D gave the product as a pale yellow oil 214 mg, 98 %.

R_f = = 0.57 (hexane/EtOAc: 98/2).

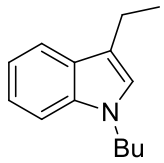
ν (liq. film) 2958, 2930, 2871, 1595, 1498, 1390, 1333, 1278, 1223, 1166, 1117.

δ_H (400MHz; $CDCl_3$) 7.28-7.19 (m, 4H), 6.88-6.81 (m, 2H), 3.73-3.69 (m, 2H), 2.34 (td, J^1 = 7.4 Hz, J^2 = 5.3 Hz, 2H), 1.63-1.53 (m, 4H), 1.39 (dq, J^1 = 15.0 Hz, J^2 = 7.5 Hz, 2H), 0.98 (q, J = 7.4 Hz, 6H).

δ_C (100MHz; $CDCl_3$) 147.7, 135.3, 129.0, 119.3, 114.2, 45.2, 35.2, 26.9, 20.9, 20.4, 13.9, 13.8.

Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.99; H, 10.13; N, 12.88.

1-Butyl-3-ethyl-1*H*-indole (3.11)



Method A gave the product as a light yellow oil, 122 mg, 61%

Method E gave the product as a light yellow oil 195 mg, 97 %.

R_f = 0.52 (8:2 hexane/EtOAc).

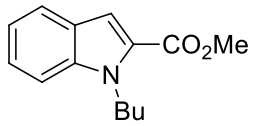
ν (liq. film) 3024, 2962, 1611, 1485, 1465, 1362, 1184, 735.

δ_H (400MHz; $CDCl_3$) 7.59 (dt, J^1= 8 Hz, J^2= 0.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.21-7.16 (m, 1H), 7.07 (td, J = 7.4 Hz, 0.9 Hz, 1H), 6.85 (s, 1H), 4.04 (t, J = 7.1 Hz, 2H), 2.77 (qd, J = 7.5 Hz, 0.9 Hz, 2H), 1.82-1.75 (m, 2H), 1.36-1.30 (m, 5H), 0.93 (t, J = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.4, 127.9, 124.4, 121.3, 119.1, 118.4, 117.2, 109.3, 45.9, 32.5, 20.3, 18.4, 14.7, 13.8.

Spectroscopical data agrees with Guru.[15]

Methyl 1-butyl-1H-indole-2-carboxylate (3.15a)



Method A gave the product as a light yellow oil, 122 mg, 61%

R_f = 0.28 (96:4 hexane/EtOAc).

ν (liq. film) 2957, 2931, 2872, 1715, 1518, 1250, 1201, 1094, 747.

δ_H (400MHz; $CDCl_3$) 7.30-7.26(2H, m, Ar), 7.06(1H, t, *J* = 6.4 Hz, Ar), 7.00-6.98(2H, m, Ar), 3.86(3H, s, CH_3), 3.68(2H, m, CH_2), 1.73(3H, s, CH_3), 1.67(2H, tt, J^1 = 7.7 Hz, J^2 = 6.6Hz, CH_2), 1.38(2H, dq, J^1 = 14.8 Hz, J^2 = 7.4 Hz, CH_2), 0.93(3H, t, *J* = 7.4 Hz, CH_3).

δ_C (100MHz; $CDCl_3$) 166.0(0), 149.2(0), 144.6(0), 129.1(1, 2C), 123.9(0), 121.9(1, 2C), 60.4(1), 52.6(3), 30.8(2), 20.0(2), 17.0(2), 13.9(3).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.33; N, 14.50.

1-Benzyl-3-ethyl-1*H*-indole (3.15b)

Method A gave the product as a light yellow oil, 80 mg, 34%

Method E gave the product as a light yellow oil 200 mg, 85 %.

R_f = 0.54 (96:4 hexane/EtOAc).

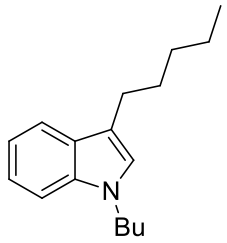
ν (liq. film) 3059, 3028, 2960, 2930, 2875, 1610, 1495, 1480, 1465, 1450, 1355, 1175, 806, 735.

δ_H (400MHz; $CDCl_3$) 7.63-7.61 (m, 1H), 7.30-7.23 (m, 4H), 7.13 (dq, J^1 = 16.2 Hz, J^2 = 8.1 Hz, 4H), 6.89 (s, 1H), 5.27 (s, 2H), 2.79 (q, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 137.9, 136.8, 128.7, 128.0, 127.5, 126.8, 124.7, 121.6, 119.1, 118.7, 118.0, 109.5, 49.8, 18.2, 14.6.

Spectroscopical data agrees with Couture.[16]

1-Butyl-3-pentyl-1*H*-indole (3.15c)



Method A gave the product as a light yellow oil, 163mg, 67%.

Method E gave the product as a light yellow oil 219 mg, 90 %.

R_f = 0.70 (98:2 hexane/EtOAc).

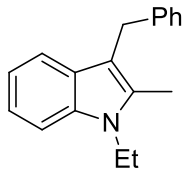
ν (liq. film) 2956, 2927, 2871, 1467, 1370.

δ_H (400MHz; $CDCl_3$) 7.59 (dt, J^1= 8 Hz, J^2 = 0.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.18 (td, J = 7.6 Hz, J^2 = 1.1 Hz, 1H), 7.07 (ddd, J^1 = 7.9 Hz, J^2 =7.0 Hz, J^3 =0.9 Hz, 1H), 6.86 (s, 1H), 4.06 (t, J = 7.1 Hz, 2H), 2.73 (td, J^1 = 7.7 Hz, J^2 = 0.4 Hz, 2H), 1.83-1.76 (m, 2H), 1.72-1.68 (m, 2H), 1.40-1.30 (m, 6H), 0.95-0.88 (m, 6H).

δ_C (100MHz; $CDCl_3$) 136.3, 128.1, 124.9, 121.1, 119.2, 118.3, 115.5, 109.2, 45.9, 32.4, 31.9, 30.1, 25.1, 22.6, 20.3, 14.1, 13.8.

Anal. Calcd for $C_{17}H_{25}N$: C, 83.90; H, 10.35; N, 5.75. Found: C, 83.82; H, 10.39; N, 5.79.

3-benzyl-1-ethyl-2-methyl-1H-indole (3.15d)



Method A gave the product as a yellow oil, 75 mg, 30%

R_f = 0.66 (hexane/EtOAc: 9/1).

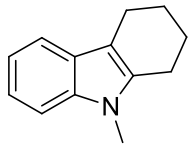
ν (liq. film) 3056, 3025, 2930, 2912, 1470, 1466, 1361, 1351, 1338, 738.

δ_H (400MHz; $CDCl_3$) 7.42(1H, d, J = 7.8Hz, Ar), 7.27(1H, d, J = 8.1 Hz, Ar), 7.25-7.17(4H, m, Ar), 7.13(2H, t, J = 7.2 Hz, Ar), 7.01(1H, t, J = 7.4 Hz, Ar), 4.14(2H, q, J = 7.2 Hz, CH_2), 4.09(2H, s, CH_2), 2.37(3H, s, CH_3), 1.33(3H, t, J = 7.2 Hz, CH_3).

δ_C (100MHz; $CDCl_3$) 141.9(0), 133.6(0), 132.7(0), 128.25(1), 128.23(1), 128.20(0), 125.6(1), 120.5(1), 118.8(1), 118.4(1), 109.9(1), 108.6(1), 37.8(3), 30.4(2), 15.4(2), 10.2(3).

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.72; H, 7.29; N, 5.65.

9-methyl-2,3,4,9-tetrahydro-1H-carbazole (3.15e)



Method A gave the product as a white solid, 102 mg, 55%, m.p. 46-48 °C.

R_f = 0.68 (hexane/EtOAc: 9/1).

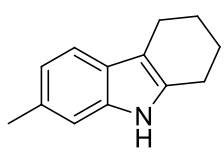
ν (liq. film) 2930, 2843, 1560, 1510, 1472, 1377, 1314, 135.

δ_H (400MHz; $CDCl_3$) 7.45(1H, d, *J* = 7.7 Hz, Ar), 7.22(1H, d, *J* = 8 Hz, Ar), 7.13(1H, t, *J* = 7.6 Hz, Ar), 7.05(1H, t, *J* = 7.4 Hz, Ar), 3.56(3H, s, CH_3), 2.73-2.66 (4H, m, $2CH_2$), 1.95-1.90(2H, m, CH_2), 1.85-1.81(2H, m, CH_2).

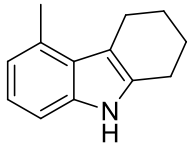
δ_C (100MHz; $CDCl_3$) 136.7(0), 135.6(0), 127.1(0), 120.4(1), 118.5(1), 117.7(1), 109.2(0), 108.4(1), 28.9(3), 23.24(2), 23.22(2), 22.1(2), 21.1(2).

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.24; H, 8.19; N, 7.57.

7-methyl-2,3,4,9-tetrahydro-1H-carbazole (3.15f) and 5-methyl-2,3,4,9-tetrahydro-1H-carbazole (3.15g)



3.15f



3.15g

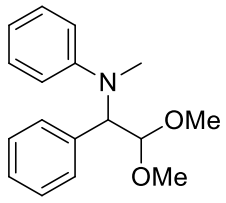
Method A gave a mixture of products **3.15f** and **3.15g** as an off-white solid, 48 mg, 26%.

R_f = 0.35 (hexane/EtOAc: 95/5).

δ_H (400MHz; $CDCl_3$) 7.31(2H, m, Ar (**3.15f** and **3.15g**)), 7.0(1H, d, *J* = 8 Hz, Ar(**3.15g**)), 6.95(1H, s, Ar(**3.15f**)), 6.88(1H, d, *J* = 7.7 Hz, Ar (**3.15f**)), 6.76(1H, d, *J* = 8 Hz, Ar(**3.15g**)), 2.67-2.61(10H, m, CH_3(3.15g) and 9H CH_2), 2.42 (3H, s, CH_3), 1.90-1.79(9H, m, 9H CH_2).

As the products could not be separated the mixture was not characterised further.

N-(2,2-dimethoxy-1-phenylethyl)-N-methylaniline (3.18)



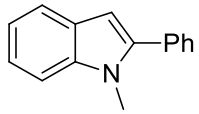
Method B gave the product as a yellow oil, 266 mg, 49 %.

R_f = 0.51 (hexane/EtOAc: 8/2).

δ_H (400MHz; $CDCl_3$) 7.34 (2H, d, J = 7.6 Hz, Ar), 7.28 (2H, d, J = 7.4 Hz, Ar), 7.26-7.18 (3H, m, Ar), 6.84 (2H, d, J = 8.4 Hz, Ar), 6.72 (1H, t, *J* = 7.3 Hz, Ar), 5.00 (1H, d, *J* = 6.9 Hz, CH), 4.85 (1H, d, *J* = 6.9 Hz, CH), 3.40 (3H, s, CH_3), 3.33 (3H, s, CH_3), 2.80 (3H, s, CH_3).

The product was used in the following reaction without further characterisation.

1-methyl-2-phenyl-1H-indole (3.21)



Method C gave the product as a pale yellow solid, 101 mg, 49%, m.p. 94-96 °C.Lit.[17] 93-95 °C.

R_f = 0.32 (hexane/EtOAc: 9/1).

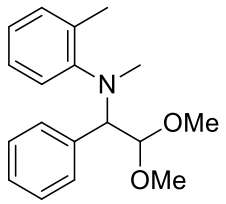
ν (liq. film) 3056,1603, 1468, 1387, 1340, 765, 749.

δ_H (400MHz; $CDCl_3$) 7.63 (1H, d, J = 7.8 Hz, Ar), 7.51 (2H, d, J = 7.6 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, , Ar), 7.40(1H, d, J = 7.5 Hz, Ar), 7.36 (1H, d, J = 8.3 Hz, Ar), 7.24(1H, t, J = 7.6 Hz, Ar), 7.14 (1H, t, *J* = 7.4 Hz, Ar), 6.56(1H, s, Ar), 3.73 (3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 141.6(0), 138.5(0), 132.9(0), 129.5(1), 128.6(1), 128.1(0), 127.9(1), 121.8(1), 120.6(1), 120.0(1), 109.7(1), 101.8(1), 31.2(3).

Spectroscopical data agrees with Huang.[18]

N-(2,2-dimethoxy-1-phenylethyl)-N,2-dimethylaniline (3.24a)



Method B gave the product with minor impurities as a yellow oil, 131 mg, 23 %.

R_f = 0.59 (hexane/EtOAc: 8/2).

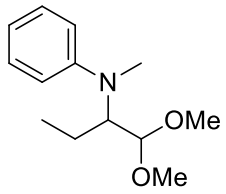
ν (liq. film) 3439, 2947, 2816, 1597, 1492, 1452, 1121, 1079, 701.

δ_H (400MHz; $CDCl_3$) 7.32-7.23 (5H, m, Ar), 7.19(1H, d, J = 7.4 Hz, Ar), 7.07 (1H, t, J = 7.5 Hz, Ar), 6.97 (1H, t, J = 7.3 Hz, Ar), 6.89 (1H, d, J = 7.9 Hz, Ar), 4.70 (1H, d, *J* = 5.7 Hz, CH), 4.24 (1H, d, *J* = 5.7 Hz, CH), 3.36 (3H, s, CH_3), 3.25 (3H, s, CH_3), 2.60 (3H, s, CH_3), 2.48(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 151.2(0), 136.9(0), 133.9(0), 131.1(1), 129.6(1), 127.6(1), 127.1(1), 126.0(1), 123.5(1), 123.0(1), 105.3(1), 68.2(1), 55.3(3), 55.2(3), 38.3(3), 18.5(3).

The product was used in the following reaction without further characterisation.

N-(1,1-dimethoxybutan-2-yl)-N-methylaniline (3.24b)



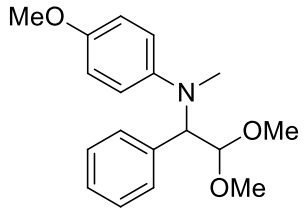
Method B gave the product with minor impurities as a colourless oil, 33 mg, 7 %.

R_f = 0.51 (hexane/EtOAc: 8/2).

