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Hydrogen Transfer Methods in Organic Synthesis

Tesi di Dottorato di
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List of Publications

This thesis is based on the following papers:

01) ***From Alcohols to Indoles: A Tandem Ru Catalyzed Hydrogen-Transfer Fischer Indole Synthesis***. Andrea Porcheddu, Manuel G. Mura, Lidia De Luca, Marianna Pizzetti, and Maurizio Taddei, *Organic Letters*, **2012**, *14*, 6112-6115.

02) ***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.

03) ***Synthesis of α,β-Unsaturated Aldehydes Based on a One Pot Phase-Switch Dehydrogenative Cross-Coupling of Primary Alcohols***. Manuel G. Mura, Lidia De Luca, Maurizio Taddei, Jonathan M. J. Williams and Andrea Porcheddu, *Organic Letters*, **2014**, *16*, 2586-2589.

04) ***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** DOI: 10.1002/adsc.201400815.

Abstract

In recent years, there has been an increasing interest in using alcohols and amines as starting materials in chemical synthesis because they are an environmentally friendly and renewable alternative to petroleum-based products. The work illustrated in the present thesis focuses on the development of new synthetic methodologies exploiting hydrogen transfer as activation strategy that consents the use of alcohols and amines as starting materials to prepare molecules of industrial and pharmaceutical interest.

Given the high importance of heterocycles in several fields of chemistry and technology, we gave great focus on privileged structures such as indoles. A new and efficient strategy for indole synthesis *via* a Ru-catalysed cross-coupling of arylhydrazines with alcohols has been developed. Our method represents the first example for indole synthesis starting from alcohols *via* a Fischer-type reaction. In a complementary work, we investigated the use of primary amines as pro-electrophiles in the synthesis of indoles using Pd/C as a heterogeneous catalyst. Exploiting the know-how acquired in hydrogen transfer strategies, we turned our attention on the synthesis of α,β-unsaturated aldehydes through a Ru-catalysed cross-dehydrogenative coupling between two different primary alcohols, which can find potential application in the preparation of jasminaldehyde and its analogues, largely used in the fragrance industries. We also extended this strategy to the synthesis of quinolines.

Abbreviations

Ac	acetyl
Ar	aryl
aq.	aqueous
BH	borrowing hydrogen methodology
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
BIPHEP	biphenylphosphine
Bn	benzyl
Boc	tert-butyloxycarbonyl
b.p.	boiling point
Bu	butyl
BQC	2,2’-biquinoline-4,4’-dicarboxylic acid dipotassium salt
°C	degrees centigrade
cat.	Catalytic
CataCXium	di-adamantyl alkyl phosphine
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
CI	chemical ionisation
cod	1,5-cyclooctadiene
Cp	cyclopentyl
CPME	cyclopentyl methyl ether
Δ	heat
d	doublet
DCM	dichloromethane
DEAD	diethyl azadicarboxylate
DMF	dimethylformamide
DMSO/dmso	dimethyl sulphoxide

Dppf	1,1′-Bis(diphenylphosphino)ferrocene
Dppp	1,3-Bis(diphenylphosphino)propane
ES	electrospray
Et	ethyl
eq.	equivalent(s)
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectroscopy
HT	hydrogen transfer
Hz	hertz
i	iso
ICP-MS	inductively coupled mass spectrometry
IR	infrared spectroscopy
J	coupling constant
L(n)	ligand
m	multiplet
m-	meta
M	metal
Me	methyl
mol.	molecular
m.p.	melting point
Ms	methanesulphonyl, mesyl
MPV	Meerwein-Ponndorf-Verley
MW	microwave
MWI	microwave induction
n-	normal
NHC	N-heterocyclic carbene
NMR	nuclear magnetic reasonance
Nu	nucleophile
o-	ortho
OLED	organic light emitting diode
OTf	triflate

p-	para
Ph	phenyl
Phth	phthalimido
ppm	parts per million
Pr	propyl
Py	pyridyl
q	quartet
quint.	quintuplet
rt	room temperature
s	singlet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Sat.	saturated
t	triplet
t-	tertiary
TAA	tert-amyl alcohol
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
Ts	toluenesulphonyl, tosyl
Å	Ångström

Chapter 1

Dehydrogenative Activation of Alcohols and Amines

1.1 Introduction

For over a century, constant growth of the global economy has led to massive exploitation of fossil reserves both for producing chemicals and to meet the energy needs. Reversing this trend by moving from today's fossil based economy to a more sustainable economy founded on a greater use of renewable resources is at the moment a top priority. This "paradigm shift" is needed for addressing the increasingly urgent environmental concerns and for favouring a sustainable development, in which living conditions and resource-use continue to meet human needs without undermining the integrity, stability and beauty of natural biotic systems. Transition to a bio-based economy has multiple drivers: an over dependency of many countries on fossil fuel imports, the anticipation that oil, gas, and coal will reach peak production in the not too distant future; the need for countries to diversify their energy sources, the global issue of climate change and the desire to reduce the emission of greenhouse gases, and the need to stimulate regional and rural development.

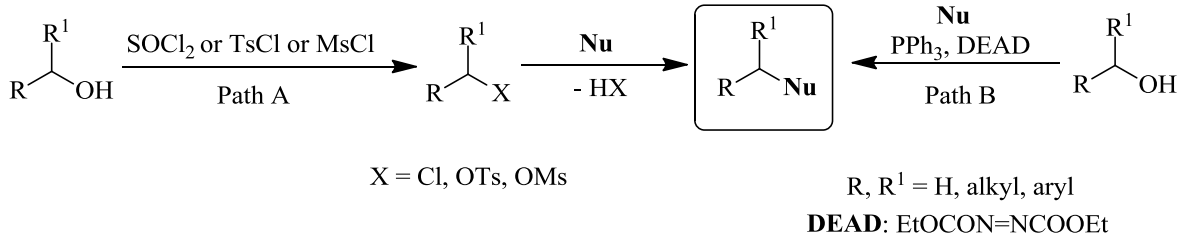
In recent years, there has been an increasing interest in using alcohols and amines as starting materials in chemical synthesis because they are an environmentally friendly and renewable alternative to petroleum-based products. Bio-based raw materials typically contain highly functionalised molecules that are rich in hydroxyl and amine functions. In this perspective, the conversion of amines and alcohols derived from biomass into fuels and value-added chemicals is currently of great interest.[1] Thus, the use of hydroxyl and amino groups in forming new C-C or C-N bonds offers more benign opportunities.[2], [3]

The work illustrated in the present thesis focuses on the development of new synthetic methodologies exploiting hydrogen transfer as activation strategy that consents the use of alcohols and amines as starting materials in the preparation of valuable classes of molecules that are of interest for industrial and pharmaceutical sectors.

1.2 Alcohols: Traditional Reactivity and New Perspectives

Alcohols are organic compounds characterised by one or more hydroxyl groups on the molecule. They are valuable building blocks in chemical synthesis because of their wide availability and stability. The use of alcohols as starting materials in C-C and C-N bond forming processes is primarily based on nucleophilic substitution reaction of the hydroxyl group.

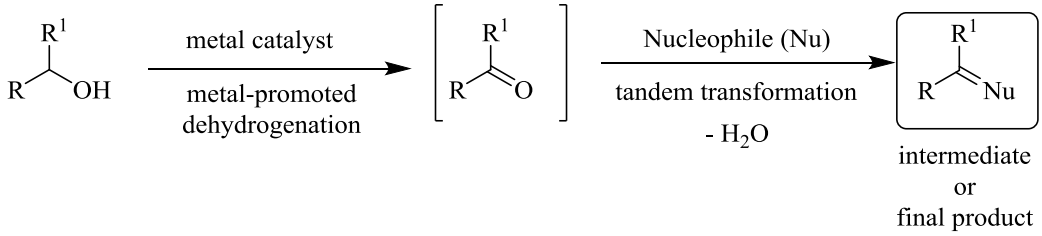
However, a previous activation by converting the OH group into a good leaving group is generally needed. Protonation would be the simplest solution for enhancing alcohol reactivity toward a nucleophilic attack, and it is a very attractive strategy as it generates water as the sole by-product. However, this method is severely limited by deactivation of the nucleophile, especially amines, that occurs in acidic conditions. Therefore, the most commonly used procedure for alcohol activation involves a previous transformation into an alkyl halide or tosylate and the subsequent reaction with a nucleophile (Scheme 1, path A). Both steps generate stoichiometric amounts of chemical waste limiting the sustainability of this method, and the toxic and mutagenic properties of some halides arouse safety concerns. An alternative strategy is offered by Mitsunobu reaction where an alcohol is activated *in situ* through a reaction with triphenylphosphine and dialkyl azodicarboxylate (e. g. diethyl azodicarboxylate, DEAD) used in stoichiometric quantities (Scheme 1, path B). Even this one-step procedure suffers from environmental and safety issues as it is accompanied by the production of stoichiometric amounts of waste material, and DEAD is a carcinogenic and explosive reactant.



Scheme 1.1
Conventional alcohol functionalisation

The development of efficient and sustainable methodologies for the activation of alcohols in direct nucleophilic substitutions is one of the most important and challenging priorities both for academia and industria as established during the ACS GCI Pharmaceutical Roundtable.[4] Catalytic activation of alcohols by hydrogen transfer methodology has attracted considerable attention in recent years as a powerful and sustainable solution for addressing some of the contemporary goals of pharmaceutical and chemical industries. Metal-catalysed removal of a hydrogen molecule from an alcohol generates the corresponding carbonyl compound. Carbonyl compounds have a much wider reactivity than alcohols and can be easily converted *in situ* by tandem transformations, exploiting its versatile chemistry and double character of electrophile and nucleophile (nucleophilic addition to carbonyl group and enol/enolate chemistry) (Scheme

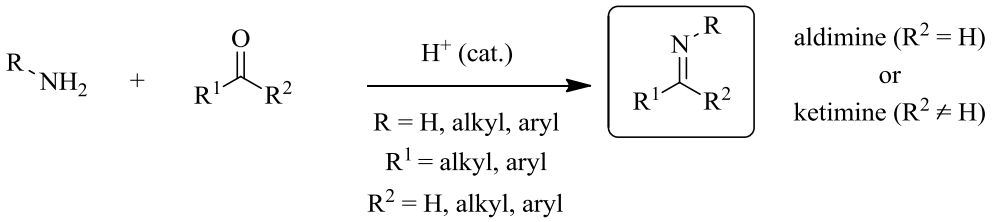
1.2).



Scheme 1.2
Dehydrogenative activation of alcohols

1.3 Amines and Imines: Traditional Reactivity and New Perspectives

The main reactivity of amines is driven by the nucleophilic properties of the amino group. Amines react with electrophilic functional groups to give addition or substitution reactions. For example, primary amines add to aldehydes and ketones forming imines characterized by a C=N double bond (Scheme 1.3).

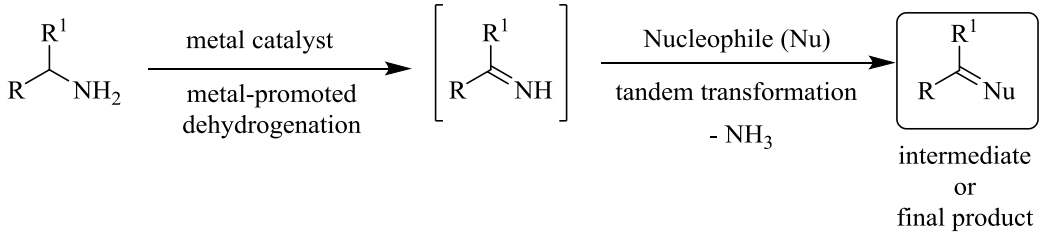


Scheme 1.3
Formation of imines from aldehydes or ketones and amines

Imines are nitrogen analogues of carbonyl compounds, and as such they exhibit electrophilic properties. In general, imines are stable enough to be isolated only if the C=N double bond is conjugated with an aromatic ring. On the contrary, imines formed from ammonia are unstable, and can be only detected in solution by spectroscopic methods. Imines are readily hydrolysed to the carbonyl compound and amine by aqueous acid or by water without any acid

or base catalysis.

Despite their low stability that makes them difficult to handle and to prepare, imines are very useful intermediates in organic synthesis and constitute major building blocks in the preparation of important nitrogen-containing compounds. Therefore generating imines from widely available and stable precursors is of great interest. Dehydrogenative bio-mimetic methods for preparing imines from amines have been explored as an alternative route to the more conventional condensation reactions between aldehydes or ketones with amines. This approach has been proposed as an amine activation strategy, analogous to dehydrogenative activation of alcohols. It allows the use of amines in a variety of organic transformations, including cyclisation reactions and reactions with nucleophiles, exploiting a reversal reactivity of amines (umpolung) that in this way can be seen as masked carbonyl compounds. Thus, a one-pot reaction sequence that firstly oxidises an amine substrate, generating an imine or iminium ion, and subsequently uses this functionality in a tandem chemical process offers an attractive approach for generating molecular complexity, reducing the total number of steps and eliminating activating groups (Scheme 1.4).