δ_H (400MHz; $CDCl_3$) 7.21(2H, t, *J* = 7.6 Hz, Ar), 6.80 (2H, d, *J* = 8.3 Hz, Ar), 6.67 (1H, t, *J* = 7.2 Hz, Ar), 4.31 (1H, d, *J* = 5.7 Hz, CH), 3.77 (1H, m, CH), 3.40 (3H, s, CH_3), 3.27 (3H, s, CH_3), 2.80 (3H, s, CH_3), 2.48(3H, s, CH_3), 1.70(2H, m, CH_2), 0.86(3H, t, *J* = 7.4 Hz, CH_3).

The product was used in the following reaction without further characterisation.

N-(2,2-dimethoxy-1-phenylethyl)-4-methoxy-N-methylaniline (3.24c)



Method B gave the product as a colourless oil, 199 mg, 33 %.

R_f = 0.26 (hexane/EtOAc: 8/2).

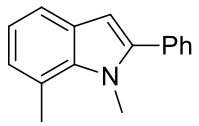
ν (liq. film) 3061,3029, 2989, 2942, 2833, 1594, 1499, 1455, 1235, 1058, 1029, 732, 700.

δ_H (400MHz; $CDCl_3$) 7.33(2H, d, *J* = 7.8 Hz, Ar), 7.30-7.17(3H, m, Ar), 6.92 (1H, t, *J* = 7.6 Hz, Ar), 6.86-6.80 (2H, m, Ar), 6.74(1H, d, *J* = 7.8 Hz, Ar), 5.03 (1H, d, *J* = 7.1 Hz, CH), 4.89 (1H, d, *J* = 7.1 Hz, CH), 3.88 (3H, s, CH_3), 3.35 (3H, s, CH_3), 3.28 (3H, s, CH_3), 2.68 (3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 152.2(0), 141.1(0), 137.5(0), 129.2(1), 127.8(1), 127.0(1), 122.0(1), 120.8(1), 120.7(1), 111.0(1), 104.5(1), 63.7(1), 55.3(3), 54.9(3), 25.9(3), 34.5(3).

The product was used in the following reaction without further characterisation.

1,7-dimethyl-2-phenyl-1H-indole (3.25a)



Method C gave the product as a pale yellow solid, 101 mg, 49%, m.p. 97-99 °C.

R_f = 0.32 (hexane/EtOAc: 9/1).

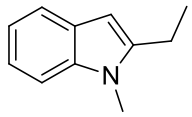
ν (liq. film) 3056,1603, 1468, 1387, 1340, 765, 749.

δ_H (400MHz; $CDCl_3$) 7.63 (1H, d, *J* = 7.8 Hz, Ar), 7.51 (2H, d, *J* = 7.6 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, , Ar), 7.40(1H, d, *J* = 7.5 Hz, Ar), 7.36 (1H, d, *J* = 8.3 Hz, Ar), 7.24(1H, t, *J* = 7.6 Hz, Ar), 7.14 (1H, t, *J* = 7.4 Hz, Ar), 6.56(1H, s, Ar), 3.73 (3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 141.6(0), 138.5(0), 132.9(0), 129.5(1), 128.6(1), 128.1(0), 127.9(1), 121.8(1), 120.6(1), 120.0(1), 109.7(1), 101.8(1), 31.2(3).

Spectroscopical data agrees with Zhao.[19]

2-ethyl-1-methyl-1H-indole (3.25b)



Method C gave the product as a pale yellow oil, 273 mg, 86%.

R_f = 0.35 (hexane/EtOAc: 9/1).

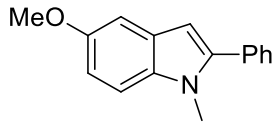
ν (liq. film) 2941, 2829, 1480, 1256,1097.

δ_H (400MHz; $CDCl_3$) 7.53 (1H, d, *J* = 7.8 Hz, Ar), 7.29-7.21(1H, m, Ar), 7.15 (1H, d, *J* = 7.5 Hz, Ar), 7.06 (1H, d, *J* = 7.4 Hz, , Ar), 6.25(1H, s, Ar), 3.66 (3H, s, CH_3), 2.76(2H,q, *J* = 7.4 Hz, CH_2), 1.35(3H, t, *J* = 7.4 Hz, CH_3).

δ_C (100MHz; $CDCl_3$)142.9(0), 137.4(0), 127.9(0), 120.5(1), 119.7(1), 119.2(1), 108.6(1), 9.8(1), 29.3(3), 20.1(2), 12.7(3).

Spectroscopical data agrees with Liu.[20]

5-methoxy-1-methyl-2-phenyl-1H-indole (3.25c)



Method C gave the product as a pale yellow solid, 101 mg, 46%, m.p. 123-125 °C.

R_f = 0.35 (hexane/EtOAc: 9/1).

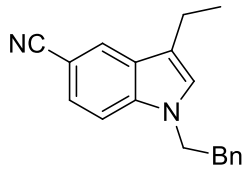
ν (liq. film) 2941, 2829, 1480, 1256,1097.

δ_H (400MHz; $CDCl_3$) 7.51-7.40(4H, m, Ar), 7.37(1H, t, *J* = 7.1 Hz, Ar), 7.21(1H, d, *J* = 7.9 Hz, Ar), 7.00(1H, t, *J* = 7.8 Hz, Ar), 6.64(1H, d, *J* = 7.7 Hz, Ar), 6.48(1H, s, Ar), 3.95(3H, s, CH_3), 3.92(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 147.9(0),142.3(0), 133.0(0), 130.2(0), 129.6(1), 128.4(1), 128.1(0), 127.8(1), 120.2(1), 113.5(1), 102.9(1), 102.3(1), 55.5(3), 34.5(3).

Spectroscopical data agrees with Yang.[21]

3-Ethyl-1-phenethyl-1*H*-indole-5-carbonitrile (3.37a)



Method E gave the product as a colourless oil 236 mg, 86 %.

R_f = 0.46 (8:2 hexane/EtOAc).

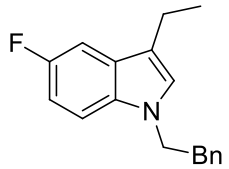
ν (liq. film) 2963, 2924, 2853, 2216 (CN), 1613, 1482, 1454, 1375.

δ_H (400MHz; $CDCl_3$) 7.91 (t, *J* = 0.7 Hz, 1H), 7.37 (dd, J^1 = 8.5, J^2 = 1.5 Hz, 1H), 7.26-7.21 (m, 4H), 7.02 (dd, J^1 = 7.5, J^2 =1.9 Hz, 2H), 6.80 (s, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.72 (qd, J^1 = 7.5 Hz, J^2 = 1.0 Hz, 2H), 1.28 (d, *J* = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 138.0, 137.7, 133.4, 128.7, 127.7, 126.9, 126.6, 124.8, 124.3, 121.1, 118.6, 109.9, 101.5, 48.1, 36.9, 18.0, 14.5.

Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.09; H, 6.65; N, 10.26.

3-Ethyl-5-fluoro-1-phenethyl-1*H*-indole (3.37b)



Method E gave the product as a colourless oil 240 mg, 90 %.

R_f = 0.74 (8:2 hexane/EtOAc).

ν (liq. film) 3062, 3027, 2962, 2929, 2873, 1578, 1486, 1454, 1194.

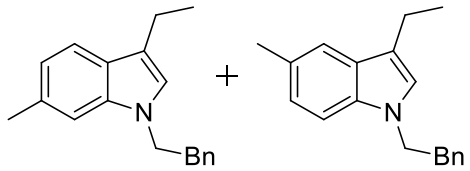
δ_H (400MHz; $CDCl_3$) 7.28-7.20 (m, 4H), 7.15 (dd, J^1 = 8.9 Hz, J^2 = 4.3 Hz, 1H), 7.06 (dd, J^1 = 7.9 Hz, 1.5 Hz, 2H), 6.91 (td, J^1 = 9.1 Hz, J^2 = 2.5 Hz, 1H), 6.74 (s, 1H), 4.25 (t, J = 7.4 Hz, 2H), 3.05 (t, J = 7.4 Hz, 2H), 2.68 (qd, J^1 = 7.5, J^2 = 0.9 Hz, 2H), 1.25 (d, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 158.6, 156.3, 138.6, 132.8, [128.8, 128.6 (1C)], [128.2, 128.1 (1C)], 126.7, 126.1, [117.3, 117.2 (1C)], [109.8, 109.7, 109.5 (1C)], 104.1, 103.9, 48.2, 36.9, 18.2, 14.5.

δ_F (376MHz; $CDCl_3$) -126.0

Anal. Calcd for $C_{18}H_{18}FN$: C, 80.87; H, 6.79; N, 5.24. Found: C, 80.81; H, 6.84; N, 5.21.

3-Ethyl-6-methyl-1-phenethyl-1*H*-indole and 3-Ethyl-4-methyl-1-phenethyl-1*H*-indole (3.37c)



Method E gave the product as a pale yellow oil 242 mg, 92 %.

R_f = 0.41 (98:2 hexane/EtOAc).

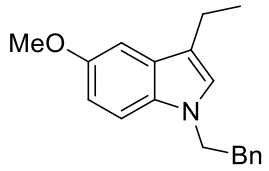
ν (liq. film) 3026, 2961, 1603, 1553, 1495, 1468, 1361, 1180.

δ_H (400MHz; $CDCl_3$) 7.47 (d, J = 8.0 Hz, 0.5 H), 7.30-7.20 (m, 3H), 7.16-7.05 (m, 3.5 H), 6.92 (dt, J^1 = 8 Hz, J^2 = 0.8 Hz, 0.5 H), 6.81 (dt, J^1 = 8 Hz, 0.8 Hz, 0.5 H), 6.67 (s, 0.5 H), 6.64 (s, 0.5 H), 4.24 (ddd, J^1 = 8.1 Hz, J^2 = 7.0 Hz, J^3 = 4.5 Hz, 2H), 3.08-3.04 (m, 2H), 2.93 (qd, $\underline{CH_2}CH_3$, J^1 = 7.4 Hz, J^2 = 1.0 Hz, 1H), 2.72 (qd, $\underline{CH_2}CH_3$, J^1 = 7.4, J^2 = 1.0 Hz, 1H), 2.70 (s, Ar-$\underline{CH_3}$, 1.5 H), 2.48 [s, Ar(C6)-$\underline{CH_3}$, 1.5 H], 1.26 [t_1($CH_2\underline{CH_3}$)+ t_2 ($CH_2\underline{CH_3}$), J = 7.5, 3H).

δ_C (100MHz; $CDCl_3$) 138.9, 138.8, 136.6, 131.4, 131.2, 128.8, 128.6, 126.6 (2xC), 125.9, 124.6, 123.8, 121.4, 120.4, 120.3 (2xC), 118.9, 118.3, 117.2, 109.2, 107.0, 47.9, 47.8, 36.9, 36.8, 22.0, 20.4, 20.3, 18.3, 15.6, 14.7.

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.62; H, 8.09; N, 5.29.

3-Ethyl-5-methoxy-1-phenethyl-1*H*-indole (3.37d)



Method E gave the product as a light yellow oil 260 mg, 93 %.

R_f = 0.65 (8:2 hexane/EtOAc).

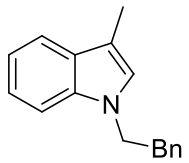
ν (liq. film) 3062, 3027, 2960, 2246, 1619, 1603, 1578, 1487, 1453, 1360, 1222.

δ_H (400MHz; $CDCl_3$) 7.28-7.16 (m, 4H), 7.09-7.03 (m, 3H), 6.86 (dd, J^1 = 8.8 Hz, J^2 = 2.5 Hz, 1H), 6.69 (s, 1H), 4.22 (t, J = 7.5 Hz, 2H), 3.86 (d, J = 5.0 Hz, 3H), 3.04 (t, J = 7.5 Hz, 2H), 2.70 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 153.6, 138.8, 131.6, 128.8, 128.6, 128.3, 126.6, 125.1, 116.8, 111.6, 110.0, 101.2, 56.0, 48.2, 37.0, 18.3, 14.6.

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.72; H, 7.61; N, 4.93.

3-Methyl-1-phenethyl-1*H*-indole (3.37e)



Method E gave the product as a dark yellow oil 221 mg, 94 %.

R_f = 0.44 (98:2 hexane/EtOAc).

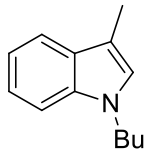
ν (liq. film) 3028, 2959, 1601, 1550, 1498, 1464, 1359, 1182.

δ_H (400MHz; $CDCl_3$) 7.61-7.58 (m, 1H), 7.34-7.20 (m, 5H), 7.16-7.10 (m, 3H), 6.78 (d, J = 1.0 Hz, 1H), 4.30 (dd, J^1 = 8.2 Hz, J^2 = 7.0 Hz, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.32 (t, J = 1.2 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 138.7, 136.1, 128.7, 128.6, 126.6, 125.4, 121.3, 119.0, 118.6, 110.2, 109.0, 107.5, 47.8, 36.9, 9.5.

Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.74; H, 7.25; N, 6.01.

1-Butyl-3-methyl-1*H*-indole (3.37f)



Method E gave the product as a colourless oil 178 mg, 95 %.

R_f = 0.55 (98:2 hexane/EtOAc).

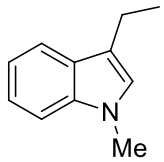
ν (liq. film) 3053, 2957, 2929, 1467, 1362.

δ_H (400MHz; $CDCl_3$) 7.55 (dt, J = 7.9 Hz, 0.9 Hz, 1H), 7.27 (dt, J^1 = 8.2, J^2 = 0.8 Hz, 1H), 7.18 (ddd, J^1 = 8.2, J^2 = 7.0 Hz, J^3 = 1.2 Hz, 1H), 7.08 (ddd, J^1 = 7.9 Hz, J^2 = 6.9 Hz, J^3 = 1.0 Hz, 1H), 6.83 (d, J = 0.9 Hz, 1H), 4.01 (t, J = 7.1 Hz, 2H), 2.31 (d, J = 1.0 Hz, 3H), 1.76 (dt, J = 14.7 Hz, J^2 =7.4 Hz, 2H), 1.31 (dq, J = 15.1 Hz, 7.5 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.3, 128.6, 125.4, 121.2, 118.9, 118.3, 109.9, 109.1, 45.7, 32.4, 20.2, 13.7, 9.6.

Spectroscopical data agrees with Nadres.[22]

3-Ethyl-1-methyl-1*H*-indole (3.37g)



Method E gave the product as a colourless oil 153 mg, 96 %.

R_f = 0.42 (98:2 hexane/EtOAc).

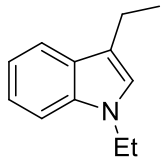
ν (liq. film) 3053, 2962, 2929, 1472, 1376.

δ_H (400MHz; $CDCl_3$) 7.59 (dt, J = 7.9, 0.9 Hz, 1H), 7.29-7.27 (m, 1H), 7.21 (ddd, J^1 = 8.1, J^2 = 7.0 Hz, J^3 = 1.1 Hz, 1H), 7.09 (ddd, J^1 = 7.9, J^2 = 6.9, J^3 = 1.0 Hz, 1H), 6.82 (s, 1H), 3.74 (s, 3H), 2.78 (qd, J^1 = 7.5, J^2 = 0.9 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 137.1, 127.8, 125.4, 121.4, 119.0, 118.4, 117.3, 109.1, 32.5, 18.3, 14.7.

Spectroscopical data agrees with Zhang.[23]

1,3-Diethyl-1*H*-indole (3.37h)



Method E gave the product as a colourless oil 168 mg, 97 %.

R_f = 0.58 (9:1 hexane/EtOAc).

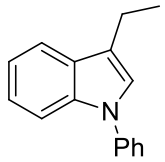
ν (liq. film) 3052, 2964, 2930, 1613, 1469, 1370, 1225, 736.

δ_H (400MHz; $CDCl_3$) 7.59 (dd, J^1 = 7.9 Hz, J^2 = 0.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.19 (ddd, J^1 = 8.2 Hz, J^2 = 7.0 Hz, J^3= 1.1 Hz, 1H), 7.08 (td, J = 7.4, 0.9 Hz, 1H), 6.88 (s, 1H), 4.11 (q, J = 7.3 Hz, 2H), 2.78 (qd, J^1 = 7.5, J^2 0.9 Hz, 2H), 1.43 (t, J = 7.3 Hz, 3H), 1.32 (t, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.1, 127.9, 123.6, 121.3, 119.2, 118.4, 117.4, 109.2, 40.7, 18.4, 15.5, 14.7.

Spectroscopical data agrees with Nishida.[24]

3-Ethyl-1-phenyl-1*H*-indole (3.37i)



Method E gave the product as a light yellow oil 126 mg, 57 %.

R_f = 0.53 (hexane).

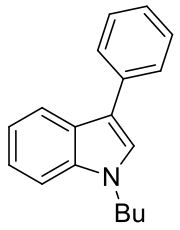
ν (liq. film) 3051, 2963, 2929, 2852, 1597, 1500, 1456, 1378, 1225.

δ_H (400MHz; $CDCl_3$) 7.65 (ddd, J^1 = 7.7 Hz, J^2 = 1.3 Hz, J^3 = 0.8 Hz, 1H), 7.56 (dt, J^1 = 8.1 Hz, J^2 = 0.9 Hz, 1H), 7.51-7.48 (m, 4H), 7.30 (ddd, J^1 = 8.7 Hz, J^2 = 4.7, J^3 = 3.9 Hz, 1H), 7.23-7.13 (m, 3H), 2.84 (qd, J^1 = 7.5 Hz, J^2 =1.1 Hz, 2H), 1.38 (t, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 140.1, 136.1, 129.6, 129.0, 125.9, 124.4, 124.1, 122.4, 119.9, 119.7, 119.3, 110.5, 18.3, 14.4.

Spectroscopical data agrees with Nishio.[25]

1-Benzyl-3-phenyl-1*H*-indole (3.37l)



Method E gave the product as a colourless crystals, 199 mg, 80 %, m.p. 62-63 °C, lit.[26] 61-63 °C.

R_f = 0.49 (9/1 hexane/EtOAc).

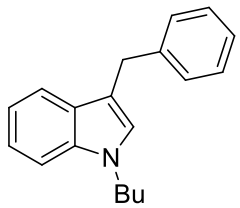
ν (liq. film) 3108, 1613, 1483, 1461, 1365, 1344, 1270, 1194.

δ_H (400MHz; $CDCl_3$) 7.97 (dd, J^1 = 6.9 Hz, J^2 = 1.4 Hz, 1H), 7.66 (dd, J^1 = 8.2, J^2 = 1.2 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.33-7.15 (m, 10H), 5.34 (s, 2H).

δ_C (100MHz; $CDCl_3$) 137.2, 137.1, 135.6, 128.9, 128.8, 127.8, 127.4, 127.0, 126.5, 125.9, 125.9, 122.2, 120.2, 120.10, 117.4, 110.1, 50.2.

Spectroscopical data agrees with Bedford.[26]

3-Benzyl-1-butyl-1*H*-indole (3.37m)



Method E gave the product as a light yellow oil 218 mg, 83 %.

R_f = 0.32 (98:2 hexane/EtOAc).

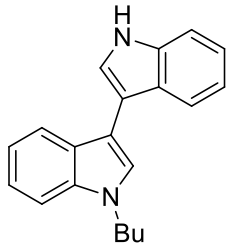
ν (liq. film) 3057, 3025, 2957, 2929, 2871, 1595, 1494, 1481, 1467.

δ_H (400MHz; $CDCl_3$) 7.50 (d, J = 7,.9 Hz, 1H), 7.31-7.24 (m, 5H), 7.20-7.16 (m, 2H), 7.04 (td, J = 7.5 Hz, 0.9 Hz, 1H), 6.80 (s, 1H), 4.10 (s, 2H), 4.05 (t, J = 7.1 Hz, 2H), 1.82-1.74 (m, 2H), 1.33 (dd, J = 15.1 Hz, 7.5 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 141.5, 136.5, 128.7, 128.3, 127.9, 126.1, 125.8, 121.4, 119.3, 118.7, 114.1, 109.3, 46.0, 32.4, 31.6, 20.3, 13.8.

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.62; H, 8.00; N, 5.38.

1-Butyl-1*H*,1'*H*-3,3'-biindole (3.37n)



Method E gave the product as a light yellow oil 138 mg, 48 %.

R_f = 0.38 (8:2 hexane/EtOAc).

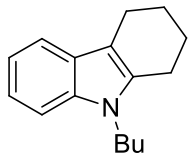
ν (liq. film) 3410 (NH), 2956, 2926, 1457, 1337, 1236.

δ_H (400MHz; $CDCl_3$) 8.19 (bs, 1H), 7.85-7.81 (m, 2H), 7.47-7.39 (m, 3H), 7.25 (s, 3H), 7.16 (dddd, *J* = 9.7, 8.0, 7.0, 1.0 Hz, 2H), 4.20 (t, *J* = 7.1 Hz, 2H), 1.93-1.86 (m, 2H), 1.45-1.39 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.4, 136.4, 127.3, 126.9, 125.3, 122.3, 121.7, 121.3, 120.3, 120.2, 119.7, 119.2, 111.3, 111.2, 109.5, 109.3, 46.2, 32.4, 20.3, 13.8.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.28; H, 7.04; N, 9.68.

9-Butyl-2,3,4,9-tetrahydro-1*H*-carbazole (3.37o)



Method E gave the product as a yellow oil 138 mg, 80%.

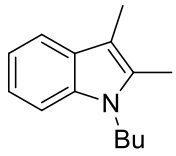
R_f = 0.38 0.41 (hexane/AcOEt: 98/2).

δ_H (400MHz; $CDCl_3$) 7.50 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.18-7.14 (m, 1H), 7.11-7.07 (m, 1H), 4.02 (dd, J^1 = 9.0 Hz, J^2 = 5.7 Hz, 2H), 2.75 (dt, J^1 = 12.7 Hz, J^2 = 6.3 Hz, 4H), 1.99-1.87 (m, 4H), 1.76-1.72 (m, 2H), 1.43-1.37 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 7.50 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.18-7.14 (m, 1H), 7.11-7.07 (m, 1H), 4.02 (dd, J^1 = 9.0 Hz, J^2 = 5.7 Hz, 2H), 2.75 (dt, J^1 = 12.7 Hz, J^2 = 6.3 Hz, 4H), 1.99-1.87

Spectroscopical data agrees with Willis.[27]

1-Butyl-2,3-dimethyl-1*H*-indole (3.37p)



Method E gave the product as a colourless oil, 173 mg, 86 %.

R_f = 0.42 (98/2 hexane/EtOAc).

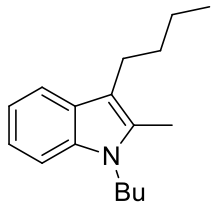
ν (liq. film) 3051, 2957, 2929, 2871, 1614, 1469.

δ_H (400MHz; $CDCl_3$) 7.48 (dd, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.25-7.23 (m, 1H), 7.12 (ddd, *J* = 8.1 Hz, 7.0, 1.2 Hz, 1H), 7.05 (ddd, *J* = 7.8 Hz, 6.9 Hz, 1.0 Hz, 1H), 4.04 (t, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 2.25 (s, 3H), 1.73-1.66 (m, 2H), 1.42-1.32 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 135.8, 132.1, 128.5, 120.3, 118.4, 117.9, 108.6, 106.3, 43.0, 32.6, 20.4, 13.9, 10.2, 8.8.

Spectroscopical data agrees with Suvorov.[28]

1,3-Dibutyl-2-methyl-1*H*-indole (3.37q)



Method E gave the product as a colourless oil 204 mg, 84 %.

R_f = 0.55 (98:2 hexane/EtOAc).

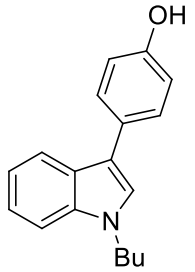
ν (liq. film) 3050, 2956, 2928, 2633, 2871, 1566, 1468, 1362.

δ_H (400MHz; $CDCl_3$) 7.51 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 7.06-7.02 (m, 1H), 4.03 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H), 1.70 (dt, J^1 = 15.1 Hz, J^2 = 7.6 Hz, 2H), 1.56 (s, 2H), 1.35 (t, *J* = 13.9 Hz, 4H), 0.93 (q, *J* = 7.4 Hz, 6H).

δ_C (100MHz; $CDCl_3$) 135.9, 132.1, 128.0, 120.2, 118.3, 118.1, 111.8, 108.7, 43.0, 33.4, 32.5, 24.2, 22.7, 20.4, 14.10, 13.9, 10.3.

Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.36; N, 5.75. Found: C, 83.91; H, 10.31; N, 5.78.

4-(1-Butyl-1*H*-indol-3-yl)phenol (3.37r)



Method E gave the product as a colourless oil 218 mg, 82 %.

R_f = 0.26 (8:2 hexane/EtOAc).

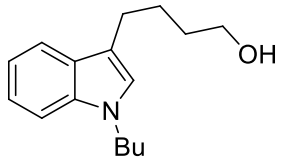
ν (liq. film) 3418, 2957, 2084, 1642, 1550, 1504, 1466, 1372, 1334, 1230, 1159, 836.

δ_H (400MHz; $CDCl_3$) 7.87 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.26-7.22 (m, 1H), 7.18-7.13 (m, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.83 (s, 1H), 4.13 (t, *J* = 7.1 Hz, 2H), 1.88-1.81 (m, 2H), 1.37 (dq, *J* = 15.1, 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 153.8, 136.7, 128.67, 128.52, 126.3, 125.0, 121.7, 119.9, 119.6, 116.3, 115.7, 109.7, 46.2, 32.4, 20.3, 13.8.

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.50; H, 7.19; N, 5.31.

4-(1-Butyl-1*H*-indol-3-yl)butan-1-ol (3.37s)



Method E gave the product as a light yellow oil 209mg, 85 %.

R_f = 0.17 (8:2 hexane/EtOAc).

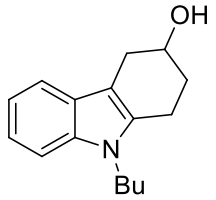
ν (liq. film) 3357 (OH), 3051, 2931, 2871, 1468, 1368, 1333.

δ_H (400MHz; $CDCl_3$) 7.58 (dt, J^1= 7.9 Hz, J^2 = 0.9 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.18 (ddd, J^1 = 8.2 Hz, J^2 = 7.0 Hz, J^3 = 1.2 Hz, 1H), 7.07 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.87 (s, 1H), 4.05 (t, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.80-2.76 (m, 2H), 1.82-1.75 (m, 4H), 1.68-1.64 (m, 2H), 1.36-1.28 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.4, 128.0, 125.1, 121.3, 119.1, 118.4, 114.9, 109.3, 63.0, 45.9, 32.7, 32.4, 26.5, 24.9, 20.3, 13.8.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.29; H, 9.40; N, 5.75.

9-Butyl-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol (3.37t)



Method E gave the product as a dark yellow oil 183 mg, 75 %.

R_f = 0.14 (8:2 hexane/EtOAc).

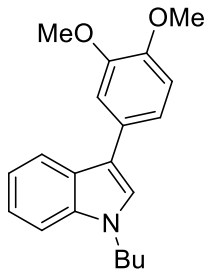
ν (liq. film) 3357, 2925, 1614, 1467, 1429, 1370, 1180.

δ_H (400MHz; $CDCl_3$) 7.48 (d, J = 7.7 Hz, 1H), 7.30-7.28 (m, 1H), 7.17 (td, J^1 = 7.6 Hz, J^2 1.1 Hz, 1H), 7.11-7.07 (m, 1H), 4.30 (bs, 1H), 4.03 (t, J = 7.4 Hz, 2H), 3.15 (ddd, J^1 = 15.1 Hz, J^2 = 4.8, J^3 = 1.0 Hz, 1H), 2.92 (dt, J^1 = 16.5 Hz, J^2 = 5.9 Hz, 1H), 2.85-2.74 (m, 2H), 2.20-2.03 (m, 2H), 1.78-1.69 (m, 3H), 1.44-1.35 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.7, 133.9, 127.1, 120.8, 118.7, 117.7, 109.0, 105.9, 67.6, 42.9, 32.5, 31.1, 30.7, 20.4, 19.7, 13.9.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.94; H, 8.67; N, 5.79.