Scheme 1.4
Dehydrogenative activation of amines

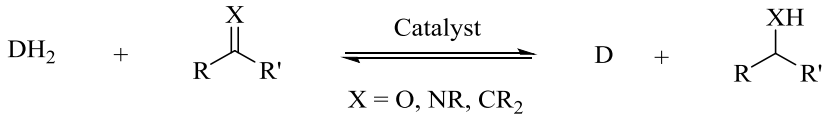
Amine activation reactions through dehydrogenation are less prevalent in the literature than those for alcohols. One possible reason for this is that the rate of elimination from amines and amido complexes is reduced. Another is the high nucleophilicity and basicity of amines, particularly that of primary amines, which are complicating properties in the presence of electrophilic imines.

1.4 Hydrogen transfer (HT)

Transfer hydrogenation reactions provide a useful means for the interconversion between alcohols and carbonyl compounds, and between amines and imines. These are both fundamental functional group transformations in organic synthesis. HT reactions offer a powerful alternative to direct hydrogenation using molecular hydrogen, and has attracted considerable attention being a safer and environmentally friendly strategy for the reduction/oxidation of a range of substrates.

1.4.1 Introduction

Hydrogen transfer is a process where a hydrogen molecule is added onto a multiple bond, using a different hydrogen source than gaseous H_2 in the presence of a catalyst.[5] The catalyst transfers a hydride and a proton from an organic substrate behaving as a hydrogen donor (DH_2) to an unsaturated substrate that acts as hydrogen acceptor (Scheme 1.5).

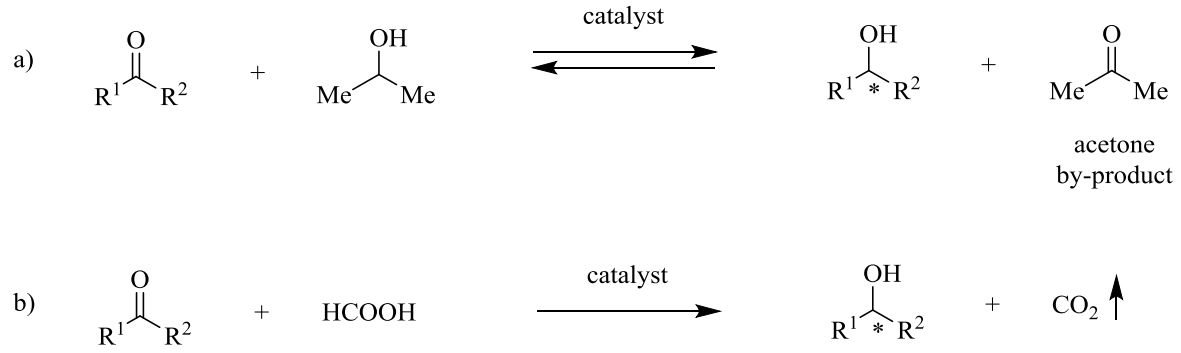


Scheme 1.5
Hydrogen transfer from a donor molecule (DH_2) to an unsaturated functional group (acceptor)

The increasing success of this technique arises from its operational simplicity: no hydrogen pressure is used and no special equipment is required. In addition, no hazardous waste is produced, as is the case in stoichiometric reduction by borane reagents, or in oxidation using common oxidising agents.

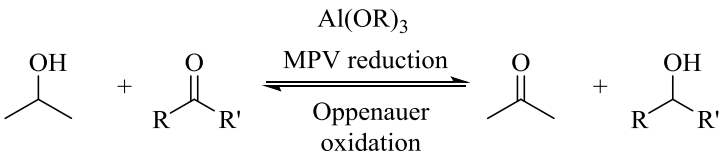
The most frequently used hydrogen donors are 2-propanol, formic acid or formate salts because of their low toxicity and low cost. When 2-propanol is used the reaction is reversible and high yields can be obtained using excess alcohol. Unfortunately, the reversibility of the reaction remains a major drawback in asymmetric hydrogen transfer (Scheme 1.6a). As the conversion increases, the rate of the reverse reaction becomes higher and thus the enantiomeric purity of the product decreases. This limitation can be overcome by continuously distilling off acetone as soon as it is formed. On the contrary, when formic acid or its salts are used the

reaction is irreversible, as the gaseous by-product CO_2 leaves the reaction mixture (Scheme 1.6b). Suitable hydrogen acceptors (H-acceptors) are ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated acids and esters, imines and nitro-compounds.



Scheme 1.6
Hydrogenation of chetones using 2-propanol (a) and using formic acid (b)

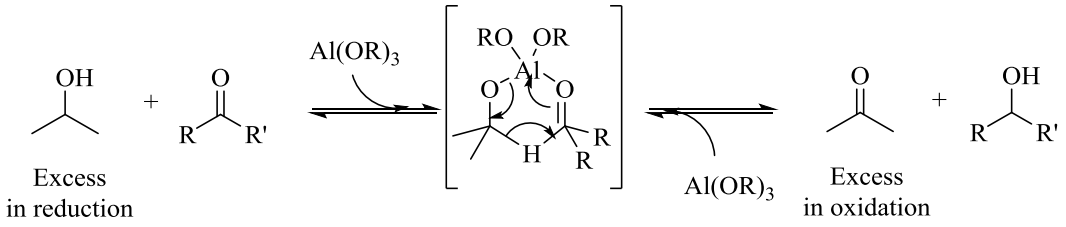
The earliest examples of transfer hydrogenation reactions were reported by Meerwein and Schmidt,[6] Ponndorf[7] and Verley[8] in the mid-1920s. In the original version of the Meerwein-Ponndorf-Verley (MPV) reduction stoichiometric amount of aluminium isopropoxide was used to promote hydrogen transfer from 2-propanol to aldehydes and ketones, giving the corresponding primary and secondary alcohols (Scheme 1.7). Over a decade later, Oppenauer reported the reverse reaction, where alcohols were oxidised to aldehydes and ketones by aluminium *tert*-butoxide, using acetone as the hydrogen acceptor.[9]



Scheme 1.7
MPV reduction and Oppenauer oxidation

The reaction is proposed to proceed through a six-membered cyclic transition state (Scheme 1.8). This is a direct H-transfer in which the hydrogen donor is coordinated to the aluminium centre as an alkoxide, while the hydrogen acceptor is coordinated by a Lewis acidic interaction, and both substrates are in close proximity. Coordination to the metal activates the aldehyde/ketone towards the nucleophilic attack of the hydride. This type of mechanism that

involves a direct hydrogen transfer is thought to be the main pathway in hydrogen transfer processes catalysed by non-transition metals.

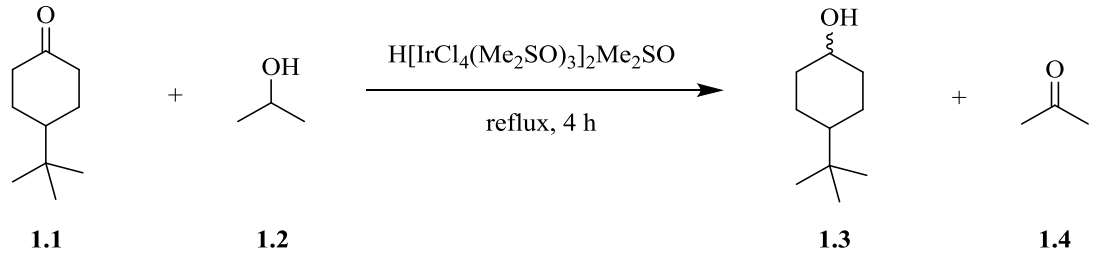


Scheme 1.8
The mechanism of the MPV/Oppenauer reactions

In 1977 Rathke and co-workers[10] described a catalytic Oppenauer oxidation of cyclohexanol using benzaldehyde as hydrogen acceptor: with 5 mol% $Al(O^tBu)_3$ and 2.5 mol % TFA the oxidation product was obtained in 80 % yield after 1 min at 0 °C. Later, Akamanchi and Noorani[11] demonstrated a similar approach for the MPV reduction using 8.3 mol % $Al(OiPr)_3$ as catalyst, 0.3 mol % TFA as co-catalyst and 2-propanol as hydrogen donor. More recently, asymmetric MPV/Oppenauer reactions have also been described.[12]

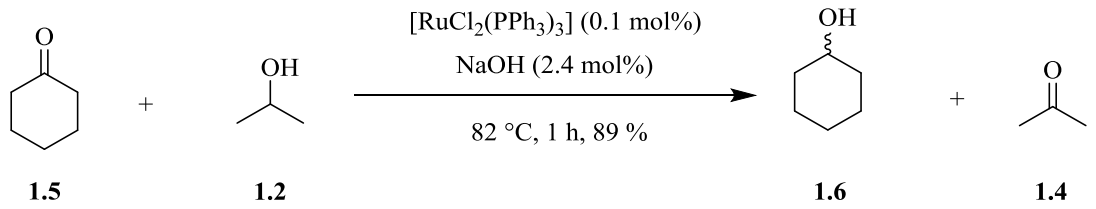
1.4.2 Transition Metal-Catalysed Transfer Hydrogenation

Use of transition metal catalysis in hydrogen transfer reactions has been well investigated in the past decades, since 1950s.[13] Since then, transfer hydrogenation has successfully been used for the reduction of imines and ketones.[14] Henbest[15] in the 1960s reported the first example of a transition metal-catalysed hydrogen transfer using an iridium hydride DMSO complex as a catalyst (Scheme 1.9). Sasson and Blum reported in 1971 the first ruthenium-catalysed hydrogen transfer reaction using $RuCl_2(PPh_3)_3$, albeit high temperatures were required with moderate turnover frequency (TOF).[16]



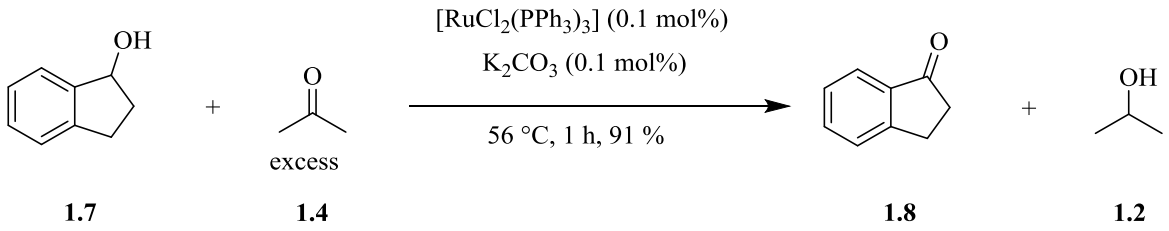
Scheme 1.9
First example of a transition metal-catalysed hydrogen transfer

Major advances accomplished in the last two decades in the discovery of more active catalysts and better hydrogen donors allowed the development of more efficient processes with higher reaction rates under milder reaction conditions.[17] In 1991, Bäckvall *et al.*[18] reported the effect of a base on the $[RuCl_2(PPh_3)_3]$-catalysed transfer hydrogenation: in the presence of NaOH (2.4 mol%), $RuCl_2(PPh_3)_3$ (0.1 mol%) catalyses efficient transfer hydrogenation from *iso*-propanol to both aliphatic and aromatic ketones with rates up to 900 turnovers per hour at 82 °C, whereas in the absence of sodium hydroxide no hydrogenation occurs (Scheme 1.10). Later Bäckvall *et al.*[18b] showed that the increased reactivity is due to the formation of a highly active dihydride species, $[RuH_2(PPh_3)_3]$.



Scheme 1.10
Effect of base in $[RuCl_2(PPh_3)_3]$-catalysed transfer hydrogenation

Bäckvall and co-workers[19] also observed the same enhancement of the catalytic activity in the Oppenauer-type oxidation (Scheme 1.11). This important breakthrough allows these reactions to proceed under mild conditions with low catalyst loading.



Scheme 1.11
Effect of base in the transfer dehydrogenation of alcohols

Mechanism elucidation showed that the oxidation/reduction process takes place *via* a metal hydride intermediate, which is formed by interaction of the catalyst with the H-donor.[5c, 20] Subsequently, the hydride is transferred from the metal hydride to the substrate. Thus, the donor and the acceptor molecules interact separately with the metal at different stages of the reaction. Depending on the ligand coordinated to the metal, either a mono- or a dihydride metal species may be involved (Figure 1.1).

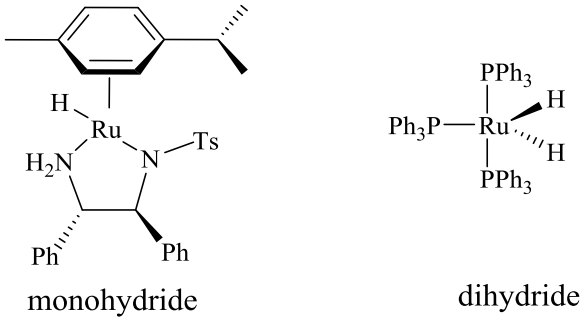
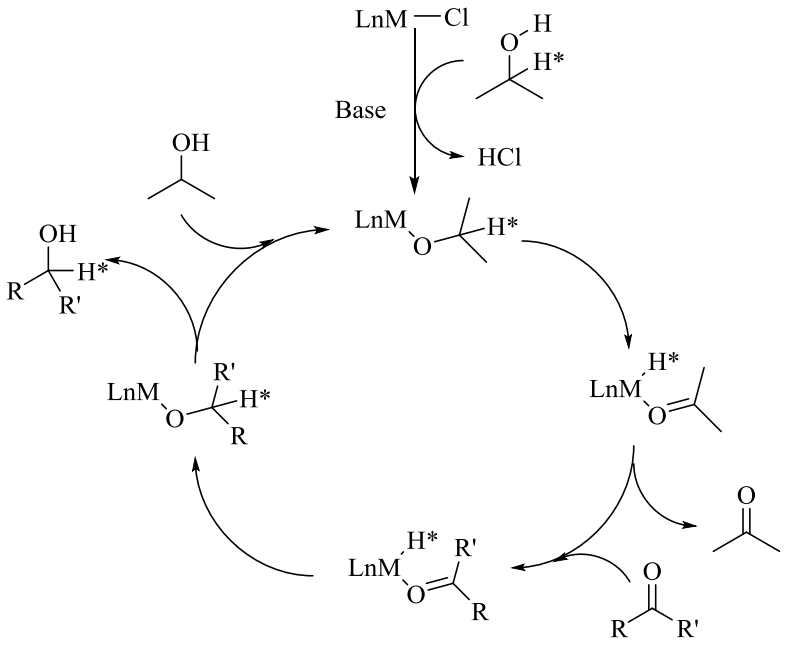


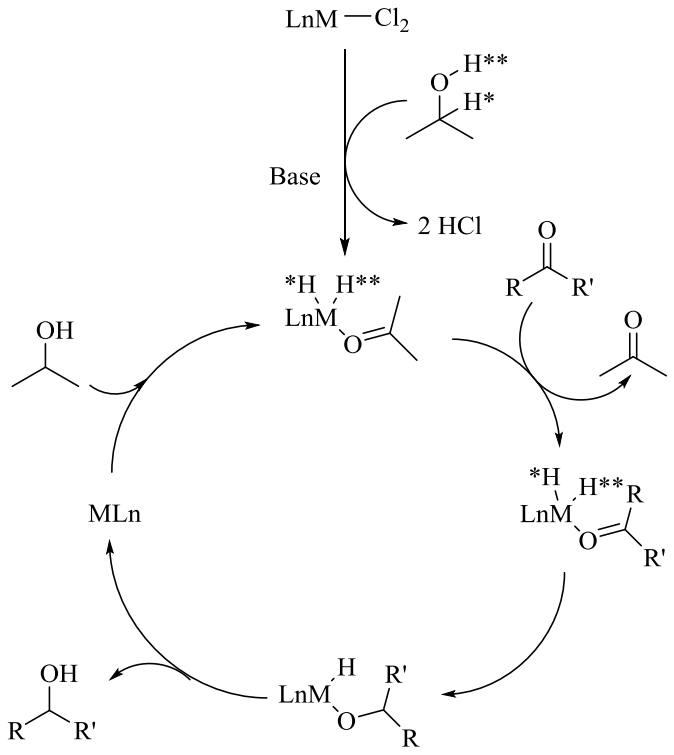
Figure 1.1
Monohydride and dihydride ruthenium complexes

A general catalytic cycle for the monohydridic route is illustrated in Scheme 1.12. The reaction begins with substitution of a chloride in the catalyst precursor by a hydrogen donor generating an alkoxide complex, and continues with β-hydride elimination from the alkoxide to generate a metal monohydride complex. The subsequent coordination of the acceptor to the metal (ligand substitution), the H-transfer from the metal to the coordinated acceptor, and the reductive elimination of the product complete the catalytic cycle. The addition of a base accelerates these reactions by increasing the concentration of alkoxide, and so favouring the precatalyst activation.[18a, 21]



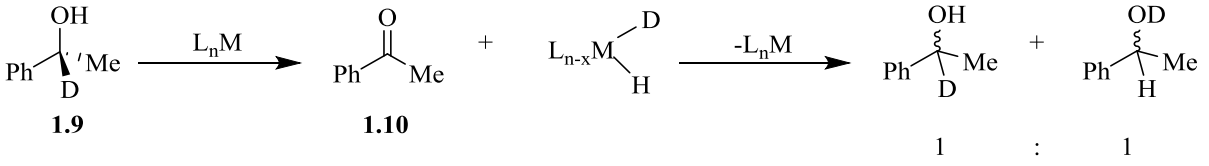
Scheme 1.12
Hydrogen transfer via a monohydride mechanism

A metal dihydride mechanism is also possible if the starting catalyst is a dichloride complex. Replacement of the two chlorides on the metal precursor by the hydrogen donor generates a metal dihydride intermediate. At this point the acceptor can coordinate to the metal *via* a ligand exchange reaction. Insertion of the ketone substrate into the metal-hydride bond followed by a reductive elimination generates the product alcohol (Scheme 1.13).



Scheme 1.13
Hydrogen transfer via a dihydride mechanism

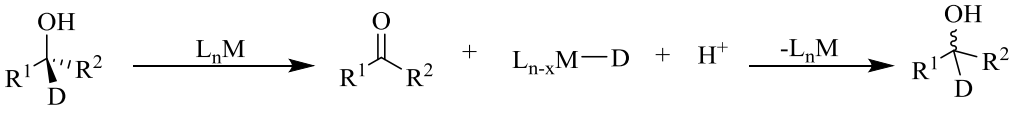
Bäckvall and co-workers[22] performed a series of deuterium labelling studies for differentiating between these two mechanisms. They studied the racemisation of (S)-α-deutero-1-phenylethanol in the presence of acetophenone catalysed by various transition metal complexes observing that if the reaction proceeds *via* a dihydridic route the O–H and the α-C–H protons from the hydrogen donor (alcohol or formic acid) lose their identity when they are transferred to the metal: the two hydrogens become equivalent after being transferred onto the metal. Thus, if the catalysts follow the dihydride mechanism, deuterium will be scrambled between carbon and oxygen (C–D : O–D ≈ 1 : 1, Scheme 1.14).



1.9 **1.10**

Scheme 1.14
Racemization of (S)-α-deutero-1-phenylethanol in the dihydride mechanism

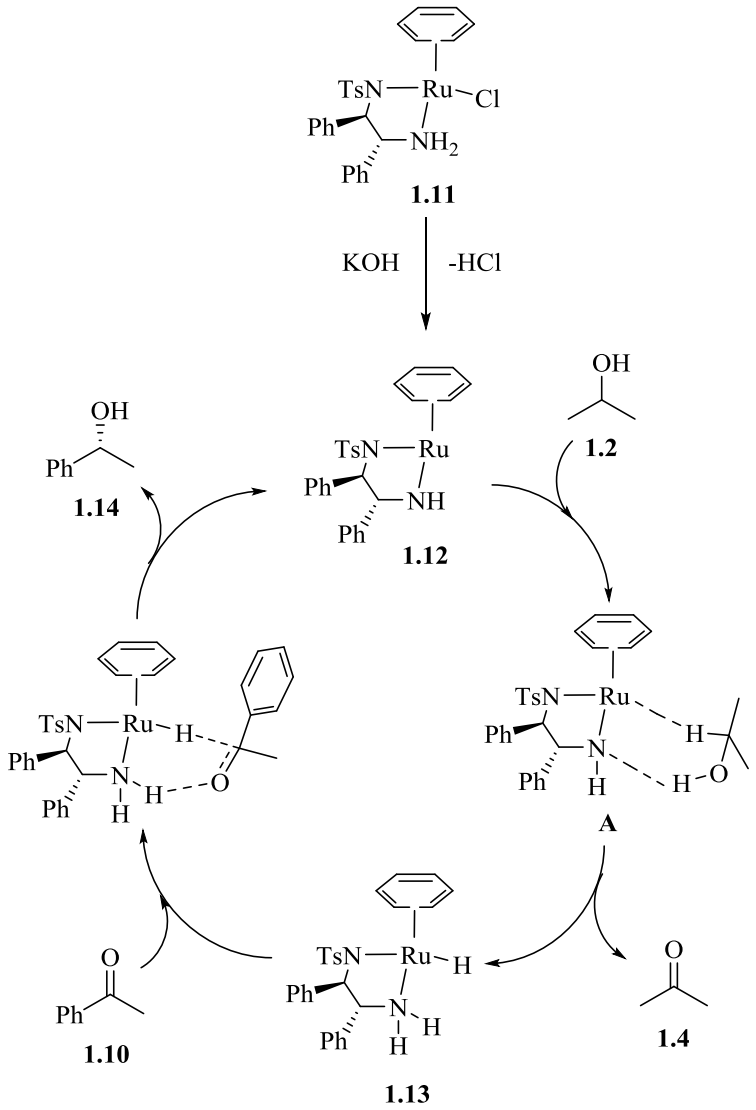
When a monohydride mechanism is operating the metal hydride originates from the α-proton of the alcohol, and so deuterium should be retained in the α-position after the racemisation has taken place (Scheme 1.15).



Scheme 1.15
Racemisation of a-deuterated chiral alcohol in the monhydride mechanism

Mechanistic studies conducted by Bäckvall *et al*.[25], [23] indicated that iridium and rhodium-catalysed hydrogen transfer followed the monohydride mechanism, while ruthenium-catalysed hydrogen transfer could follow either the dihydride or monohydride pathway depending on the ligands.

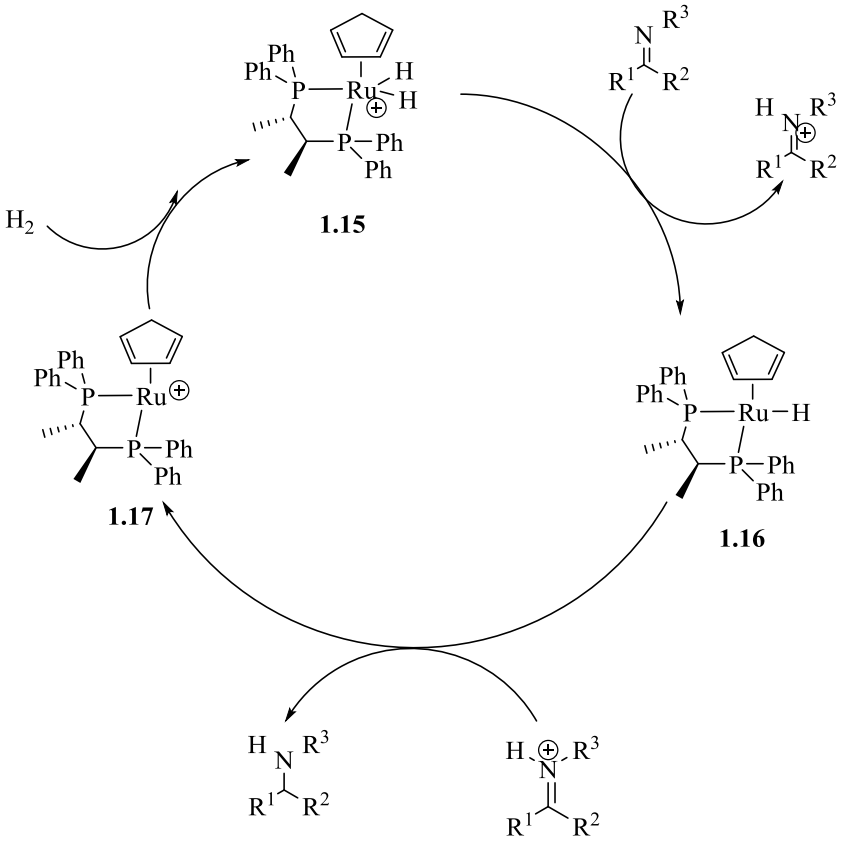
Mechanisms in which a substrate binds to the metal centre during catalysis are inner sphere mechanisms. Outer-sphere mechanisms in which the hydrogen is transferred without coordination of the substrate to the metal, and so without involvement of a metal alkoxide, are also known. This type of mechanism was first described by Noyori *et al*.[24] (Scheme 1.16) who proposed that it starts with conversion of pre-catalyst **1.11** to coordinatively unsaturated ruthenium species **1.12** by base promoted elimination of HCl. The active ruthenium hydride **1.13** is then generated by concerted hydride and proton transfer from 2-propanol to **1.12**, *via* a cyclic six-membered transition state **A**. The ketone is converted to a chiral alcohol in the same way, through simultaneous transfer of the hydride from ruthenium and the proton from the amine ligand of **1.13**. It is important to note that the reaction proceeds without coordination of either alcohol or ketone (aldehyde) to the metal. Catalysts that operate according to this mechanism are often called metal-ligand bi-functional catalysts.