1-Butyl-3-(3,4-dimethoxyphenyl)-1*H*-indole (3.37u)



Method E gave the product as a colourless oil 266 mg, 86 %.

R_f = 0.37 (8:2 hexane/EtOAc).

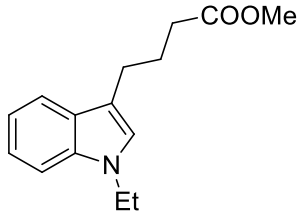
ν (liq. film) 2957, 2923, 2631, 1585, 1548, 1508, 1466, 1249, 1136.

δ_H (400MHz; $CDCl_3$) 7.90 (dd, J = 7.9, 0.8 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.27-7.15 (m, 5H), 6.97-6.95 (m, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.94 (d, J = 10.2 Hz, 6H), 1.90-1.83 (m, 2H), 1.44-1.34 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 149.2, 147.4, 136.7, 128.7, 126.3, 125.1, 121.8, 119.9, 119.7, 119.6, 116.6, 111.8, 111.1, 109.7, 56.1, 56.0, 46.2, 32.4, 20.3, 13.8.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.67; H, 7.42; N, 4.58.

Methyl 4-(1-ethyl-1*H*-indol-3-yl)butanoate (3.37v)



Method E gave the product as a yellow oil 159 mg, 65 %.

R_f = 0.34 (9:1 hexane/EtOAc).

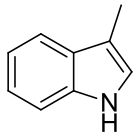
ν (liq. film) 3053, 2983, 2927, 2853, 1732, 1461, 1437, 1421, 1374, 1265, 1013, 737.

δ_H (400MHz; $CDCl_3$) 7.58 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.19 (td, *J* = 7.6, 1.1 Hz, 1H), 7.08 (td, *J* = 7.4, 0.9 Hz, 1H), 6.90 (s, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 3.66 (s, 3H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.04 (quintet, *J* = 7.4 Hz, 2H), 1.44 (t, *J* = 7.3 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 174.2, 136.1, 129.1, 124.5, 121.4, 119.1, 118.6, 114.2, 109.2, 51.5, 40.7, 33.8, 25.6, 24.5, 15.5.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.38; H, 7.79; N, 5.73.

3-Methyl-1*H*-indole (3.45)



Method F gave the product as a white crystalline solid, 56 mg, 43%. mp 95-97 °C, lit.[29] 96 °C.

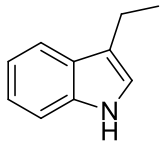
R_f = 0.47 (9:1 hexane/EtOAc).

δ_H (400MHz; $CDCl_3$) 7.88 (bs, NH, 1H), 7.60 (ddt, J^1 = 7.7 Hz, J^2 = 1.5 Hz, J^2 = 0.8 Hz, 1H), 7.40-7.30 (m, 1H), 7.26- 7.07 (m, 2H), 6.97 (dd, *J* = 2.2, 1.1 Hz, 1H), 2.35 (d, *J* = 1.1 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.5, 129.7, 122.0, 121.7, 119.3, 119.0, 111.9, 111.1, 9.8.

Spectroscopic data agrees with Ling.[30]

3-Ethyl-1*H*-indole (3.46)



Method F gave the product as a clear oil, 119 mg, 43%.

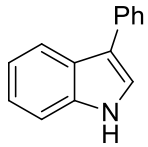
R_f = 0.49 (9:1 hexane/EtOAc).

δ_H (400MHz; $CDCl_3$) 7.90 (bs, NH, 1H), 7.63 (d, J = 9 Hz, 1H), 7.35 (dt, J^1 = 7.34, J^2 = 3 Hz, 1H), 7.20 (td, J^1 = 9, J_2 = 0.9 Hz, 1H), 7.12 (td, J^1 = 9, J^2 = 0.9 Hz, 1H), 6.98 (ps, 1H), 2.80 (qd, J^1 = 7.5 Hz, J^2 = 1.0 Hz, 2H), 1.40-1.23 (t, J = 7.5 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 136.5, 132.2, 127.5, 121.9, 120.4, 119.1, 118.9, 110.0, 18.3, 14.4.

Spectroscopic data agrees with Banwell.[31]

3-Phenyl-1*H*-indole (3.47)



Method F gave the product as a white solid, 141 mg, 73 %. M.p. 86-87 °C, lit.[32] 86-88 °C.

R_f = 0.50 (98/2 hexane/EtOAc).

ν (liq. film) 3410, 3391, 3052, 3030, 2927, 1594, 1539, 1485, 1457, 1418, 1338, 1260, 1239, 1185, 1118, 1012, 955, 910.

δ_H (400MHz; $CDCl_3$) 8.15 (d, J = 0.2 Hz, 1H), 7.94 (dd, J = 8.7, 3.9 Hz, 1H), 7.66 (td, J = 5.1, 2.5 Hz, 2H), 7.46-7.39 (m, 3H), 7.30-7.19 (m, 3H).

δ_C (100MHz; $CDCl_3$) 136.7, 135.6, 128.8, 127.5, 126.0, 125.8, 122.5, 121.8, 120.4, 119.9, 118.4, 111.4.

Spectroscopical data agrees with Kandukuri.[32]

6.4 Experimental for Chapter 4

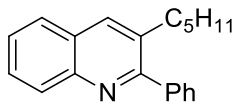
6.4.1 General Procedure for the Synthesis of Quinolines

The procedure for the synthesis of quinoline **4.30** is illustrative: to a 10 mL MW tube aniline **1.63** (140 mg, 1.5 mmol), benzyl alcohol **1.18** (195 mg, 1.8 mmol), crotononitrile (134 mg, 2.0 mmol), $RuH_2CO(PPh_3)_3$ (37 mg, 4 mol%) and Xantphos (23 mg, 4 mol%) were added. The reaction mixture

was irradiated in a sealed tube at 130 °C for 1 h to allow complete conversion into the Schiff base **4.26** (monitored by ^{1}H NMR). Then, 1-heptanol **3.3** (116 mg, 1.0 mmol) and crotononitrile (148mg, 2.2 mmol) were added to the resulting solution and the reaction was subjected to microwave irradiation for 3 h at 130 °C in a monomodal microwave oven. The crude reaction mixture was then concentrated to afford the crude product as slightly orange oil, which was further purified by flash column chromatography (hexane/ethyl acetate 9/1) to give the expected quinoline **4.30** in 71% yield (196 mg). All products prepared by the above procedure were characterized spectroscopically as shown below.

6.4.2 Characterisation Data for Quinolines

3-Pentyl-2-phenylquinoline (4.28)



The general procedure gave the product as a ahite solid, 195 mg, 71%, m.p. 42-44 °C, lit.[33] 43-44 °C.

R_f = 0.59 (8:2 hexane/EtOAc).

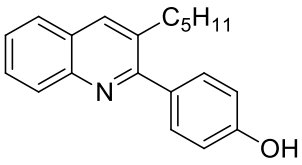
ν (liq. film) 3059, 2955, 2927, 2858, 1636, 1487, 1418, 1007.

δ_H (400MHz; $CDCl_3$) 8.12 (d, *J* = 8Hz, 1 H), 8.03 (s, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.66 (t, *J* = 7 Hz, 1 H), 7.53 (t, *J* = 8 Hz, 3 H), 7.50-7.41 (m, 3 H), 2.76 (t, *J* = 8 H, 2 H), 1.54 (quint. *J* = 7 Hz, 2 H), 1.25-1.20 (m, 4 H), 0.81 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 160.8,146.4, 141.0, 135.7, 134.1, 129.3, 128.8, 128.7 (2C), 128.2 (2C), 128.0, 127.6, 126.9, 126.3, 32.8, 31.5, 30.2, 22.3, 13.9.

Spectroscopical data agrees with Tanaka.[33]

4-(3-Pentylquinolin-2-yl)phenol (4.31a)



The general procedure gave the product as a yellow oil, 149 mg, 51%

R_f = 0.3 (7:3 hexane/EtOAc).

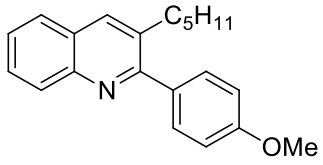
ν (liq. film) 2959, 2924, 2855, 2367, 1646, 1275.

δ_H (400MHz; $CDCl_3$) 8.19 (d, *J* = 8 Hz, 1 H), 8.05 (s, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.67 (t, *J* = 8 Hz, 1 H), 7.52 (t, *J* = 8 Hz, 1 H), 7.31 (d, *J* = 8 Hz, 2 H), 6.74 (d, *J* = 8 Hz, 1 H), 2.77 (t, *J* = 8 Hz, 2 H), 1.54 (quint. *J* = 6 Hz, 2 H), 1.26-1.21 (m, 5 H), 0.82 (t, *J* = 6 Hz, 3 H)

δ_C (100MHz; $CDCl_3$) 160.8, 156.9, 145.8, 136.2, 134.7, 131.8, 130.0 (2C), 129.1, 128.2, 127.6, 126.9, 126.4, 116.0 (2C), 32.8, 31.5, 30.2, 22.3, 13.9.

HRMS (ES) $C_{20}H_{21}NO$ $[M+H]^+$ requires 292.1701, found 292.1705.

2-(4-methoxyphenyl)-3-pentylquinoline (4.31b)



The general procedure gave the product as a white solid, 150 mg, 49%), m.p. 43-45 °C, lit.[33] 44-45 °C.

R_f = 0.6 (7:3 hexane/EtOAc).

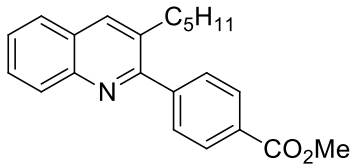
ν (liq. film) 3058, 3000, 2955, 2929, 2858, 1608, 1515, 1420, 1247, 1174.

δ_H (400MHz; $CDCl_3$) 8.11 (d, *J* = 8 Hz, 1 H), 8.01 (s, 1 H), 7.78 (d, *J* = 8 Hz, 1 H), 7.64 (t, *J* = 7 Hz, 1 H), 7.51-7.48 (m, 3 H), 7.01 (d, *J* = 8 Hz, 2 H), 3.87 (s, 3 H), 2.78 (t, *J* = 8 Hz, 2 H), 1.55 (quint. *J* = 7 Hz, 2 H), 1.25-1.22 (m, 4 H), 0.83 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 160.4, 159.5, 146.4, 135.6, 134.2, 133.5, 130.1 (2C), 129.2, 128.6, 127.5, 126.8, 126.1, 113.7 (2C), 55.3, 32.9, 31.5, 30.2, 22.3, 13.9.

Spectroscopical data agrees with Tanaka.[33]

Methyl 4-(3-pentylquinolin-2-yl)benzoate (4.31c)



The general procedure gave the product as a yellow oil, 203 mg, 61%.

R_f = 0.6 (7:3 hexane/EtOAc).

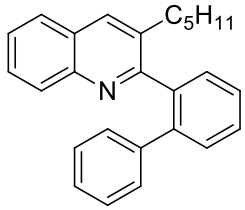
ν (liq. film) 3060, 2953, 2928, 2858, 1724, 1612, 1435, 1277, 1112, 1016.

δ_H (400MHz; $CDCl_3$) 8.17 (d, *J* = 8 Hz, 2 H), 8.11 (d, *J* = 8 Hz, 1 H), 8.05 (s, 1 H), 7.81 (d, *J* = 8 Hz, 1H), 7.68 (t, *J* = 7 Hz, 1 H), 7.63 (d, *J* = 8 Hz, 2 H), 7.54 (t, *J* = 8 Hz, 1H), 3.96 (s, 3 H), 2.74 (t, *J* = 8 Hz, 2 H), 1.52 (quint. *J* = 7 Hz, 2 H), 1.23-1.19 (m, 4 H), 0.81 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 167.0, 159.6, 146.4, 145.5, 136.0, 133.9, 129.7, 129.6, 129.3, 129.1, 129.0, 127.8, 127.0, 126.7, 52.2, 32.7, 31.5, 30.3, 22.3, 13.9.

HRMS (ES) $C_{22}H_{24}NO_2$ $[M+H]^+$ requires 334.1807, found 334.1810.

2-(Biphenyl-2-yl)-3-pentylquinoline (4.31d)



The general procedure gave the product as a colourless oil, 53 mg, 15%).

R_f = 0.38 (9:1 hexane/EtOAc).

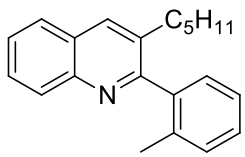
ν (liq. film) 3059, 2954, 2926, 2856, 2359, 1621, 1598, 1488.

δ_H (400MHz; $CDCl_3$) 8.16 (d, *J* = 8 Hz, 1 H), 7.76 (s, 1 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.68 (t, *J* = 7 Hz, 1 H), 7.53-7.48 (m, 5 H), 7.20-7.16 (m, 2 H), 7.09-7.07 (m, 3 H), 2.11 (br m, 2 H), 1.10-1.00 (m, 6 H), 0.76 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 161.4, 146.2, 140.9, 140.4, 139.5, 134.8, 134.6, 130.3, 129.7, 129.5 (2C), 129.2, 128.60, 128.56, 127.9 (2C), 127.7, 127.6, 127.0, 126.7, 126.2, 31.9, 31.4, 29.2, 22.2, 13.9.

HRMS (ES) $C_{26}H_{26}N$ $[M+H]^+$ requires 352.2065, found 352.2063.

3-Pentyl-2-o-tolylquinoline (4.31e)



The general procedure gave the product as a colourless oil, 203 mg, 70%).

R_f = 0.44 (9:1 hexane/EtOAc).

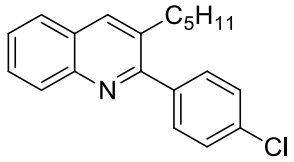
ν (liq. film) 2955, 2926, 2857, 1636, 1487, 1417, 1262.

δ_H (400MHz; $CDCl_3$) 8.11 (d, *J* = 8 Hz, 1 H), 8.03 (s, 1 H), 7.82 (d, *J* = 8 Hz, 1 H), 7.66 (t, d = 7 Hz, 1 H), 7.53 (t, *J* = 8 Hz, 1H), 7.35-7.24 (m, 4 H), 2.55 (br s, 2 H), 2.09 (s, 3 H), 1.50 (quint. *J* = 7 Hz, 2 H), 1.23-1.19 (m, 4H), 0.80 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 161.3, 146.4, 140.2, 135.6, 135.2,134.6, 130.2, 129.2, 128.7, 128.5, 128.1, 127.7, 127.0, 126.3, 125.7, 32.4, 31.4, 29.8, 22.3, 19.6, 13.9.