Scheme 1.16
Concerted outer-sphere mechanism via six-membered cyclic transition state A

Hydrogen transfer in an outer-sphere mechanism may proceed not only in a concerted manner (as for Noyori's catalyst), but also in two distinct steps, where protonation of the substrate precedes hydride transfer to the metal. Norton and Bullock[25] proposed for the first time these types of mechanisms - usually referred to as ionic mechanisms - for different types of transition metal catalysts. The proposed mechanisms differ slightly, depending on the substrate. For imines the catalytic cycle starts with formation of the active hydrogenation catalyst **1.16** by deprotonation of metal dihydride **1.15** by the substrate imine (Scheme 1.17). The hydride transfer from **1.16** to the iminium ion is suggested to occur without prior coordination of the double bond to the metal, and produces an amine and an unsaturated catalyst

1.17. Hydrogen gas finally regenerates dihydride **1.15** and completes the cycle.



Scheme 1.17
Catalytic cycle of the ionic hydrogenation of imines

1.5 Borrowing Hydrogen Methodology

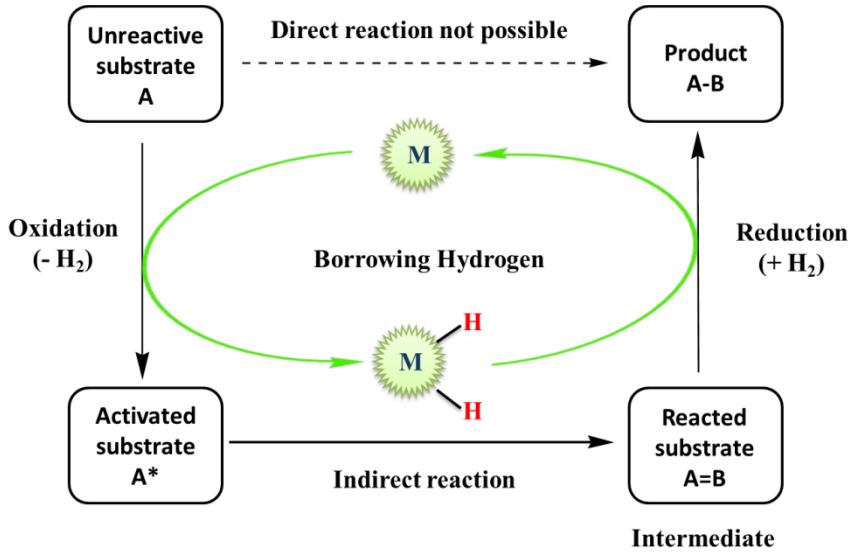
1.5.1 Introduction

Combining the advantages of transfer hydrogenation with additional *in situ* transformations, borrowing hydrogen (BH) methodology has received great attention in recent years as a greener alternative to conventional alkylation reactions. BH is a domino process based on catalytic dehydrogenative activation of the substrates (alkanes, alcohols, and amines) that allows the formation of new C-C and C-N bonds in a very elegant way, without stoichiometric oxidants or pre-functionalisation of substrates.

In a typical BH process a metal catalyst, usually an iridium or ruthenium complex, enhances the electrophilic properties of a substrate, typically an alcohol or an amine, by abstracting a hydrogen molecule. The activated substrate is then converted through an *in situ* reaction into an unsaturated intermediate. Finally, the metal hydride returns the hydrogen to the intermediate converting it into a final product (Scheme 1.18). No net oxidation or reduction occurs, only a metal-mediated hydrogen transfer from the initial substrate to the final product, with the overall formation of a new C-C or C-N bond.

If there is no hydrogen loss by side reactions or gas evolution, no additional hydrogen sources are needed. In addition, this strategy does not involve extra steps for substrate activation and the overall transformation takes place in one-step. Borrowing hydrogen methodology is very attractive for its potential, operational simplicity and atom economy, offering several environmental benefits over traditional approaches.

Today BH is used in numerous applications that show a good tolerance of other functional groups in both C-C and C-N bond forming processes.[26] Current research focuses on novel applications for the synthesis of complex target molecules, on the development of more efficient catalysts for performing reactions at ambient temperature and on increasing enantioselectivity.[27]



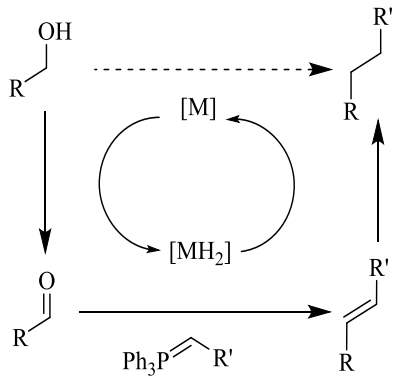
Scheme 1.18
The Borrowing Hydrogen (BH) concept

1.5.2 Activation of Alcohols Using Borrowing Hydrogen Methodology

Borrowing hydrogen methodology can be used for activating alcohols in addition reactions (e. g. condensation and Wittig reactions). Alcohol reactivity is enhanced by *in situ* conversion into the corresponding carbonyl compound through temporary hydrogen abstraction. Combination of this dehydrogenative activation with additional indirect reactions available for carbonyl compounds has allowed the development of a number of new synthetic protocols involving alcohols as environmentally friendly substrates instead of more conventional reagents such as alkyl halides.

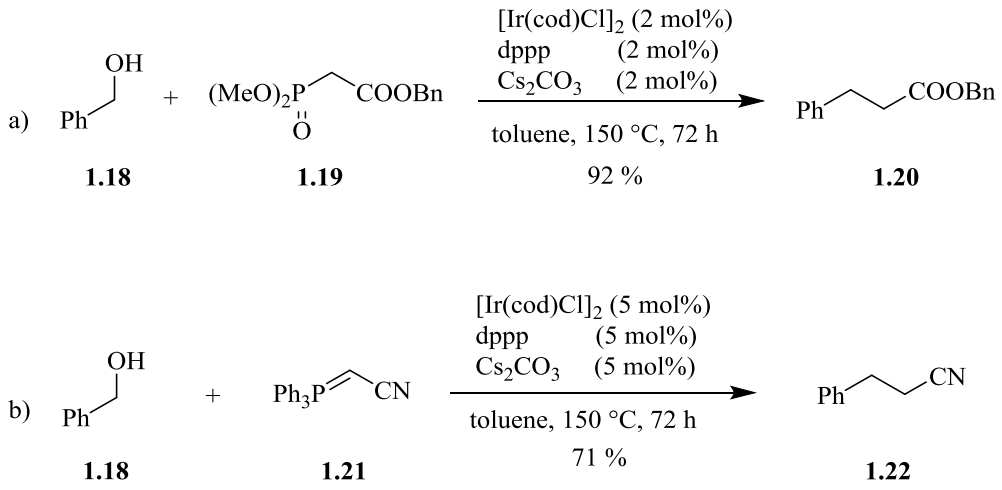
1.5.2.1 Alcohols in Indirect Wittig Reactions

When an ylide is present in the reaction mixture the aldehyde or ketone, generated *in situ* from the corresponding alcohol *via* a dehydrogenative pathway, undergoes a Wittig reaction to give an alkene intermediate that is immediately reduced to an alkane (Scheme 1.19).



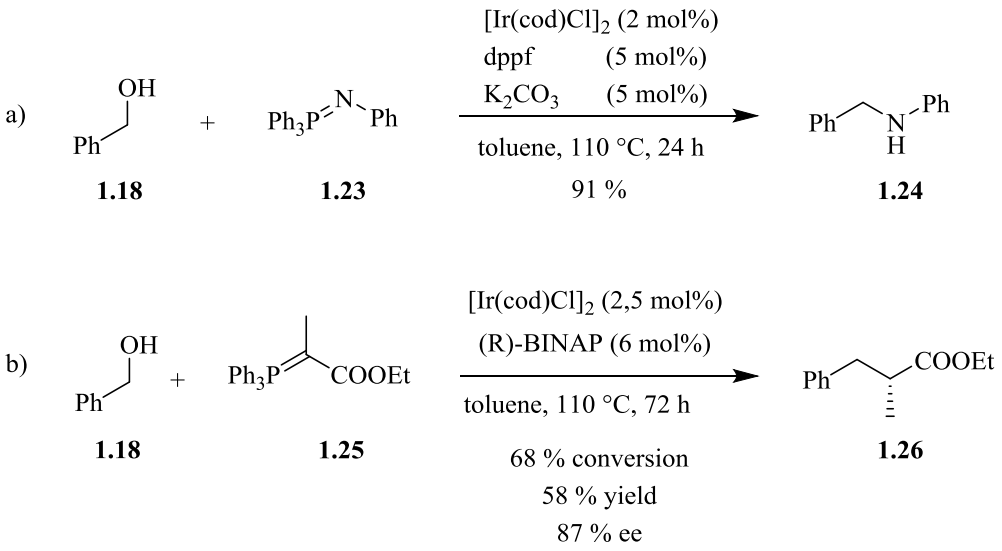
Scheme 1.19
Indirect Wittig reaction with alcohols

Williams and co-workers explored the possibility of extending the use BH into Wittig type transformations. They were the first to carry out indirect *Horner-Wadsworth-Emmons* reaction of benzyl alcohols with phosphonates,[28] (Scheme 1.20a) and *Wittig* reactions with cyanoylides[29] (Scheme 1.20b). Unfortunately in these early examples the reaction conditions were harsh and the reaction scope was somewhat limited.



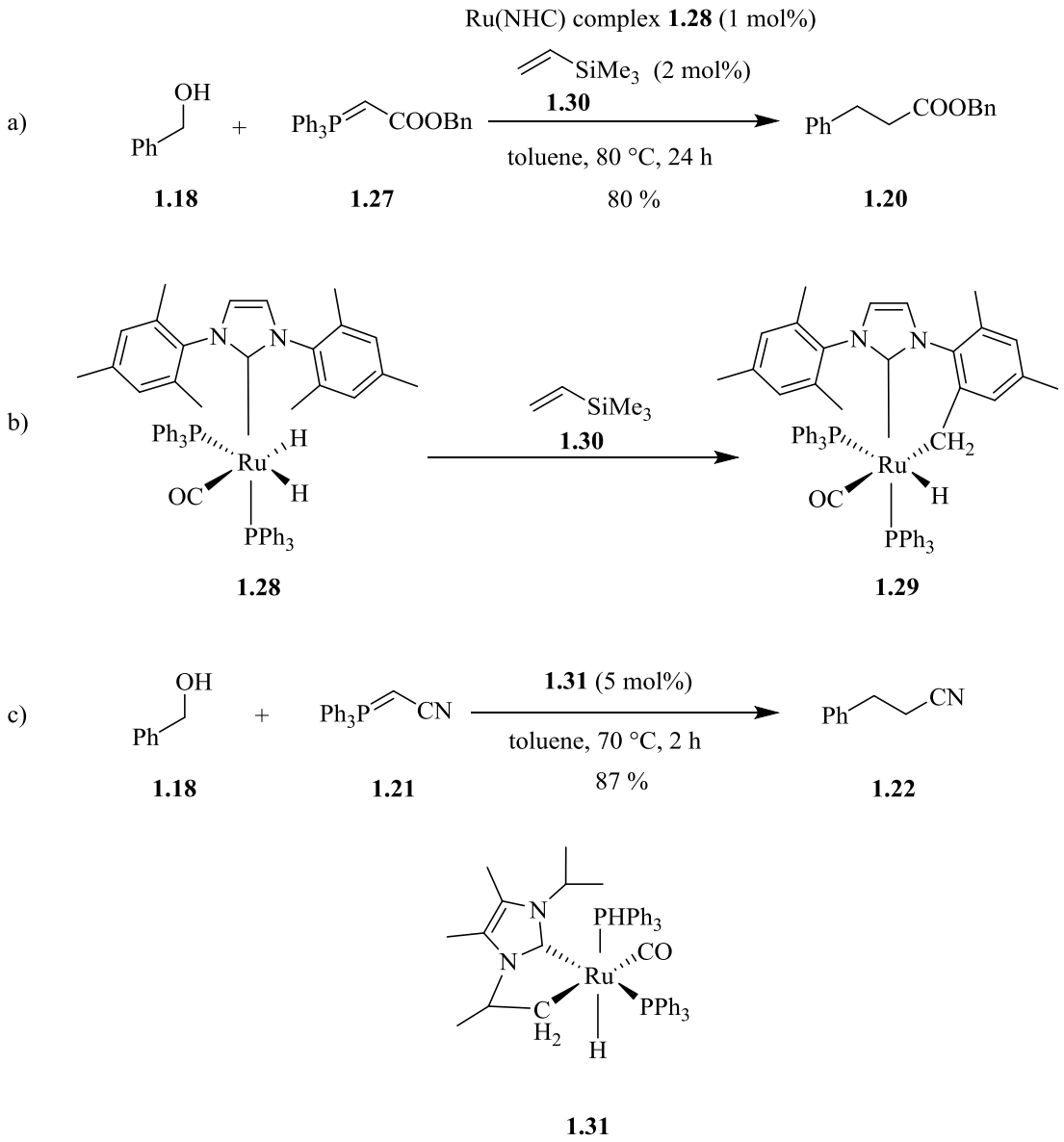
Scheme 1.20
Indirect Horner-Wadsworth-Emmons (a) and Wittig (b) reactions with alcohols by Williams

Using the same catalyst, but changing the ligand from dppp to dppf, consented to carry out conversion of alcohols into *N*-alkyl anilines *via* an indirect aza-Wittig reaction with phenyliminophosphoranes (Scheme 1.21a).[30] Notably, also asymmetric transformations were possible using the chiral ligand BINAP (Scheme 1.21b).[31]



Scheme 1.21
Indirect aza-Wittig reaction with iminophosphoranes (a) and asymmetric Wittig reaction (b) by Williams

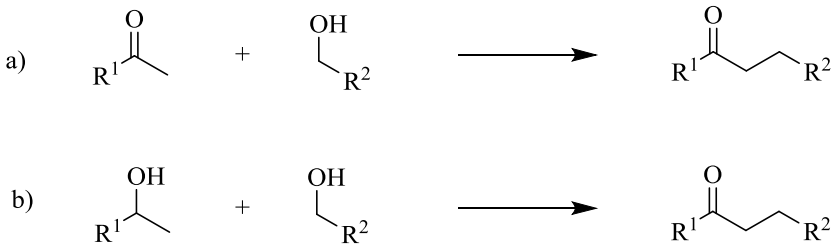
Later, Williams[32] used an improved catalytic system, the ruthenium N-heterocyclic carbene (NHC) complex **1.28**, that allowed to use alcohols in Wittig type transformations under significantly milder reaction conditions (Scheme 1.22a). However, with this new and improved method vinyltrimethylsilane **1.30** was necessary for the activation of the NHC catalyst (Scheme 1.22b). Vinylsilane acts as a hydrogen acceptor generating complex **1.29**, that is then able to remove hydrogen from an alcohol, regenerating the dihydride complex **1.28**. Complex **1.28** then delivers hydrogen back to the alkene, that is formed by the reaction of benzaldehyde with ylide **1.27** (Scheme 1.22a). Subsequently, complex **1.31** proved to be a more active catalyst in transfer hydrogenation and Wittig reactions with cyanoylides, without the need of preactivation (Scheme 1.22c).[33]



Scheme 1.22
*Indirect Wittig reactions with alcohols catalysed by complexes **1.28** (a) and **1.31** (c) by Williams*

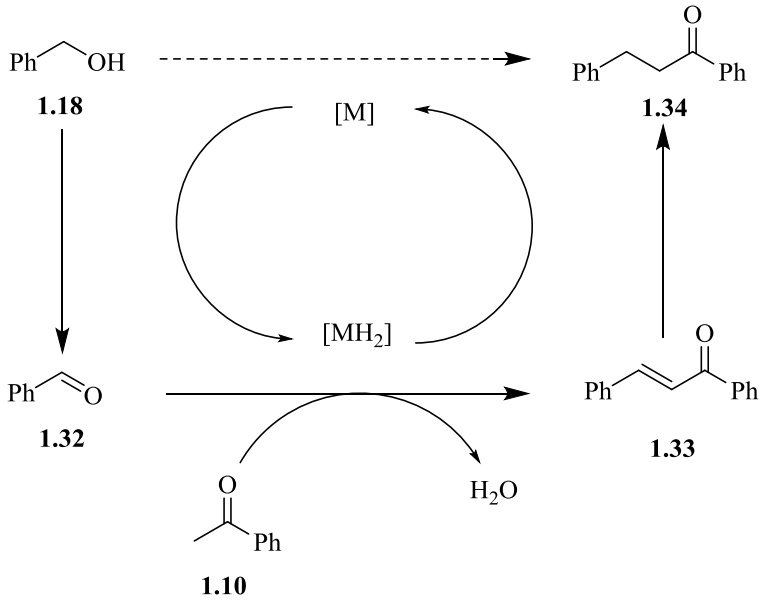
1.5.2.2 Alcohols in Indirect Aldol Condensation Reactions

Borrowing hydrogen in combination with enol/enolate chemistry of carbonyl compounds led to new interesting C-C bond forming processes in which an alcohol acts as an alkylating agent in the α-alkylation of ketones or in the β-alkylation of a secondary alcohol (Scheme 1.23).



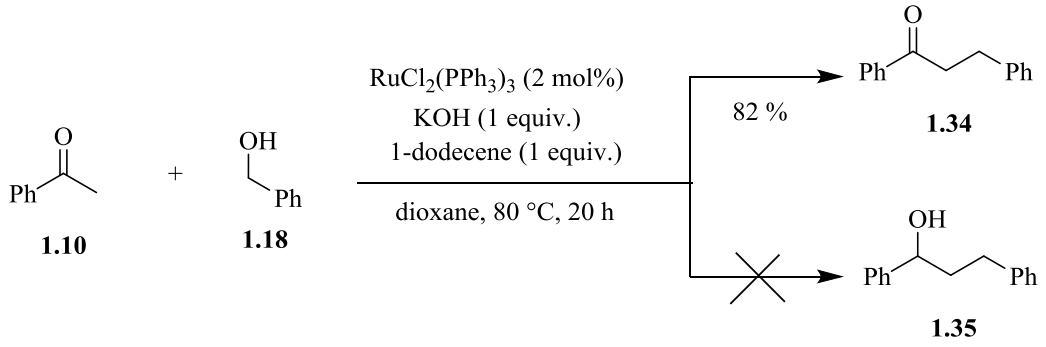
Scheme 1.23
α-Alkylation of ketones (a) and β-alkylation of secondary alcohols (b)

α-Alkylation of ketones with alcohols has been widely investigated, and a number of homogeneous and heterogeneous catalysts have been successfully developed for this reaction. Scheme 1.24 depicts a general pathway for alkylation of acetophenone **1.10** with benzyl alcohol **1.18**. The initial removal of hydrogen from benzyl alcohol generates benzaldehyde **1.32**, that can then undergo an aldol condensation reaction with acetophenone **1.10**, giving α,β-unsaturated ketone **1.33**. Return of the hydrogen to the intermediate **1.33** leads to saturated ketone **1.34**. It is not clear whether this latter reduction process occurs *via* direct reduction of the C=C bond or *via* reduction of the ketone intermediate to give an allylic alcohol followed by isomerisation to the more stable ketone **1.34**.



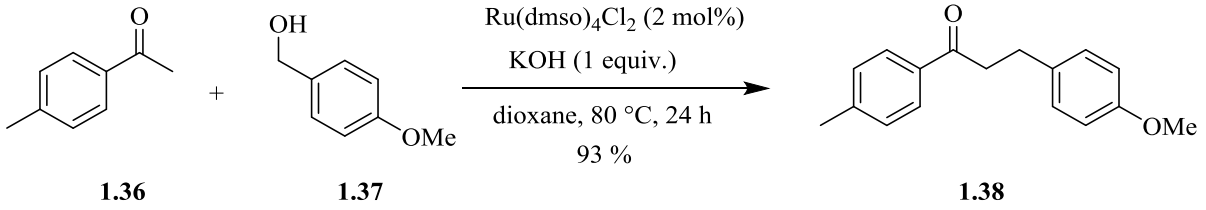
Scheme 1.24
α-Alkylation of acetophenone with benzyl alcohol

Cho, Shim and co-workers[34] applied this strategy using $RuCl_2(PPh_3)_3$ with KOH to carry out a range of ketone alkylations, including alkylation of acetophenone **1.10** with benzyl alcohol **1.18** (Scheme 1.25). They found that addition of one equivalent of 1-dodecene favoured the selective formation of ketone **1.34** as a final product, avoiding the formation of the corresponding alcohol **1.35**.



Scheme 1.25
Alkylation of acetophenone with benzyl alcohol by Cho

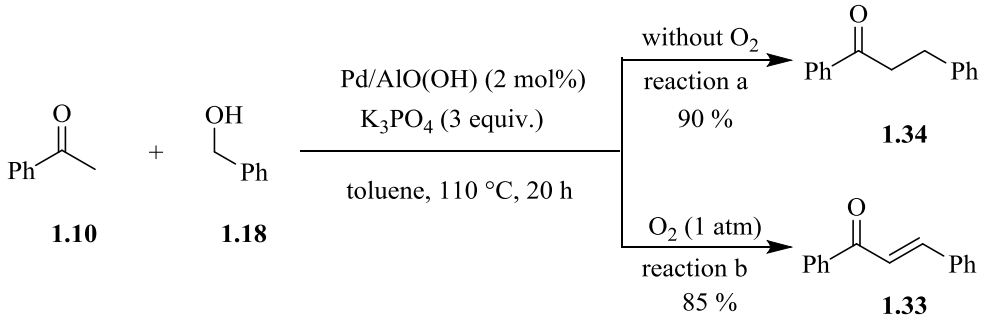
A same type of transformation was described in 2005 by Yus *et al.*[35] where in a $[Ru(DMSO)_4]Cl_2$ catalysed process a successive hydrogen-transfer reaction and an aldol condensation of **1.36** and **1.37** led to ketone **1.38** in 93% yield (Scheme 1.26).



Scheme 1.26
Alkylation of ketones with benzyl alcohols by Yus

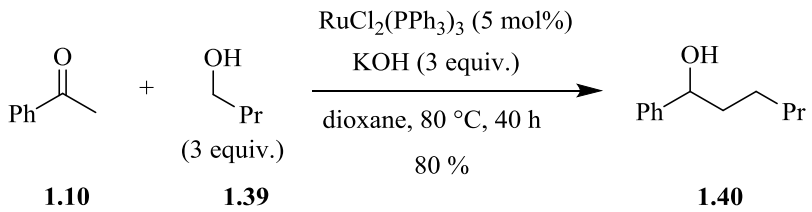
The need to recycle the catalyst has encouraged the quest for reusable heterogeneous catalysts that can be used in indirect aldol reactions with alcohols. Park *et al.*[36] used an air-stable, heterogeneous, and recyclable catalyst composed of palladium nanoparticles entrapped in aluminum hydroxide for a highly selective α-alkylation of ketones with alcohols. A range of ketones were alkylated with various alcohols using 0.2 mol% of this catalyst. For example, alkylation of ketone **1.10** with benzyl alcohol **1.18** gave the expected product **1.34** in 90% yield

(Scheme 1.27, reaction a). By performing the same reaction under an oxygen atmosphere, α,β-unsaturated ketone **1.33** was the major product (Scheme 1.27, reaction b), presumably due to the preferential reaction of hydrogen with O_2 rather than with the alkene.



Scheme 1.27
Recyclable palladium catalyst for α-alkylation of ketones with alcohols by Park

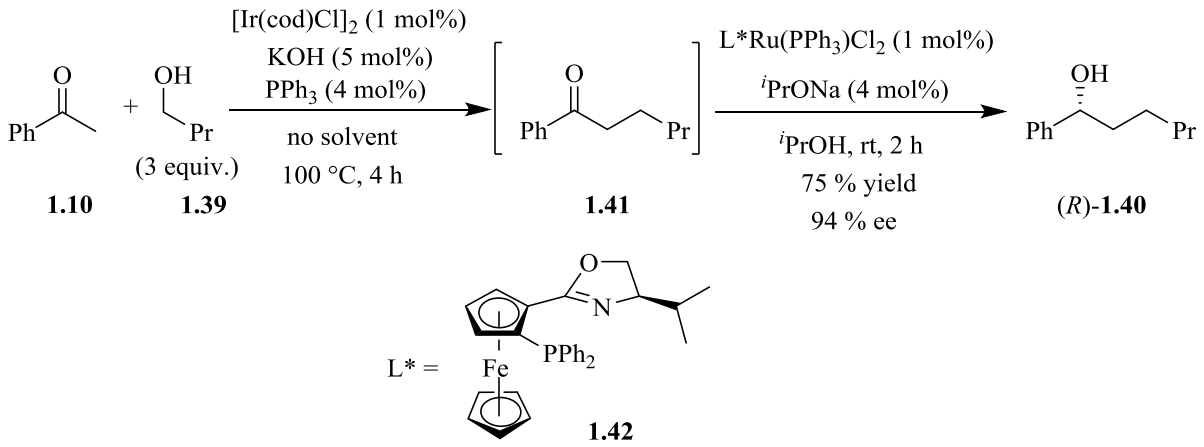
Several groups have reported a related process where α-alkylation of ketones gave an alcohol as the final product. Cho and Shim[37] showed that the reaction of acetophenone **1.10** with *n*-butanol **1.39** using dioxane as solvent gave alcohol **1.40** as a product through an alkylation/reduction process (Scheme 1.28). 1,4-Dioxane acts as hydrogen source required to form the product at the alcohol oxidation level. Yus and co-workers[35] suggested that excess alcohol could also act as reducing agent.