HRMS (ES) $C_{21}H_{24}N$ $[M+H]^+$ requires 290.1909, found 290.1911.

2-(4-chlorophenyl)-3-pentylquinoline (4.31f)



The general procedure gave the product as a brown oil, 226 mg, 73%.

R_f = 0.52 (9:1 hexane/EtOAc).

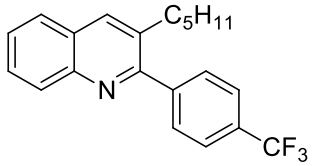
ν (liq. film) 2955, 2927, 2858, 1647, 1488, 1419, 1091.

δ_H (400MHz; $CDCl_3$) 8.09 (d, *J* = 8 Hz, 1 H), 8.04 (s, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.67 (t, *J* = 7 Hz, 1H), 7.55-7.45 (m, 5 H), 2.75 (t, *J* = 8 Hz, 2H), 1.54 (quint. *J* = 7 Hz, 2 H), 1.25-1.22 (m, 4 H), 0.83 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 159.4, 146.4, 139.4, 135.9, 134.2, 133.9, 130.2 (2C), 129.2, 130.0, 128.5 (2C), 127.7, 126.9, 126.6, 32.8, 31.5, 30.3, 22.3, 13.9.

HRMS (ES) $C_{20}H_{21}ClN$ $[M+H]^+$ requires 310.1363, found 310.1360.

3-Pentyl-2-(4-(trifluoromethyl)phenyl)quinoline (4.31g)



The general procedure gave the product as a brown oil, 262 mg, 76%, m.p. 65-67 °C

R_f = 0.53 (9:1 hexane/EtOAc).

ν (liq. film) 2959, 2923, 2859, 1646, 1328, 1164, 1125, 1107, 1068.

δ_H (400MHz; $CDCl_3$) 8.11 (d, *J* = 8 Hz, 1 H), 8.10 (s, 1 H), 7.82 (d, *J* = 8 Hz, 1 H), 7.76 (d, *J* = 8 Hz, 2 H), 7.70-7.66 (m, 3 H), 7.55 (t, *J* = 7 Hz, 1 H), 2.75 (t, *J* = 8 Hz, 2 H),

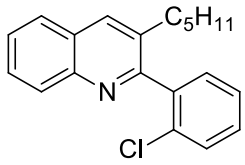
1.54 (quint. *J* = 7 Hz, 2 H), 1.24-1.23 (m, 4 H), 0.82 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 159.2, 146.4, 144.6, 136.1, 133.7, (130.7, 130.4, 130.1, 129.8) [q, $J_{C\text{-}F}$ = 32 Hz, 1C], 129.29, 129.26, 129.1, (128.3, 125.6, 122.9, 120.2) [q, $J_{C\text{-}F}(CF_3)$ = 269 Hz, 1C], 127.8, 127.0,126.8, (125.4, 125.34, 125.30, 125.26) [q, *J*C-F = 3 Hz, 1C], 32.7, 31.4, 30.3, 22.3, 13.9.

δ_F (376MHz; $CDCl_3$) -62.55

HRMS (ES) $C_{21}H_{21}F_3N$ $[M+H]^+$ requires 344.1626, found 344.1624.

2-(2-Chlorophenyl)-3-pentylquinoline (4.31h)



The general procedure gave the product as a colourless oil, 201 mg, 65%.

R_f = 0.6(DCM).

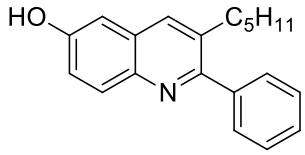
ν (liq. film) 3059, 2954, 2927, 2858, 2359, 2332, 1489, 1435, 1418, 1067.

δ_H (400MHz; $CDCl_3$) 8.13 (d, J = 8Hz, 1 H), 8.04 (s, 1 H), 7.82 (d, *J* = 8 Hz, 1 H), 7.67 (t, *J* = 7 Hz, 1 H), 7.56-7.48 (m, 2 H), 7.39-7.36 (m, 3 H), 2.60 (m, 2 H), 1.53 (m, 2 H), 1.22-1.20 (m, 4 H), 0.80 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 158.7, 146.2, 139.6, 135.2, 134.7, 132.8, 130.5, 129.50, 129.45, 129.2, 128.8, 128.0, 127.0, 126.8, 126.6, 32.2, 31.4, 29.6, 22.2, 13.6.

HRMS (ES) $C_{20}H_{21}ClN$ $[M+H]^+$ requires 310.1363, found 310.1367.

3-Pentyl-2-phenylquinolin-6-ol (4.34a)



The general procedure gave the product as a white solid, 152 mg, 52%, m.p. 191-193 °C, lit.[26] 190-193 °C

R_f = 0.2 (7:3 hexane/EtOAc).

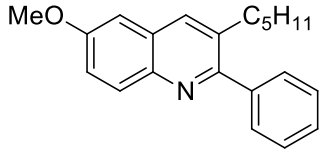
ν (liq. film) 3418 (br), 3060, 2956, 2928, 2858, 2250, 1621, 1492, 1458, 1394, 1345, 1228.

δ_H (400MHz; $CDCl_3$) 8.88 (br s, 1 H), 7.91 (d, *J* = 9 Hz, 1 H), 7.50 (d, *J* = 9 Hz, 1 H), 7.49(s, 2 H), 7.42-7.36 (m, 3 H), 7.10 (d, *J* = 9 Hz, 1 H), 6.91 (s, 1 H), 2,70 (t, *J* = 8 Hz, 2 H), 1,50 (quint., *J* = 7 Hz, 2 H), 1.25-1.20 (m, 4 H), 0.81 (t, *J* = 7 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 157.7, 155.1, 141.1, 140.1, 134.9, 134.4, 129.5, 129.1, 128.8 (2C), 128.2 (2C), 128.1, 121.7, 108.3, 32.7, 31.5, 30.3, 22.3, 13.9.

Spectroscopic data agrees with Tanaka.[33]

6-Methoxy-3-pentyl-2-phenylquinoline (4.34b)



The general procedure gave the product as a white solid, 150 mg, 49%, m.p. 30-32 °C, lit.[26] 31-32 °C.

R_f = 0.22 (9:1 hexane/EtOAc).

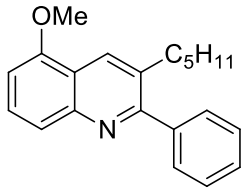
ν (liq. film) 3060, 2955, 2928, 2858, 1625, 1490, 1227, 1029.

δ_H (400MHz; $CDCl_3$) 8.01 (d, *J* = 8 Hz, 1 H), 7.92 (s, 1 H), 7.52 (d, *J* = 8 Hz, 1 H), 7.51 (s, 1H), 7.46 (t, *J* = 8 Hz, 2 H), 7.42 (q, *J* = 8 Hz, 1 H), (dd, *J*1 = 3Hz, *J*2 = 9Hz, 1 H), 7.06 (d, *J* = 3 Hz, 1 H), 3.93 (s, 3 H), 2.73 (t, *J* = 8 Hz, 2 H), 1.53 (quint, *J* = 7 Hz, 2 H), 1.23-1.20 (m, 4H), 0.81 (t, *J* = 7 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 158.3, 157.7, 142.5, 141.1, 134.6, 134.4, 130.7, 128.8 (2C), 128.6, 128.2 (2C), 127.9, 121.5, 104.4, 55.5, 32.8, 31.5, 30.3, 22.3, 13.9.

Spectroscopic data agrees with Tanaka.[33]

5-Methoxy-3-pentyl-2-phenylquinoline (4.34d)



The general procedure gave the product as a colourless oil, 101 mg, 33%.

R_f = 0.46(8:2 hexane/EtOAc).

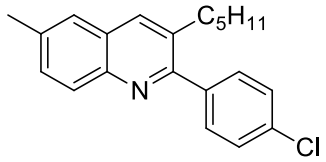
ν (liq. film) 2955, 2926, 2856, 1625, 1489, 1222.

δ_H (400MHz; $CDCl_3$) 7.96 (s, 1 H), 7.68 (d, *J* = 9 Hz, 1 H), 7.52 (d, *J* = 8 Hz, 1 H), 7.52 (s, 1 H), 7.49-7.40 (m, 4 H), 7.18 (dd, *J*1 = 2 Hz, *J*2 = 9 Hz, 1 H), 3.92 (s, 3 H), 2.72 (t, *J* = 8 Hz, 2 H), 1.52 (quint, *J* = 7 Hz, 2 H), 1.26-1.19 (m, 4 H), 0.81 (*J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 160.8, 160.3, 147.9, 141.1, 135.6, 131.8 (2C), 128.7 (2C), 127.9 (2C), 122.9 (2C), 119.7, 107.2, 55.5, 32.6, 31.5, 30.4, 22.3, 13.9.

HRMS (ES) $C_{21}H_{24}NO$ $[M+H]^+$ requires 306.1858, found 306.1861.

5-Methoxy-3-pentyl-2-phenylquinoline (4.34e)



The general procedure gave the product as a colourless oil, 204 mg, 63%.

R_f = 0.49 (DCM).

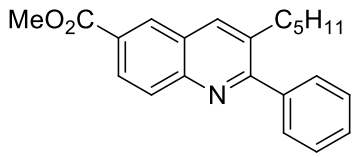
ν (liq. film) 2955, 2927, 2858, 1598, 1488, 1092, 1011.

δ_H (400MHz; $CDCl_3$) 7.98 (d, *J* = 8 Hz, 1H), 7.92 (s, 1 H), 7.54 (s, 1 H), 7.49-7.43 (m, 5 H), 2.72 (t, *J* = 8H, 2 H), 2.52 (s, 3 H), 1.52 (quint. *J* = 7 Hz, 2 H), 1.26-1.21 (m, 4 H), 0.82 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 158.4, 145.0, 139.5, 136.3, 135.2, 134.0, 133.7, 131.2, 130.2 (2C), 128.8, 128.4 (2C), 127.7, 125.7, 32.7, 31.4, 30.2, 22.3, 21.6, 13.9.

HRMS (ES) $C_{21}H_{23}ClN$ $[M+H]^+$ requires 324.1519, found 324.1516.

Methyl 3-pentyl-2-phenylquinoline-6-carboxylate (4.34f)



The general procedure gave the product as a white solid, 127 mg, 38%, m.p. 123-126 °C.

R_f = 0.31 (DCM).

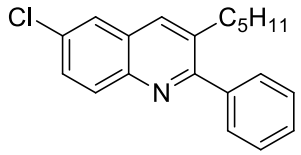
ν (liq. film) 2952, 2926, 2857, 2361, 2331, 1712, 1621, 1446, 1256, 1197.

δ_H (400MHz; $CDCl_3$) 8.60 (s, 1 H), 8.25 (d, *J* = 9 Hz, 1 H), 8.17 (d, *J* = 9 Hz, 1H), 8.12 (s, 1 H), 7.55 (d, *J* = 8 Hz, 1 H), 7.54 (s, 1 H), 7.51-7.45 (m, 3 H), 4.00 (s, 3 H), 2.79 (t, *J* = 8 Hz, 2 H), 1.54 (m, 2 H), 1.32-1.20 (m, 4 H), 0.82 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 166.9, 163.0, 148.2, 140.5, 136.9, 135.1, 130.2, 129.5, 128.7, 128.40, 128.36, 128.3, 127.8, 126.8, 52.4, 32.8, 31.4, 30.1, 22.3, 13.9.

HRMS (ES) $C_{22}H_{24}NO_2$ $[M+H]^+$ requires 334.1807, found 334.1808.

6-Chloro-3-pentyl-2-phenylquinoline (4.34g)



The general procedure gave the product as a colourless oil, 127 mg, 41%.

R_f = 0.63 (DCM).

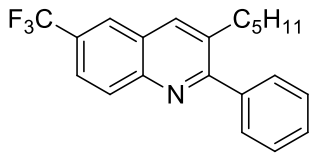
ν (liq. film) 3059, 2955, 2927, 2858, 2355, 2337, 1593, 1551, 1475, 1339, 1268.

δ_H (400MHz; $CDCl_3$) 8.04 (d, *J* = 9 Hz, 1 H), 7.92 (s, 1 H), 7.77 (s, 1 H), 7.57 (d, *J* = 9 Hz, 1 H), 7.52 (d, *J* = 8 Hz, 1 H), 7.52 (s, 1 H), 7.50-7.42 (m, 3 H), 2.75 (t, *J* = 8 Hz, 2 H), 1.52 (quint. *J* = 7 Hz, 2H), 1.25-1.19 (m, 4 H), 0.81(t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 161.0, 144.75, 140.6, 135.2, 134.7, 132.0, 130.9, 129.7, 128.7 (2C), 128.3 (2C), 128.26, 128.24, 125.6, 32.8, 31.5, 30.2, 22.3, 13.9.

HRMS (ES) $C_{20}H_{21}ClN$ $[M+H]^+$ requires 310.1363, found 310.1361.

3-Pentyl-2-phenyl-6-(trifluoromethyl)quinoline (4.34h)



The general procedure gave the product as a white solid, 148mg, 43%, m.p. 81-84 °C.

R_f = 0.48 (9:1 hexane/EtOAc).

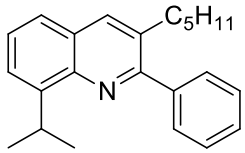
ν (liq. film) 2953, 2933, 1635, 1453, 1287, 1121.

δ_H (400MHz; $CDCl_3$) 8.22 (d, *J* = 9 Hz, 1 H), 8.12 (br s, 2 H), 7.83 (d, *J* = 9 Hz, 1 H), 7.56-7.45 (m, 5 H), 2.80 (t, *J* = 8 Hz, 2 H), 1.53 (m, 2 H), 1.26-1.23 (m, 4 H), 0.82 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 162.9, 147.2, 140.3, 136.4, 135.6, 130.4, 128.6, 128.4, 128.3, 126.5, 125.1, 125.0, 124.9, 124.4, 32.8, 31.4, 30.1, 22.3, 13.9.

HRMS (ES) $C_{21}H_{21}F_3N$ $[M+H]^+$ requires 344.1626, found 344.1624.

8-Isopropyl-3-pentyl-2-phenylquinoline (4.34i)



The general procedure gave the product as a colourless oil, 184mg, 43%.

R_f = 0.65 (8:2 hexane/EtOAc).

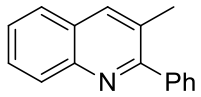
ν (liq. film) 2957, 2926, 2860, 1646, 1476, 1465, 1276.

δ_H (400MHz; $CDCl_3$) 7.99 (s, 1 H), 7.63-7.61 (m, 3 H), 7.54 (d, *J* = 9 Hz, 1 H), 7.50-7.41 (m, 4 H), 4.36 (sept., *J* = 7 Hz, 1 H), 2.81 (t, *J* = 8 Hz, 2 H), 1.36 (d, *J* = 7 Hz, 6 H), 1.25-1.23 (m, 6 H), 0.82 (t, *J* = 6 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 158.7, 147.4, 144.3, 141.6, 136.0, 133.4, 129.2 (2C), 128.0 (2C), 127.8, 127.6, 126.3, 124.6, 124.3, 32.8, 31.6, 30.4, 27.2, 23.4 (2C), 22.3, 13.9.

HRMS (ES) $C_{23}H_{28}N$ $[M+H]^+$ requires 318.2222, found 318.2223.

3-Methyl-2-phenylquinoline (4.35a)



The general procedure gave the product as a colourless oil, 127mg, 58%.

R_f = 0.47 (8:2 hexane/EtOAc).

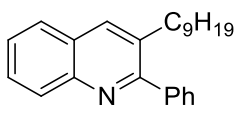
ν (liq. film) 3059, 2925, 1636, 1599, 1488, 1411, 1271.

δ_H (400MHz; $CDCl_3$) 8.12 (d, *J* = 8 Hz, 1 H), 8.02 (s, 1 H), 7.78 (d, *J* = 8 Hz, 1 H), 7.66 (t, *J* = 7 Hz, 1 H), 7.60-7.58 (d, *J* = 8 Hz, 2 H), 7.53-7.41 (m, 4 H), 2.46 (s, 3 H).

δ_C (100MHz; $CDCl_3$) 160.5, 146.6, 140.9, 136.7, 129.3, 129.2, 128.8 (2C), 128.7, 128.3 (2C), 128.1, 127.6, 126.7, 126.4, 20.6.

Spectroscopic data agrees with Martìnez.[34]

3-Nonyl-2-phenylquinoline (4.35b)



The general procedure gave the product as a colourless oil, 245mg, 74%.

R_f = 0.47 (9:1 hexane/EtOAc).

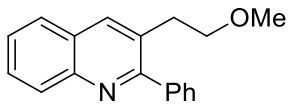
ν (liq. film) 3059, 2925, 2853, 1646, 1487, 1418, 1268.

δ_H (400MHz; $CDCl_3$) 8.12 (d, *J* = 8 Hz, 1 H), 8.03 (s, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.66 (t, *J* = 7 Hz, 1 H), 7.55-7.52 (m, 3 H), 7.50-7.41 (m, 3 H), 2.76 (t, *J* = 8 Hz, 2 H), 1.53 (quint. *J* = 7 Hz, 2 H), 1.27-1.19 (m, 12 H), 0.87 (t, *J* = 7 Hz, 3H).

δ_C (100MHz; $CDCl_3$) 160.8, 146.4, 141.0, 135.7, 134.1, 129.3, 128.8 (3C), 128.3 (2C), 128.0, 127.7, 126.9, 126.4, 32.9, 31.9, 30.6, 29.4, 29.3 (3C), 22.7, 14.1.

HRMS (ES) $C_{24}H_{30}N$ $[M+H]^+$ requires 332.2378, found 332.2376.

3-(2-Methoxyethyl)-2-phenylquinoline (4.35c)



The general procedure gave the product as a brown oil, 155 mg, 59%.

R_f = 0.32 (8:2 hexane/EtOAc).

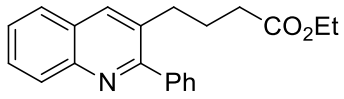
ν (liq. film) 3059, 2925, 2359, 2320, 1647, 1635, 1488, 1111.

δ_H (400MHz; $CDCl_3$) 8.13-8.11 (m, 2H), 7.82 (d, *J* = 8 Hz, 1 H), 7.68 (t, *J* = 7 Hz, 1 H), 7.56-7.53 (m, 3 H), 7.51-7.42 (m, 3 H), 3.52 (t, *J* = 7 Hz, 2H), 3.26 (s, 3 H), 3.06 (t, *J* = 7 Hz, 2H).

δ_C (100MHz; $CDCl_3$) 160.7, 146.6, 140.7, 136.6, 130.3, 129.3, 129.1, 128.8 (2C), 128.4 (2C), 128.2, 127.5, 127.1, 126.5, 72.3, 58.6, 33.0.

HRMS (ES) $C_{18}H_{18}NO$ $[M+H]^+$ requires 264.1388, found 264.1391.

Ethyl 4-(2-phenylquinolin-3-yl)butanoate (4.35d)



The general procedure gave the product as a brown oil, 134 mg, 42%.

R_f = 0.29 (8:2 hexane/EtOAc).

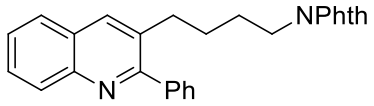
ν (liq. film) 3058, 2979, 2935, 2870, 2360, 1731, 1487, 1419, 1017.

δ_H (400MHz; $CDCl_3$) 8.12 (d, *J* = 8 Hz, 1H), 8.06 (s, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), (t, *J* = 7 Hz, 1 H), 7.54 (d, *J* = 8Hz, 2 H), 7.53 (s, 1 H), 7.50-7.42 (m, 3 H), 4.05 (q, *J* = 7 Hz, 2 H), 2.83 (t, *J* = 8 Hz, 2 H), 2.23 (t, *J* = 7 Hz, 2 H), 1.87 (quint. *J* = 8Hz, 2H), 1.20 (t, *J* = 7 Hz, 3 H).

δ_C (100MHz; $CDCl_3$) 173.1, 160.6, 146.5, 140.7, 136.0, 132.7, 129.3, 129.0, 128.7 (2C), 128.3 (2C), 128.1, 127.5, 126.9, 126.5, 60.3, 33.7, 32.1, 25.6, 14.1.

HRMS (ES) $C_{21}H_{22}NO_2$ $[M+H]^+$ requires 320.1651, found 320.1655.

2-(4-(2-Phenylquinolin-3-yl)butyl)isoindoline-1,3-dione (4.35e)



The general procedure gave the product as a white solid, 167mg, 64%, m.p. 146-153 °C.

R_f = 0.32 (7:3 hexane/EtOAc).

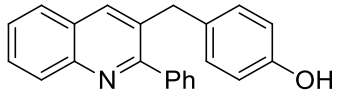
ν (liq. film) 2940, 2863, 2321, 1770, 1710, 1646, 1396, 1036.

δ_H (400MHz; $CDCl_3$) 8.10 (d, *J* = 8 Hz, 1 H), 8.03 (s, 1 H), 7.83-7.79 (m, 3 H), 7.71-7.64 (m, 3 H), 7.54-7.49 (m, 3 H), 7.43-7.34 (m, 3 H), 3.60 (t, *J* = 7 Hz, 2 H), 2.83 (t, *J* = 8 Hz, 2 H), 1.61-1.51(m, 4 H).

δ_C (100MHz; $CDCl_3$) 168.3 (2C), 160.6, 146.5, 140.8, 135.9, 133.9 (2C), 133.2, 132.1 (2C), 129.3, 128.9, 128.6 (2C), 128.3 (2C), 128.1, 127.6, 126.9, 126.4, 123.2 (2C), 37.5, 32.5, 28.2, 27.5.

HRMS (ES) $C_{27}H_{23}N_2O_2$ $[M+H]^+$ requires 407.1760, found 407.1762.

4-((2-Phenylquinolin-3-yl)methyl)phen (4.35f)



The general procedure gave the product as a white solid, 218mg, 70%, m.p. 255-260 °C.

R_f = 0.3 (7:3 hexane/EtOAc).

ν (liq. film) 3449 (br), 3059, 3024, 2924, 2855, 1613, 1514, 1454, 1265.

δ_H (400MHz; $CDCl_3$) 9.20 (bs, 1 H), 8.12 (s, 1 H), 7.99 (d, *J* = 8 Hz, 1 H), 7.93 (d, *J* = 8 Hz, 1H), 7.73 (t, *J* = 7 Hz, 1 H), 7.58 (t, *J* = 8 Hz, 1 H), 7.50-7.47 (m, 5 H), 6.76 (d, *J* = 8 Hz, 2 H), 6.61 (d, *J* = 8Hz, 2 H), 4.03 (s, 2 H).

δ_C (100MHz; $CDCl_3$) 160.0, 155.5, 145.9, 140.4, 136.6, 133.1, 130.0, 129.6 (2C), 129.2, 128.9 (2C), 128.6, 128.0, 127.9 (2C), 127.3, 127.1, 126.6, 115.2 (2C), 37.4.

HRMS (ES) $C_{22}H_{18}NO$ $[M+H]^+$ requires 312.1388, found 312.1386.

6.5 Experimental for Chapter 5

6.5.1 General Method for the Synthesis of*cis*- β-Lactams (Method A)

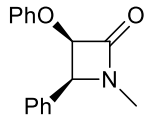
N-benzylmethylamine (128 μl, 1 mmol), was dissolved in MeCN (2 ml) under Ar and NCS (150 mg, 1.1 mmol). The reaction mixture was stirred at rt for 1h, and TEA (248 μl, 2.5 mmol) was added and the reaction mixture was stirred at rt for 3h. Phenoxyacetyl chloride (138 μl, 1 mmol) was slowly added and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. Finally the crude product was purified by column chromatography (30-60% EtOAc in hexane) to give compound **5.42a** as a white solid (177 mg, 72 %).

6.5.2 General Method for the Synthesis of *Tans*- β-Lactams (Method B)

N-benzylmethylamine (128 μl, 1 mmol), was dissolved in MeCN (3 ml) under Ar and NCS (150 mg, 1.1 mmol). The reaction mixture was stirred at rt for 1h, and TEA (490 μl, 3.5 mmol) was added and the reaction mixture was stirred at rt for 3h. The reaction mixture was heated to 60 °C over 15 min, phenylacetyl chloride (138 μl, 2 mmol) was added dropwise and the reaction mixture was stirred at 80 °C for 3 h and at rt overnight. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (30-60% EtOAc in hexane) to give compound **5.48a** as a yellow oil (95 mg, 40 %).

6.5.3 Characterisation Data for β-Lactams

(3R,4S)-1-methyl-3-phenoxy-4-phenylazetidin-2-one (5.42a)



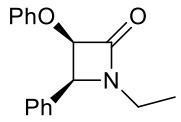
Method A gave the product as a white solid, 215 mg, 85%. M.p 97-100 °C.

R_f = 0.40 (1:1 hexane/EtOAc).

ν (liq. film) 3419, 3064, 2917, 1761, 1599, 1495, 1235, 1047, 867, 755, 701.

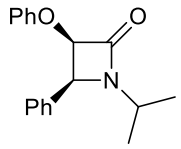
δ_H (400MHz; $CDCl_3$) 7.30-7.26(5H, m, Ar), 7.12(2H, d, *J* = 7.5 Hz, Ar), 6.87(1H, t, *J* = 7.3 Hz, Ar), 6.73(2H, d, *J* = 8.0 Hz, Ar), 5.44(1H, d, *J* = 4.3 Hz, CH), 4.87(1H, d, *J* = 4.3 Hz, CH), 2.85(3H, s, CH_3).
δ_C (100MHz; $CDCl_3$) 166.1(0), 156.9(0), 132.8(0), 129.2(1), 128.7(1), 128.4(1), 128.3(1), 122.0(1), 115.6(1), 82.5(1), 63.7(1), 28.7(3).
HRMS (ES) $C_{16}H_{15}NO_2$ $[M+H]^+$ requires 254.1176, found 254.1180.

(3R,4S)-1-ethyl-3-phenoxy-4-phenylazetidin-2-one (5,42b)



Method A gave the product as a white solid, 233 mg, 87%. M.p. 105-107 °C.
R_f = 0.55 (1:1 hexane/EtOAc).
ν (liq. film) 3054, 2984, 1761, 1496, 1457, 1266, 1239, 739.
δ_H (400MHz; $CDCl_3$) 7.35-7.28(5H, m, Ar), 7.11(2H, t, *J* = 7.6 Hz, Ar), 6.87(1H, t, *J* = 7.4 Hz, Ar), 6.72(2H, d, *J* = 8.0 Hz, Ar), 5.41(1H, d, *J* = 4.3 Hz, CH), 4.94(1H, d, *J* = 4.3 Hz, CH), 3.57(1H, dq, J^1 = 7.3, J^2 = 14.4 Hz, $C\underline{H}_AH_B$), 3.07(1H, dq, J^1 = 7.3 Hz, J^2 = 14.4 Hz, $CH_A\underline{H}_B$), 1.13(3H, t, *J* = 7.3 Hz, CH_3).
δ_C (100MHz; $CDCl_3$) 165.6(0), 156.9(0),133.3(0), 129.2(1), 128.7(1), 128.6(1), 128.2(1), 121.9(1), 115.6(1), 81.8(1), 61.7(1), 35.3(2), 12.6(3).
HRMS (ES) $C_{17}H_{17}NO_2$ $[M+H]^+$ requires 268.1333, found: 268.1329.

(3R,4S)-1-isopropyl-3-phenoxy-4-phenylazetidin-2-one (5.42c)

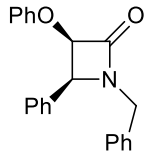


Method A gave the product as a white solid, 155 mg, 55%. M.p. 132-135 °C.
R_f = 0.50 (1:1 hexane/EtOAc).
ν (liq. film) 3419, 2086, 1748, 1646, 1339, 1244, 1117, 751.
δ_H (400MHz; $CDCl_3$) 39(2H, d, *J* = 7.5Hz,Ar), 7.33-7.19(3H,m,Ar), 7.10(2H, t, *J* = 7.5Hz, Ar),6.85(1H, t, *J* = 7.3Hz, Ar), 6.71(2H, d, *J* = 8.0Hz, Ar), 5.34(1H, d, *J* = 4.3Hz, CH), 4.94(1H, d, *J* = 4.3Hz, CH), 3.87(1H, hept, *J* = 6.7Hz, CH), 1.58(3H, s, CH_3), 1.31(3H, d, *J* = 6.7Hz, CH_3), 1.08(3H, d, *J* = 6.7Hz, CH_3).