Scheme 1.28
α-Akylation/reduction of ketones to give alcohols by Cho and Shim

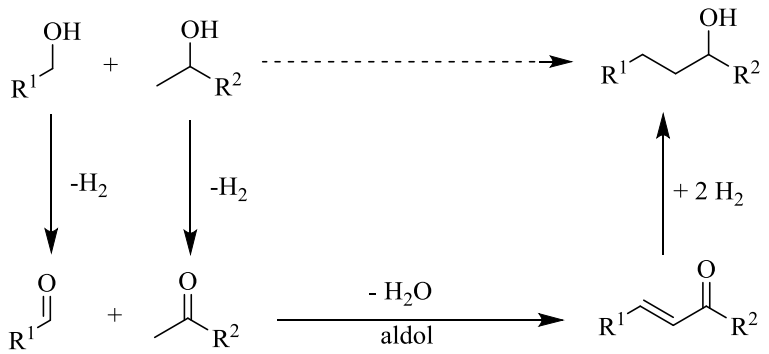
Nishibayashi and co-workers[38] described an interesting ketone alkylation-asymmetric reduction procedure: in the presence of $[Ir(cod)Cl]_2$, acetophenone **1.10** underwent α-alkylation with *n*-butanol **1.39** to give ketone **1.41**, that was then reduced by adding an enantiomerically pure ruthenium catalyst with isopropanol as reducing agent (Scheme 1.29). The isolated product

(*R*)-**1.40** was obtained with a good level of enantioselectivity.



Scheme 1.29
Two-step enantioselective alkylation/reduction of ketones by Nishibayashi

Aldol chemistry has also been exploited for β-alkylation of secondary alcohols with primary alcohols (Scheme 1.30).

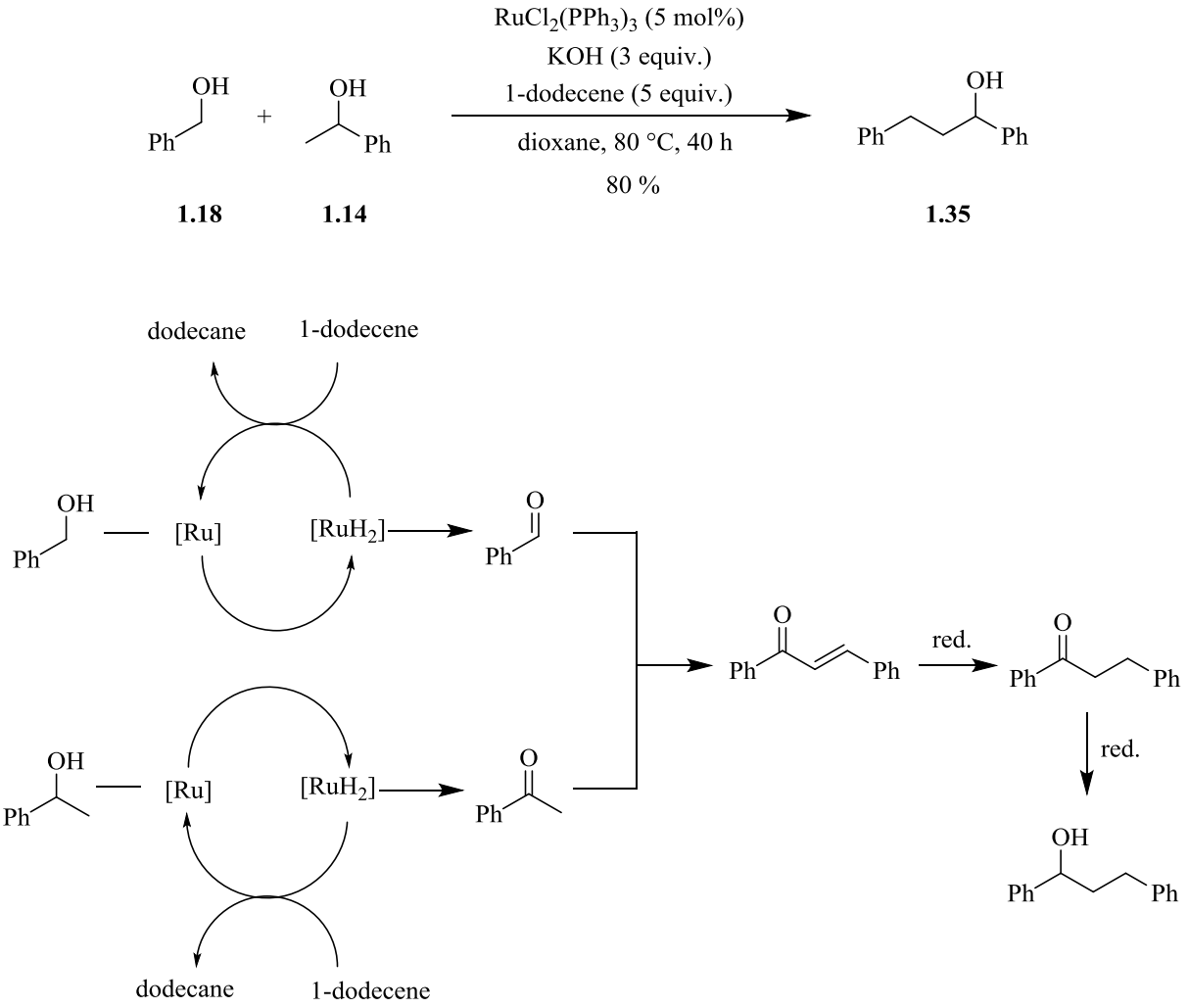


Scheme 1.30
Combined activation of primary and secondary alcohols by borrowing hydrogen

Both alcohols are converted into the corresponding carbonyl compounds by temporary removal of hydrogen. An aldol condensation then leads to the formation of an α,β-unsaturated ketone, that in turn undergoes alkene and ketone reduction by return of the hydrogen to give the saturated alcohol product.

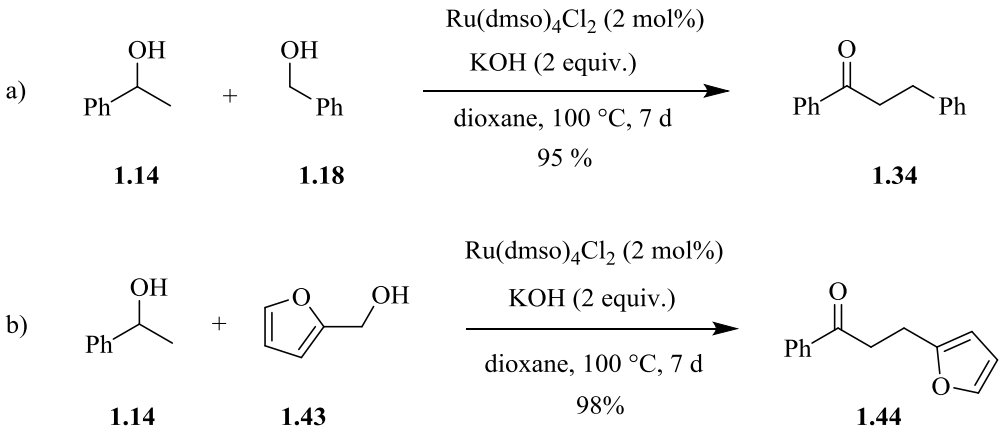
Cho, Shim and co-workers[39] alkylated a range of secondary alcohols with primary alcohols using a ruthenium-catalysed procedure. For example, alcohol **1.14** was alkylated with benzyl

alcohol **1.10** to give alcohol **1.35** (Scheme 1.31). In this reaction 1-dodecene acts as a hydrogen acceptor and 1,4-dioxane as a hydrogen donor, and hence the process does not proceed exclusively *via* a borrowing hydrogen pathway (Scheme 1.31).



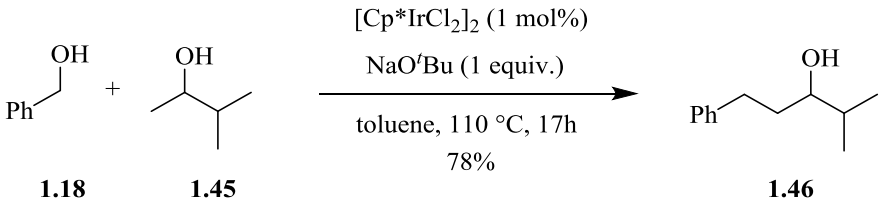
Scheme 1.31
β-Alkylation of secondary alcohols with alcohols developed by Cho and Shim

Ramón and Yus[40] used $RuCl_2(dmso)_4$ as catalyst for β-alkylation of secondary alcohols without the need for additional hydrogen donors or acceptors, obtaining alcohol **1.34** in 95% yield, although very long reaction times were required (Scheme 1.32a). Other benzylic alcohols were also suitable substrates, including furfuryl alcohol **1.43** which gave the expected product **1.44** in an excellent isolated yield (Scheme 1.32b).



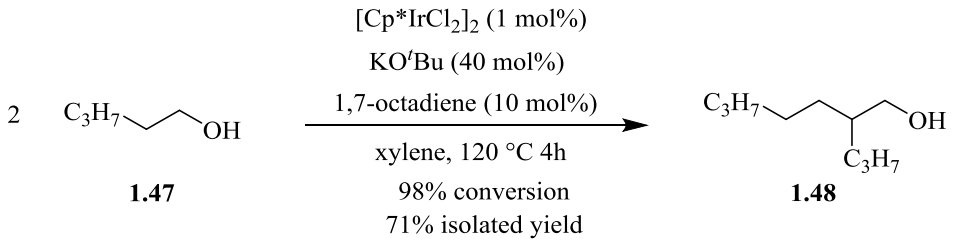
Scheme 1.32
β-alkylation of secondary alcohols with primary alcohols by Yus

β-alkylation of secondary alcohols has also been investigated using other metals. In 2005 Fujita *et al.*[41] reported the use of $[Cp^*IrCl_2]_2$ complex in reactions of various secondary alcohols with primary alcohols. Interestingly, they obtained good yields for a wide range of substrates, including not only benzylic but also other aliphatic secondary and primary alcohols. For example, alkylation of *sec*-isoamyl alcohol **1.45** with benzyl alcohol **1.18** was achieved providing product **1.46** in good yield (Scheme 1.33).



Scheme 1.33
Alkylation of secondary alcohols developed by Fujita

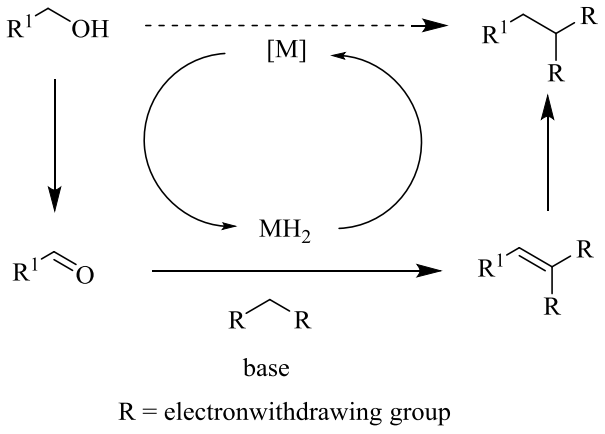
The same catalyst also allowed self-condensation of primary alcohols. Ishii and co-workers[42] converted 1-pentanol **1.47** into 2-propyl-1-heptanol **1.48** with an almost quantitative conversion (Scheme 1.34).



Scheme 1.34
Self-condensation of 1-pentanol reported by Ishii

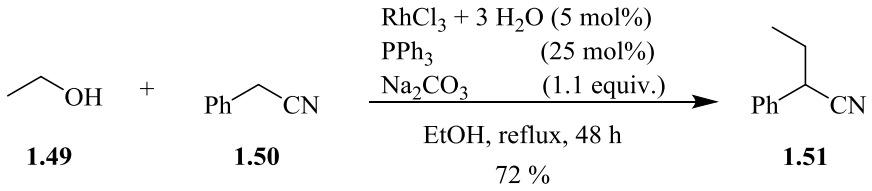
1.5.2.3 Alcohols in Indirect Knoevenagel Reactions

Another interesting way for using alcohols as alkylating agents (Scheme 1.35) has been investigated since 1981, when Grigg and co-workers[43] reported the alkylation of active methylene compounds with alcohols through a Knoevenagel reaction using a catalyst generated *in situ* from $RhCl_3$ and PPh_3 (Scheme 1.36).