δ_C (100MHz; $CDCl_3$) 165.5(0), 156.9(0), 134.4(0), 129.1(1), 128.8(1), 128.6(1), 128.1(1), 121.8(1), 115.6(1), 80.9(1), 61.1(1), 45.1(1),21.3(3), 20.2(1).

HRMS (ES) $C_{18}H_{19}NO_2$ $[M+H]^+$ requires 282.1489, found: 282.1487.

(3R,4S)-1-benzyl-3-phenoxy-4-phenylazetidin-2-one (5.42d)



Method A gave the product as a white solid, 193 mg, 86%. M.p. 97-100 °C.

R_f = 0.80 (1:1 hexane/EtOAc).

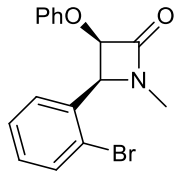
ν (liq. film) 3434, 3063, 2923, 1763, 1599, 1495, 1234, 1029, 754.

δ_H (400MHz; $CDCl_3$) 7.49(1H, d, *J* = 8.0 Hz, Ar), 7.37-7.32(2H, m, Ar), 7.15(3H, t, *J* = 7.3 Hz, Ar), 6.90(1H, d, *J* = 7.3 Hz, Ar), 6.82(2H, d, *J* = 7.9 Hz, Ar), 5.49(1H, d, *J* = 4.4 Hz, CH), 5.35(1H, d, *J* = 4.4 Hz, CH), 2.92(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.3(0), 157.0(0), 132.9(1), 132.7(0), 129.9(1), 129.2(1), 128.7(1), 127.4(1), 124.2(0), 122.2(1), 116.0(1), 82.8(1), 62.8(1), 27.3(3).

HRMS (ES) $C_{22}H_{19}NO_2$ $[M+H]^+$ requires 330.1489, found 330.1493.

(3R,4S)-4-(2-bromophenyl)-1-methyl-3-phenoxyazetidin-2-one (5.42g)



Method A gave the product as a yellow oil, 279 mg, 84%.

R_f = 0.50 (1:1 hexane/EtOAc).

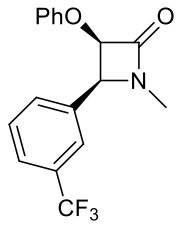
ν (liq. film) 3434, 3063, 2923, 1763, 1599, 1495, 1234, 1029, 754.

δ_H (400MHz; $CDCl_3$) 7.49(1H, d, *J* = 8.0 Hz, Ar), 7.37-7.32(2H, m, Ar), 7.15(3H, t, *J* = 7.3 Hz, Ar), 6.90(1H, d, *J* = 7.3 Hz, Ar), 6.82(2H, d, *J* = 7.9 Hz, Ar), 5.49(1H, d, *J* = 4.4 Hz, CH), 5.35(1H, d, *J* = 4.4 Hz, CH), 2.92(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.3(0), 157.0(0), 132.9(1), 132.7(0), 129.9(1), 129.2(1), 128.7(1), 127.4(1), 124.2(0), 122.2(1), 116.0(1), 82.8(1), 62.8(1), 27.3(3).

HRMS (ES) $C_{16}H_{14}BrNO_2$ $[M+H]^+$ requires 332.0281, found 332.0278.

(3R,4S)-1-methyl-3-phenoxy-4-(3-(trifluoromethyl)phenyl)azetidin-2-one (5.42h)



Method A gave the product as a white solid, 253 mg, 79%. M.p. 90-92 °C.

R_f = 0.47 (1:1 hexane/EtOAc).

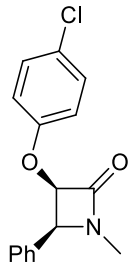
ν (liq. film) 3446, 3063, 2923, 1770, 1599, 1591, 1496, 1329, 1235, 1168, 1126, 867.

δ_H (400MHz; $CDCl_3$) 7.47-7.24(3H, m, Ar), 7.36(1H, t, *J* = 7.9 Hz, Ar), 7.05(2H, t, *J* = 7.5 Hz, Ar), 6.81(1H, t, *J* = 7.3 Hz, Ar),6.63(2H, d, *J* = 8.0 Hz, Ar), 5,42(1H, d, *J* = 4.3 Hz, CH), 4.86(1H, d, *J* = 4.3 Hz, CH), 2.80(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 165.7(0), 156.5(0), 134,2(0), 131,5(0), 130.8(q, *J* = 32 Hz, 0), 129,3(1), 128.8(1), 125,6(q, *J* = 3.7 Hz, 0), 125.4(q, *J* = 3.7 Hz, 0), 122.2(1), 115,4(0), 82.3(1), 63.1(1), 26.9(3).

HRMS (ES) $C_{17}H_{14}F_3NO_2$ $[M+H]^+$ requires 322.1044, found 322.1093.

(3R,4S)-3-(4-chlorophenoxy)-1-methyl-4-phenylazetidin-2-one (5.42i)



Method A gave the product as a white solid, 205 mg, 71%. M.p. 135-137 °C.

R_f = 0.49 (1:1 hexane/EtOAc).

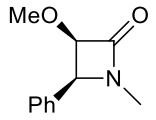
ν (liq. film) 3424, 2305, 1757, 1646, 1489, 1265, 1240, 826.

δ_H (400MHz; $CDCl_3$) 7.33-7.28(6H, m, Ar), 7.07(2H, d, *J* = 8.6Hz, Ar), 6.67(2H, d, *J* = 8.6Hz, Ar), 5.39(1H, d, *J* = 4.3Hz, CH), 4.87(1H, d, *J* = 4.3Hz, CH), 2.86(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 165.7(0), 155.5(0), 132.5(0), 129.1(1), 128.9(1), 128.4(1), 128.35(1), 127.0(0), 116.9(1),82.5(1),63.5(1), 26.7(3).

HRMS (ES) $C_{16}H_{14}ClNO_2$ $[M+H]^+$ requires 288.0786, found: 288.0780.

(3R,4S)-3-methoxy-1-methyl-4-phenylazetidin-2-one (5.43a)



Method A gave the product as a white solid, 144 mg, 75%. M.p. 66-68 °C.

R_f = 0.54 (1:1 hexane/EtOAc).

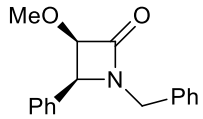
ν (liq. film) 3495, 3034, 2991, 2930, 2834,1755, 1456, 1393, 1361, 1210, 1061, 997, 703.

δ_H (400MHz; $CDCl_3$) 7.42-7.31(5H, m, Ar), 4.69-4.68(2H, m, 2CH), 3.11(3H, s, CH_3), 2.78(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 167.2(0), 133.5(0), 128.6(1),128.5(1),128.2(1), 86.1(1),63.3(1), 58.1(3), 26.4(3).

HRMS (ES) $C_{11}H_{13}NO_2$ $[M+H]^+$ requires 192.1020, found: 192.1023.

(3R,4S)-1-benzyl-3-methoxy-4-phenylazetidin-2-one (5.43b)



Method A gave the product as a colourless oil, 145 mg, 54%.

R_f = 0.51 (1:1 hexane/EtOAc).

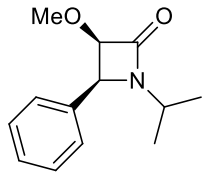
ν (liq. film) 3032, 2928, 1759, 1496, 1456, 1399, 1360, 1266, 1211,1037, 736, 700.

δ_H (400MHz; $CDCl_3$) 7.40-7.32(3H, m, Ar), 7.32-7.23(5H, m, Ar), 7.12(2H, d, *J* = 7.0 Hz, Ar), 4.82(1H, d, *J* = 14.8 Hz, $C\underline{H}_AH_B$), 4.66(1H, d, *J* = 4.3 Hz, CH), 4.56(1H, d, *J* = 4.3 Hz, CH), 3.81(1H, d, *J* = 14.8 Hz, $CH_A\underline{H}_B$), 3.09(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.8(0), 135.0(0), 133.4(0), 128.8(1),128.61(1), 128.59(1), 128.5(1), 128.4(1), 127.9(1), 85.8(1), 61.1(1), 58.2(3), 43.9(2).

HRMS (ES) $C_{13}H_{17}NO_2$ $[M+H]^+$ requires 220.1333, found: 220.1401.

(3R,4S)-1-methyl-3-phenoxy-4-(3-(trifluoromethyl)phenyl)azetidin-2-one (5.43c)



Method A gave the product as a white solid, 90 mg, 39%. M.p. 66-68 °C.

R_f = 0.38 (1:1 hexane/EtOAc).

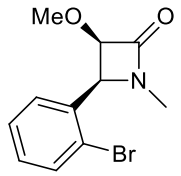
ν (liq. film) 2974, 2926, 1752, 1392,1349, 1128, 1028.

δ_H (400MHz; $CDCl_3$) 7.46-7.36(5H, m, Ar), 4.74(1H, d, *J* = 4.3 Hz, CH), 4.59(1H, d, *J* = 4.3 Hz, CH), 3.81(1H, quint., *J* = 6.7 Hz, CH), 3.06(6H, s, CH_3), 1,26(3H, d, *J* = 6.5 Hz, CH_3), 1.04(3H, d, *J* = 6.5 Hz, CH_3).

δ_C (100MHz; $CDCl_3$) 166.7(0), 135.2(0), 128.6(1), 128.5(1), 128.2(1), 84.6(1), 60.6(1), 58.0(3), 44.8(1), 21.4(3), 20.2(3).

HRMS (ES) $C_{13}H_{17}NO_2$ $[M+H]^+$requires 220.1333, found: 220.1401.

(3R,4S)-4-(2-bromophenyl)-3-methoxy-1-methylazetidin-2-one (5.43d)



Method A gave the product as a yellow oil, 144 mg, 56%.

R_f = 0.43 (1:1 hexane/EtOAc).

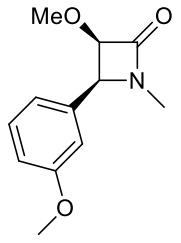
ν (liq. film) 2930, 1763,1469, 1442, 1390, 1209, 1060, 996, 754.

δ_H (400MHz; $CDCl_3$) 7.60(1H, d, *J* = 8.0Hz, Ar), 7.39(1H, t, *J* = 7.5Hz, Ar), 7.28(1H, d, *J* = 7.7 Hz, Ar), 7.23(1H, t, *J* = 7.6 Hz, Ar), 5.14(1H, d, *J* = 4.3 Hz, CH), 4.79(1H, d, *J* = 4.3 Hz, CH), 3.21(3H, s, CH_3), 2.87(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 167.2(0), 133.4(0), 133.0(1), 129.7(1),128.6(1)127.5(1),123.6(0),86.3(1), 63.2(1), 58.9(3), 27.0(3).

HRMS (ES) $C_{11}H_{12}BrNO_2$ $[M+H]^+$ requires 270.0125, found 270.0105.

(3R,4S)-3-methoxy-4-(3-methoxyphenyl)-1-methylazetidin-2-one (5.43e)



Method A gave the product as a white solid, 179 mg, 81%. M.p. 149-151 °C.

R_f = 0.31 (1:1 hexane/EtOAc).

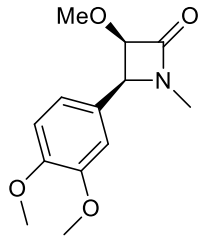
ν (liq. film) 3419, 1750, 1652, 1489, 1231, 1050, 756.

δ_H (400MHz; $CDCl_3$) 7.22(1H, t, *J* = 7.7 Hz, Ar), 7.14(2H, t, *J* = 7.4Hz, Ar), 6.90-6.87(2H, m, Ar), 6.83(1H, s, Ar), 6.82(1H, d, *J* = 8.0Hz, Ar), 6.76(1H, d, *J* =8.0Hz, Ar), 5.44(1H, d, *J* = 4.3Hz, CH), 4.85(1H, d, *J* = 4.3Hz, CH, 3.76(3H, s, CH_3), 2.86(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.0 (0),159.6(0), 157.0(0), 134.5(0), 129.3(1), 129.2(1), 122.0(1), 120.8(1), 115.7(1), 114.4(1), 113.8(1), 82.5(1), 63.6(1), 55.3(3), 26.7(3).

HRMS (ES) $C_{12}H_{15}NO_3$ $[M+H]^+$ requires 222.1125, found 222.1126.

(3R,4S)-4-(3,4-dimethoxyphenyl)-3-methoxy-1-methylazetidin-2-one (5.43f)



Method A gave the product as a white solid, 191 mg, 76%. M.p. 90-92 °C.

R_f = 0.27 (1:1 hexane/EtOAc).

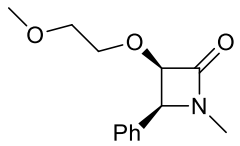
ν (liq. film) 2934, 2837, 1761, 1598, 1516, 1259, 1237, 1141, 1026, 758.

δ_H (400MHz; $CDCl_3$) 7.13(2H, t, *J* = 7.3Hz, Ar), 6.90-6.85(2H, m, Ar), 6.18(1H, s, Ar), 6.79(1H, d, *J* = 8.3Hz, Ar), 6.75(2H, d, *J* = 7.9Hz, Ar), 5.43(1H, d, *J* = 4.1Hz, CH), 4.8(1H, d, *J* = 4.1Hz, CH), 3.84(3H, s, CH_3), 3.82(3H, s, CH_3), 2.84(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.1(0), 156.9(0), 149.4(0), 148.9(0), 129.2(1), 125.1(0), 122.0(1),121.3(1), 115.5(1), 111.1(1), 110.7(1), 82.4(1), 63.5(1), 56.0(3),55.8(3), 26.6(3).

HRMS (ES) $C_{13}H_{17}NO_4$ $[M+H]^+$ requires 252.1231, found: 252.1235.

(3R,4S)-3-(2-methoxyethoxy)-1-methyl-4-phenylazetidin-2-one (5.43h)



Method A gave the product as a yellow oil, 101 mg, 43%.