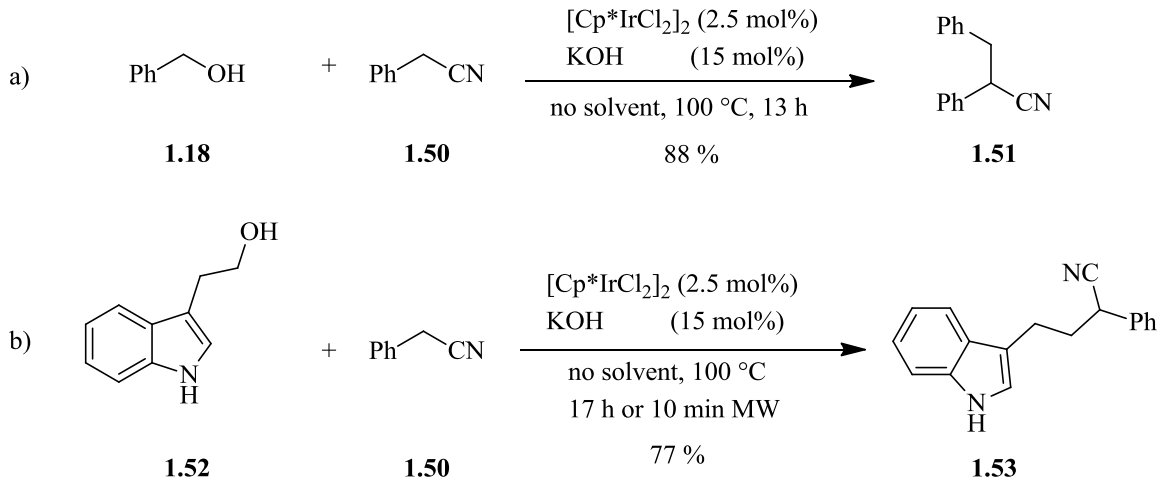
Scheme 1.35
Borrowing hydrogen combined with an indirect Knoevenagel reaction

They synthesised a small library of monoalkylated arylacetonitriles from arylacetonitrile derivatives and a limited selection of primary and secondary alcohols. It is important to note that benzylic alcohols did not react easily, requiring longer reaction times and still giving only moderate yields.



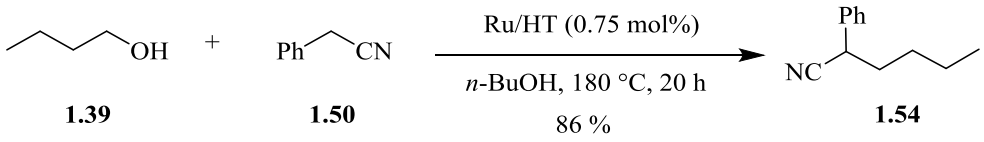
Scheme 1.36
The first example of an indirect Knoevenagel reaction reported by Grigg

More recently, Grigg and co-workers[44] extended the scope of this reaction using $[Cp^*IrCl_2]_2$ as catalyst for monoalkylation of arylacetonitriles with alcohols under milder reaction conditions. A wide range of alcohols and nitriles, including alcohols **1.18** and **1.52** with nitrile **1.50** (Scheme 1.37), were converted to the corresponding alkylated nitriles.



Scheme 1.37
Monoalkylation of arylacetonitriles with alcohols reported by Grigg

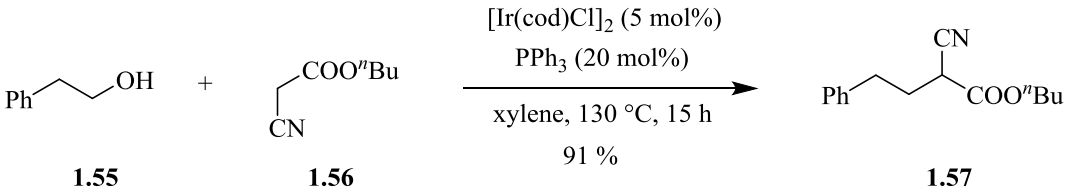
An interesting contribution to α-alkylation of nitriles was given by Kaneda and co-workers[45] who used heterogeneous ruthenium-grafted hydrotalcite (Ru/HT) instead of more conventional homogeneous complexes. Unfortunately, this catalyst worked only for primary alcohols and more forcing reaction conditions were required. For example, nitrile **1.50** was alkylated with *n*-butanol to give product **1.54** in 86% isolated yield (Scheme 1.38). Ruthenium-grafted hydrotalcide works through cooperative catalysis between the Ru species and the surface base sites, and no additional base or additives were required for promoting the knoevenagel reaction.



1.39 **1.50** **1.54**

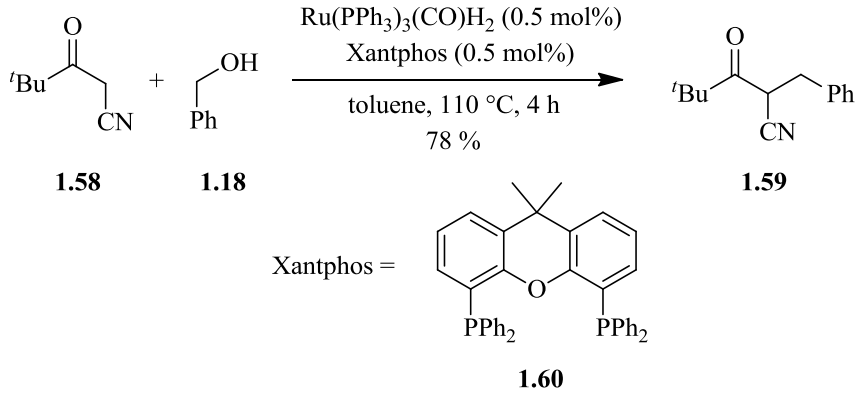
Scheme 1.38
α-Alkylation of nitriles using ruthenium-grafted hydrotalcite by Kaneda

Various other substrates have been alkylated with alcohols under hydrogen transfer conditions, including nitroalkanes (nitroaldol reaction),[46] barbituric acids[47] and various other active methylene compounds.[14], [48] Examples include alkylation of **1.56** with a range of alcohols, such as 2-phenylethanol **1.55**, using $[Ir(cod)Cl]_2/PPh_3$ (Scheme 1.39),[48a] and alkylation of ketonitrile **1.58** with benzyl alcohol **1.18** using a combination of $Ru(PPh_3)_3(CO)H_2$ with xantphos (Scheme 1.40).[48b]



1.55 **1.56** **1.57**

Scheme 1.39
*Alkylation of nitrile **1.56** with 2-phenylethanol described by Ishii*



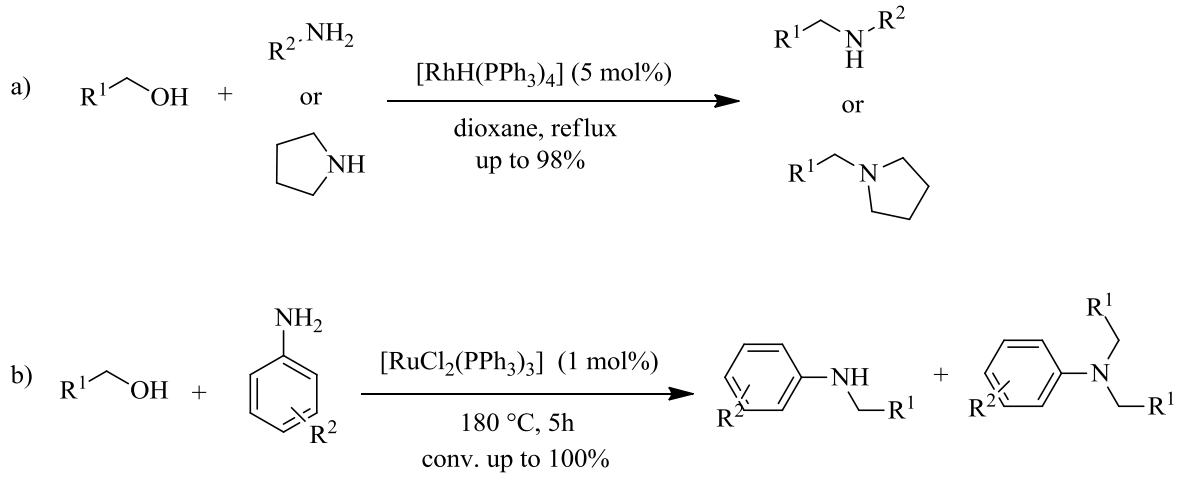
1.58 **1.18** **1.59**

1.60

Scheme 1.40
*Alkylation of chetonitrile **1.58** with benzyl alcohol by Williams*

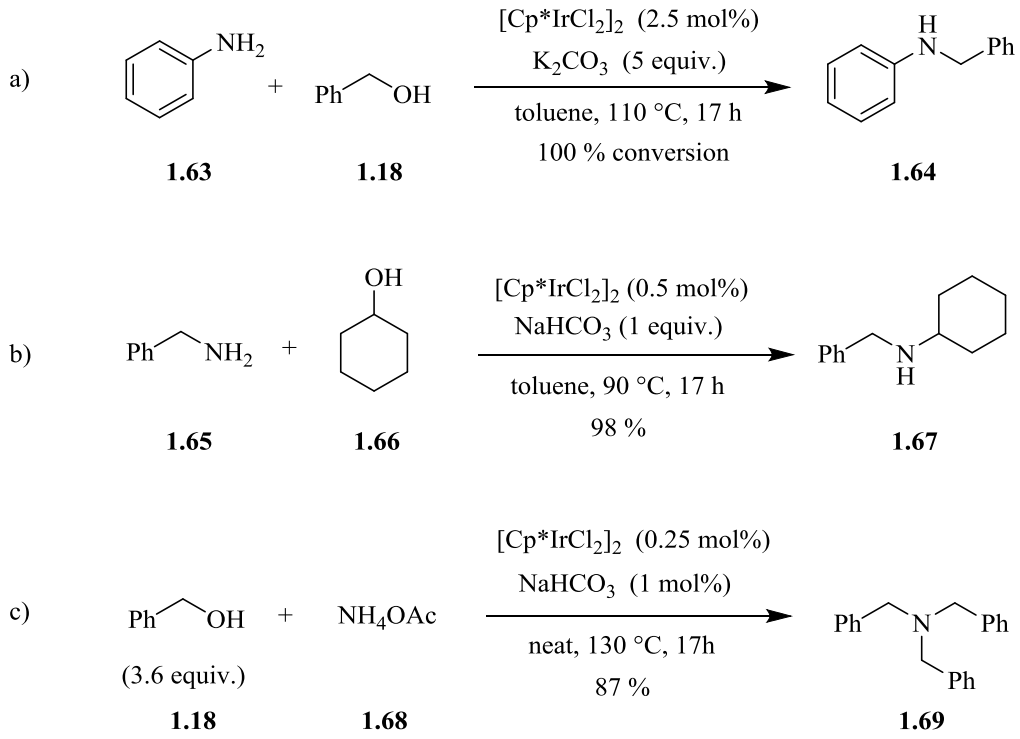
1.5.2.4 N-*Alkylation of Amines with Alcohols*

The first *N*-alkylation of amines with alcohols using a homogeneous catalyst was reported independently by Grigg *et al.*[50] and Watanabe *et al.*[51] in 1981. Grigg and co-workers described *N*-alkylation of primary and secondary alkyl amines with simple primary alcohols using $[RhH(PPh_3)_4]$ as catalyst (Scheme 1.41a). Watanabe and co-workers reported ruthenium-catalyzed *N*-alkylation of aniline derivatives using both alcohols and aldehydes (Scheme 1.41b). Grigg and Watanabe applied their methodologies only to primary alcohols.