R_f = 0.24 (1:3 hexane/EtOAc).

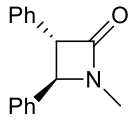
ν (liq. film) 2923, 1756, 1457, 1395, 1125, 1069, 703.

δ_H (400MHz; $CDCl_3$) 7.41-7.32(5H, m, Ar), 4.89(1H, d, *J* = 4 Hz, CH), 4.68 (1H, d, *J* = 4 Hz, CH), 3.49(1H, m, $C\underline{H}^AH^B$), 3.28-3.11(3H, m, $CH^A\underline{H}^B$, CH_2), 3.14(3H, s, CH_3), 2.78(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 167.1(0), 133.8(0), 128.5(1), 128.4(1), 128.3(1), 85.6(1), 71.4(2), 69.9(2), 63.8(1), 58.8(3), 26.4(3).

HRMS (ES) $C_{13}H_{17}NO_3$ $[M+H]^+$ requires 236.1282, found: 236.1302.

(3S,4R)-1-methyl-3,4-diphenylazetidin-2-one (5.48a)



Method B gave the product as a yellow oil, 171 mg, 72%.

R_f = 0.55 (1:1 hexane/EtOAc).

ν (liq. film) 3446, 1756, 1653, 1496, 1456, 1388, 698.

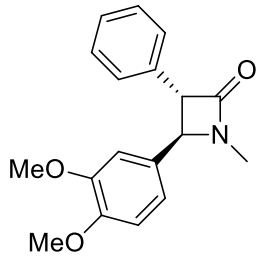
δ_H (400MHz; $CDCl_3$) 7.5-7.25 (10H, m, Ar), 4.45(1H, s, CH), 4.17(1H, s, CH), 2.87(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 168.5(0), 137.4(0), 135.1(0), 129.2(1), 128.9(1), 128.7(1), 127.7(1), 127.4(1), 126.3(1), 65.7(1), 65.4(1), 27.1(3).

HRMS (ES) $C_{16}H_{15}NO$ $[M+H]^+$ requires 238.1227, found: 238.1214.

Spectroscopic data agrees with Paul et al.[35]

(3S,4R)-4-(3,4-dimethoxyphenyl)-1-methyl-3-phenylazetidin-2-one (5.48b)



Method B gave the product as yellow solid, 211 mg, 71%. M.p. 127-129 °C.

R_f = 0.32 (1:1 hexane/EtOAc).

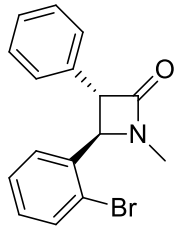
ν (liq. film) 3060, 3028, 3001, 2935, 2836, 1753, 1517, 1454, 1426, 1388, 1261, 1236, 1161, 1139, 1026, 699.

δ_H (400MHz; $CDCl_3$) 7.37-7.34(2H,m, Ar), 7.30-7.29(3H, m, Ar), 6.90(2H,s, Ar), 6.82(1H, s, Ar), 4.39(1H,s, CH), 4.16(1H, s, CH), 3.90(6H, s, 2xCH_3), 2.86(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 168.6(0), 149.8(0), 149.4(0), 135.1(0), 129.7(0), 128.9(1), 127.6(1), 127.4(1), 119.1(1), 111.6(1), 108.7(1), 65.7(1), 65.3(1), 56.06(3), 56.02(3), 27.0(3).

HRMS (ES) $C_{18}H_{19}NO_3$ $[M+H]^+$ requires 298.1438, found: 298.1442.

(3S,4R)-4-(2-bromophenyl)-1-methyl-3-phenylazetidin-2-one (5.48c)



Method B gave the product as yellow oil, 171 mg, 71%.

R_f = 0.34 (7:3 hexane/EtOAc).

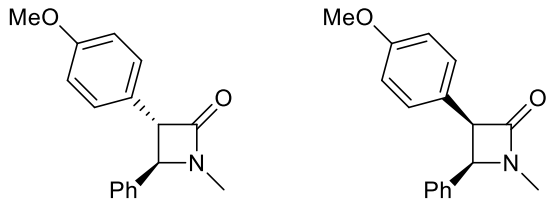
ν (liq. film) 3061, 3030, 2944, 1754, 1651, 1568, 1469, 1441, 1389, 1028, 990, 755, 733, 698.

δ_H (400MHz; $CDCl_3$) 7.60(1H, d, *J* = 8.0 Hz, Ar), 7.43-7.26(7H, m, Ar), 7.21(1H, t, *J* = 7.5 Hz, Ar), 5.01(1H, s, CH), 4.12(1H, s, CH), 2.92(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 168.6(0), 137.0(0), 134.9(0), 133.5(1), 129.8(1), 128.8(1), 128.2(1), 127.7(1), 127.6(1), 126.5(1), 123.3(0), 65.7(1), 63.6(1), 27.5(3).

HRMS (ES) $C_{16}H_{14}BrNO$ $[M+H]^+$ requires 317.1999, found 317.1996.

(3S,4R)-3-(4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (5.49a) and (3R,4R)-3-(4-methoxyphenyl)-1-methyl-4-phenylazetidin-2-one (5.49b)



Method B gave the trans product as a yellow oil, 210 mg, 79%, and cis product as a yellow oil, 48 mg, 18%.

TRANS R_f = 0.53 (1:1 hexane/EtOAc).

ν (liq. film) 2908, 2839, 1753, 1513, 1388, 1250, 1179, 1031, 700.

δ_H (400MHz; $CDCl_3$) 7.44-7.31(5H, m, Ar), 7.21(2H, d, J = 7.9 Hz, Ar), 6.89(2H, d, J = 7.9 Hz, Ar), 4.40(1H, s, CH), 4.10(1H, s, CH), 3.80(3H, s, CH3), 2.86(3H, s,CH_3).

δ_C (100MHz; $CDCl_3$) 168.9(0), 159.1(0), 137.5(0), 129.2(1), 128.6(1), 128.5(1), 127.2(0), 126.3(1), 114.3(1), 65.7(1), 65.2(1),55.3(3), 27.0(3).

HRMS (ES) $C_{17}H_{17}NO_2$ $[M+H]^+$ requires 268.1333, found: 268.1324.

Spectroscopical data agrees with Wang et al.[36]

CIS R_f = 0.38 (1:1 hexane/EtOAc).

ν (liq. film) 2924, 2854, 1750,1611, 1514, 1249, 1179, 1032, 764, 701.

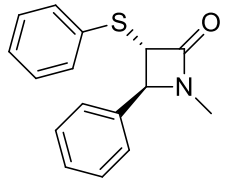
δ_H (400MHz; $CDCl_3$) 7.18-7.10(3H, m, Ar), 7.00(2H, d, *J* = 7.0 Hz, Ar), 6.91(2H, d, *J* = 8.0 Hz, Ar), 6.59(2H, d, *J* = 8.0 Hz, Ar), 4.92(1H, d, *J* = 5.3 Hz, CH), 4.81(1H, d, *J* = 5.2 Hz, CH), 3.66(3H, s, CH_3), 2.91(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 168.8(0),158.4(0), 135.0(0), 129.8(1), 128.2(1), 127.9(1), 127.3(1),124.8(0), 113.5(1), 62.4(1), 60.7(1), 55.1(3), 27.3(3).

HRMS (ES) $C_{17}H_{17}NO_2$ $[M+H]^+$ requires 268.1333, found: 268.1326.

Spectroscopical data agrees with Wang et al.[36]

(3S,4S)-1-methyl-4-phenyl-3-(phenylthio)azetidin-2-one (5.49c)



Method B gave the product as yellow oil, 171 mg, 50%.

R_f = 0.34 (7:3 hexane/EtOAc).

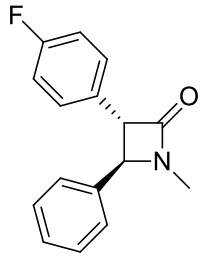
ν (liq. film) 3060, 2916, 1761, 1647, 1582, 1456, 1439, 1419, 1386, 1070, 986, 739, 699.

δ_H (400MHz; $CDCl_3$) 7.47-7.45(2H, m, Ar), 7.40-7.33(3H, m, Ar), 7.28-7.24(5H, m, Ar), 4.30(1H, s, CH), 7.15(1H, s, CH), 2.71(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 166.14(0), 136.19(0), 132.6(0), 132.1(1), 129.2(1), 129.1(1), 129.0(1),127.8(1), 126.3(1), 64.7(1), 61.9(1), 27.3(3).

HRMS (ES) $C_{16}H_{15}NOS$ $[M+H]^+$ requires 270.0948, found 270.0954.

(3S,4R)-3-(4-fluorophenyl)-1-methyl-4-phenylazetidin-2-one (5.49d)



Method B gave the product as colourless oil, 97 mg, 38%.

R_f = 0.48 (7:3 hexane/EtOAc).

ν (liq. film) 3064, 3034, 2921, 2852, 1755, 1658, 1604, 1510, 1456, 1421, 1389, 1225, 1159, 700.

δ_H (400MHz; $CDCl_3$) 7.44-7.38(3H, m, Ar), 7.33-7.32(2H, m, Ar), 7.28-7.25(2H, m, Ar), 7.04(2H, t, *J* = 8 Hz, Ar), 4.44(1H, s, CH), 4.14(1H,s, CH), 2.86(3H, s, CH_3).

δ_C (100MHz; $CDCl_3$) 168.2(0), 162.3(d, *J* = 246 Hz, 0), 137.2(0), 130.9(d, *J* = 3 Hz, 0), 129.2(1), 129.0(d, *J* = 8 Hz, 1), 128.8(1), 126.3(1), 115.8(d, *J* = 22 Hz, 1), 65.5(1), 64.9(1), 27.1(3).

HRMS (ES) $C_{16}H_{14}FNO$ $[M+H]^+$ requires 256.1133, found 256.1129.

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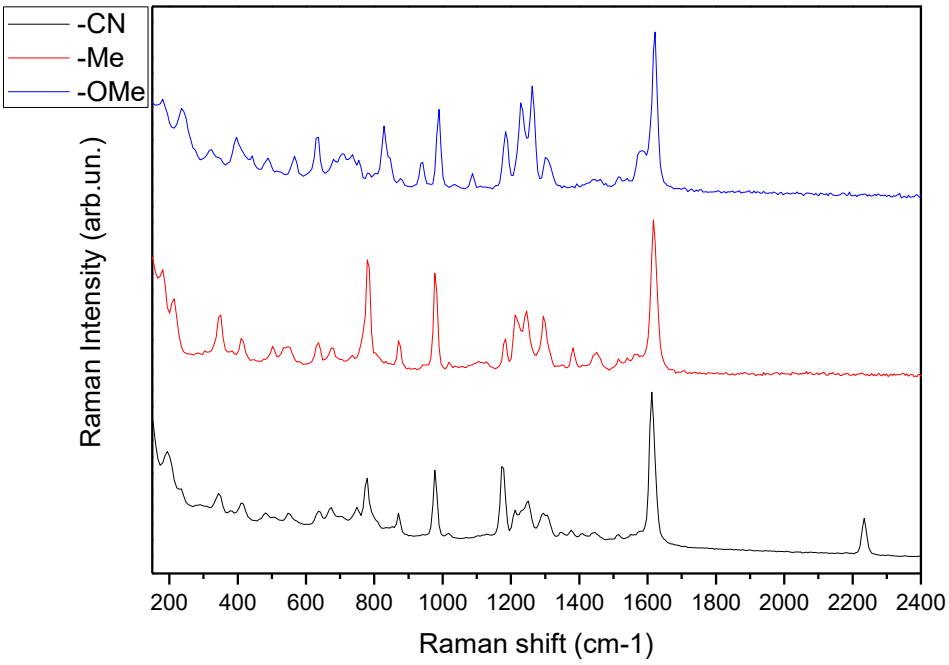
Appendix 1 Raman Spectra

The Raman spectra and the main optical figures (absorption and emission) were collected on the three samples (-CN, -Me and OMe) are reported in below The experimental Raman modes were compared with the theoretical frequencies computed accordingly (see below for details).

CN		Me		OMe		Assignement
Exp	Calc	Exp	Calc	Exp	Calc	
2230	2345					CN stretch
1615	1626	1618	1626	1620	1637	Phenyl quadrant ring stretch
		1565	1578	1580	1578	β(NH)+ ν (CN)
1539	1565	1539	1564	-	1564	β(NH)
-	1533	1515	1531	1515	1542	ν (CC)
		1450	1489	1452	1479	$\beta(CH)^{twisting}_{methyl}$
		1379	1390	-	1391	$\beta(CH)^{wagging}_{methyl}$
1316	1260	1296	1253	1300	1277	ν (CC)
1248	1245	1243	1216	1262	1249	β(NH)+ β(CH)
1219	1222	1214	1210	1230	1211	β(CH)
1182	1177	1183	1185	1184	1185	β(CH)
				1088		
986	953	976	952	985	950	Ring breathing mode I
942	903	942	923	938	933	$\beta(CH)^{op}$
850	901	871	903	877	893	$\beta(CH)^{op}$
778	777	780	778	826	768	β(CC)+ β(CN)
642	694	635	688	631	686	β(CN)+ β(CC)
550		549				
		501		488		
445				487		
443				443		
409	436	415		396	408	β(CC)
341		346	340	341		$\beta(CH)^{op}$
		210	215	240	246	β(CH)
179		176	187	176		β(CN)

β :bending ; ν : stretching


-CN
-Me
-OMe
Raman Intensity (arb.un.)
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
Raman shift (cm-1)

Appendix 2 List of Publications

Palladium-Catalysed Dehydrogenative Generation of Imines from Amines. A Nature-Inspired Route to Indoles via Cross-Couplings of Amines with Arylhydrazines. Maurizio Taddei, Manuel G. Mura, Suvi Rajamäki, Lidia De Luca, and Andrea Porcheddu, *Advanced Synthesis and Catalysis*, **2013**, *355*,3002-3013.

A mild and Efficient Synthesis of Substituted Quinolines via a Cross-Dehydrogenative Coupling of (Bio)available Alcohols and Aminoares. Manuel G. Mura, Suvi Rajamäki, Lidia De Luca, Elena Cini, Andrea Porcheddu. *Advanced Synthesis and Catalysis*, **2014**, *357*, 576-582.