Scheme 1.41
The first homogeneous N-*alkylation of amines with alcohols by Grigg (a) and Watanabe (b)*

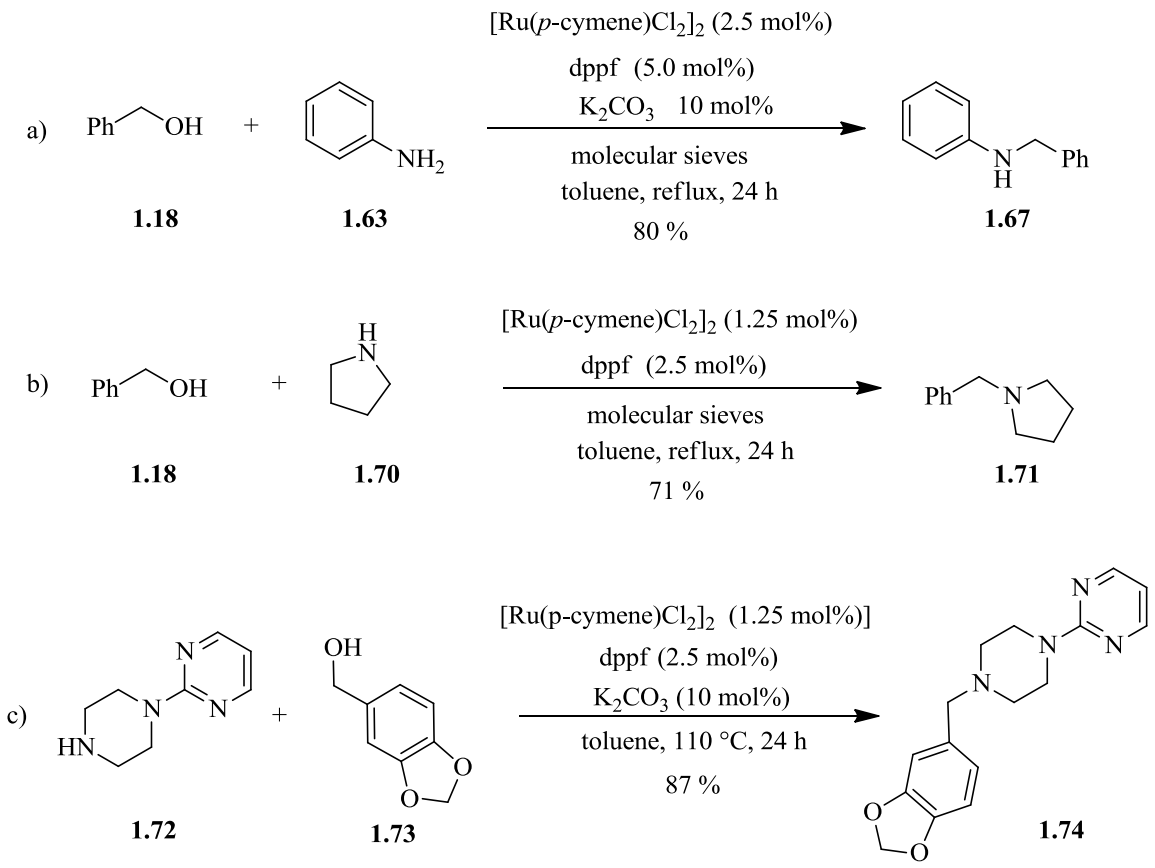
Since these first examples of homogeneously catalysed *N*-alkylation of amines extensive progress has been achieved in this field, mostly with ruthenium or iridium catalysts. Fujita and Yamaguchi[52] used commercially available $[Cp^*IrCl_2]_2$ in combination with K_2CO_3 as an effective catalyst for example for the alkylation of aniline **1.63** with benzyl alcohol **1.18** to give *N*-benzylaniline **1.64** with quantitative conversion (Scheme 1.42a).[53] The reaction has also been successfully applied to the alkylation of alkylamines with primary and secondary alcohols as illustrated by the reaction of benzylamine **1.65** with cyclohexanol **1.66** to give secondary amine **1.67** (Scheme 1.42b).[54] Multiple alkylation reactions were also developed using this catalyst, as illustrated by the reaction of benzyl alcohol **1.18** with ammonium acetate to give tribenzylamine **1.69** (Scheme 1.42c).[55]



Scheme 1.42
N-*alkylation of amines with alcohols by Fujita*

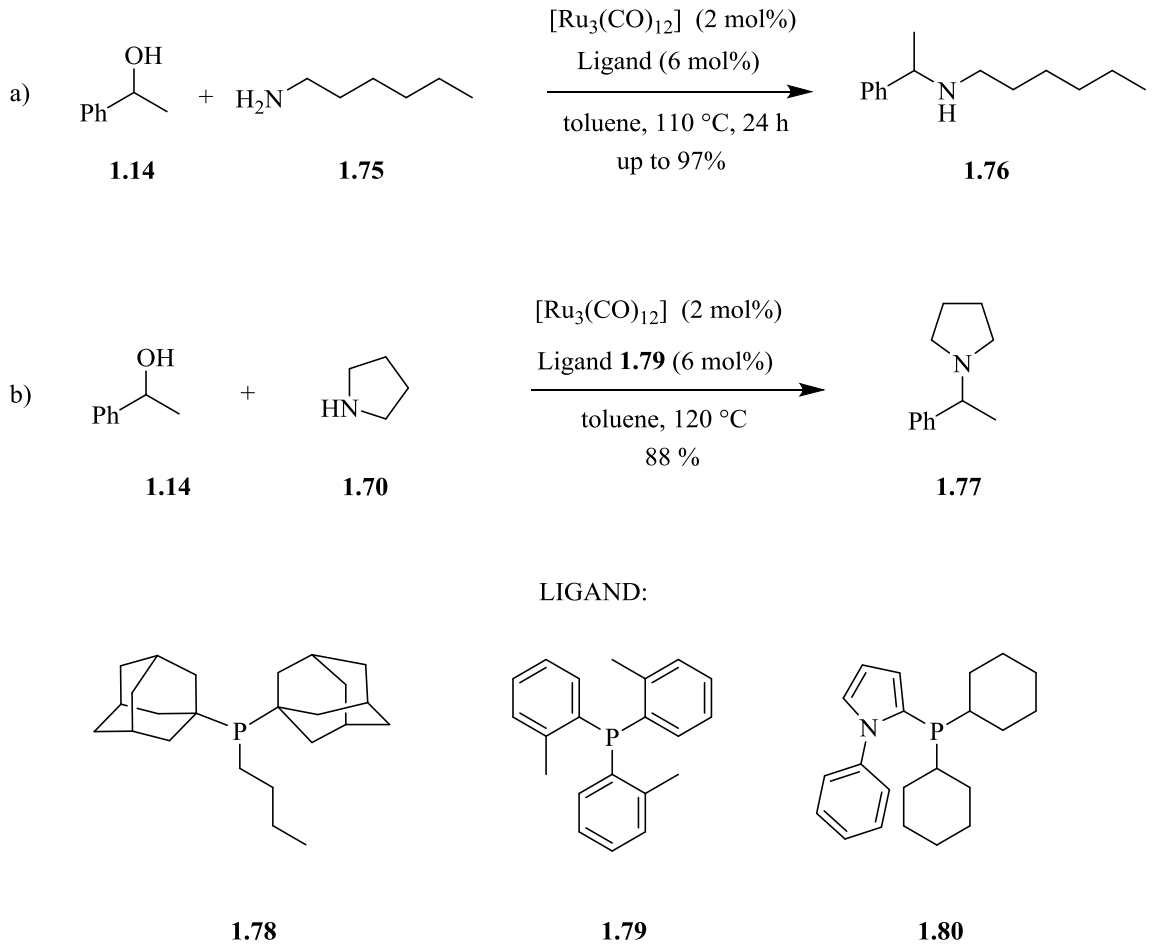
Some other iridium catalysts, including $[Ir(cod)Cl]_2$ with dppf[56] or $[Ir(cod)Cl]_2$ with P, N-ligands such as $Py_2NP(iPr)_2$, have also been proven successful in alkylation of amines by alcohols.[57]

Several ruthenium complexes have also been used for alcohol amination reactions, including $RuCl_2(PPh_3)_3$,[58] $RuCl_3 \cdot nH_2O$–$3P(OBu)_3$,[59] $CpRu(PPh_3)_2Cl$[60] and $[Ru(PPh_3)_2(MeCN)_3Cl][BPh_4]$.[61] Williams and co-workers[62] found that the combination of $[Ru(p\text{-cymene})Cl_2]_2$ with bidentate phosphine dppf forms a highly active complex for the conversion of primary amines into secondary or tertiary amines with primary alcohols (Scheme 1.43a). They applied this catalytic system in the alkylation of aryl amines and cyclic aliphatic amines such as pyrrolidine, morpholine and piperidine (Scheme 1.43b). An important example of pharmaceutical interest is the reaction piperazine **1.72** with piperonyl alcohol **1.73** to give the dopamine agonist Piribedil **1.74** (Scheme 1.43c).[63]



Scheme 1.43
N-alkylation of amines with alcohols developed by Williams

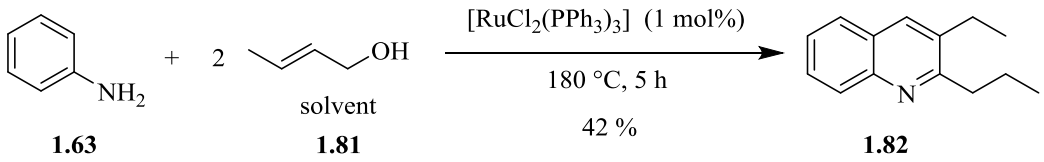
Beller and co-workers[64] used a combination of $Ru_3(CO)_{12}$ with sterically hindered phosphines for a range of alcohol amination reactions. This ruthenium cluster was found to be active for reactions involving amination of secondary alcohols, such as a reaction of 1-phenylethanol **1.14** with hexylamine **1.75** (Scheme 1.44a).[39a][39b] Furthermore, applying the same procedure, secondary amines were converted to the corresponding tertiary amines in high yields.[65] In the presence of a catalyst generated *in situ* from $Ru_3(CO)_{12}$ and N-phenyl-2(dicyclohexylphoshino)pyrrole (ligand **1.80**, cataCXium®PCy), a selective amination with cyclic amines such as piperidines, pyrrolidines, and piperazines takes place in both high yields and excellent selectivity (Scheme 1.44b).



Scheme 1.44
N-alkylation of amines with secondary alcohols developed by Beller

1.5.2.5 Synthesis of N*-Heterocycles*

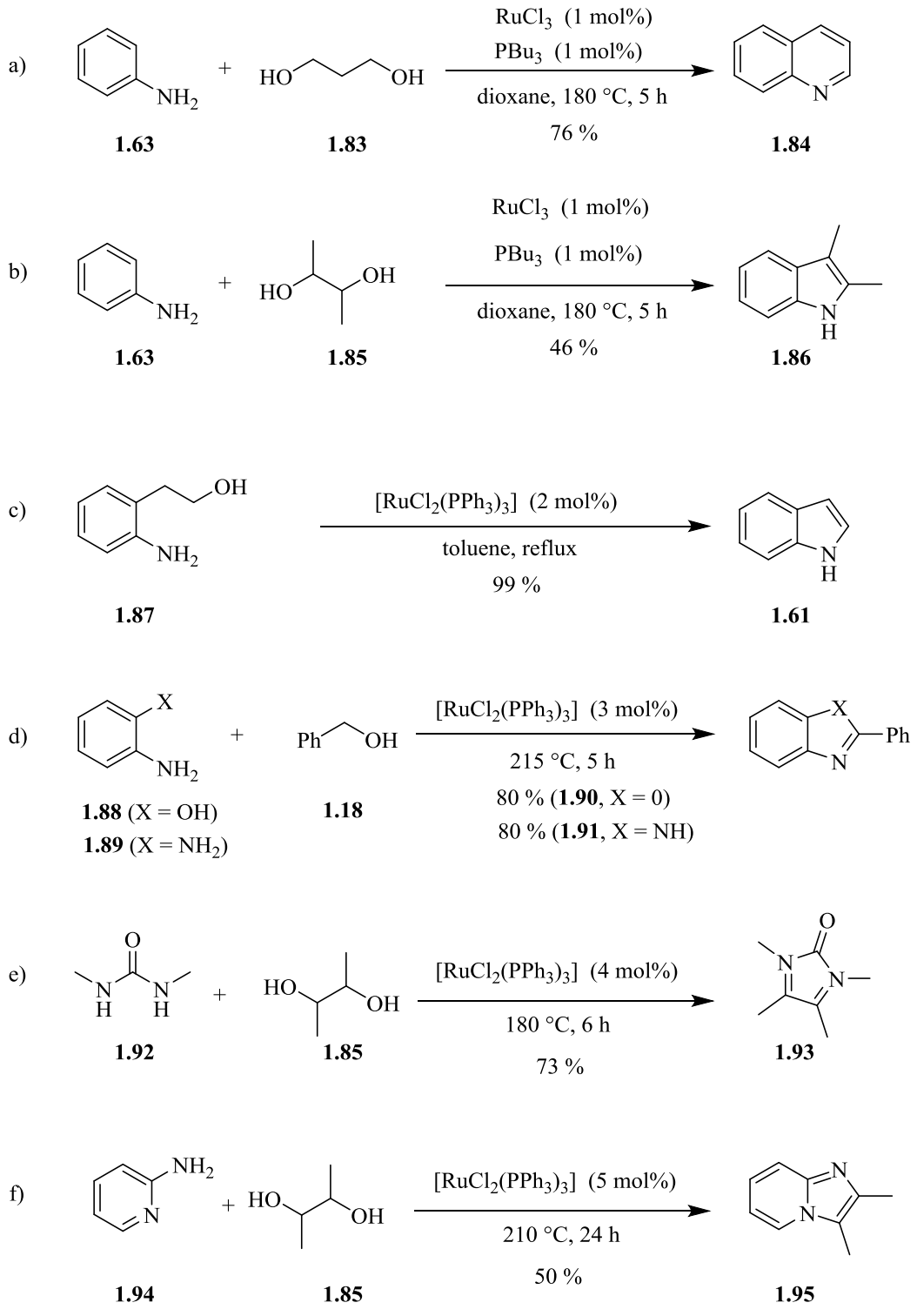
Borrowing hydrogen strategy has also been applied to the conversion of primary amines into *N*-heterocycles *via* an alkylation process with alcohols. In 1981 Watanabe *et al.*[51] described the first *N*-heterocyclisation reaction: the synthesis of 2,3-alkylquinolines was achieved starting from anilines and 2,3-unsaturated alcohols such as crotylalcohol **1.81** in moderate yields (Scheme 1.45).



1.63 **1.81** **1.82**

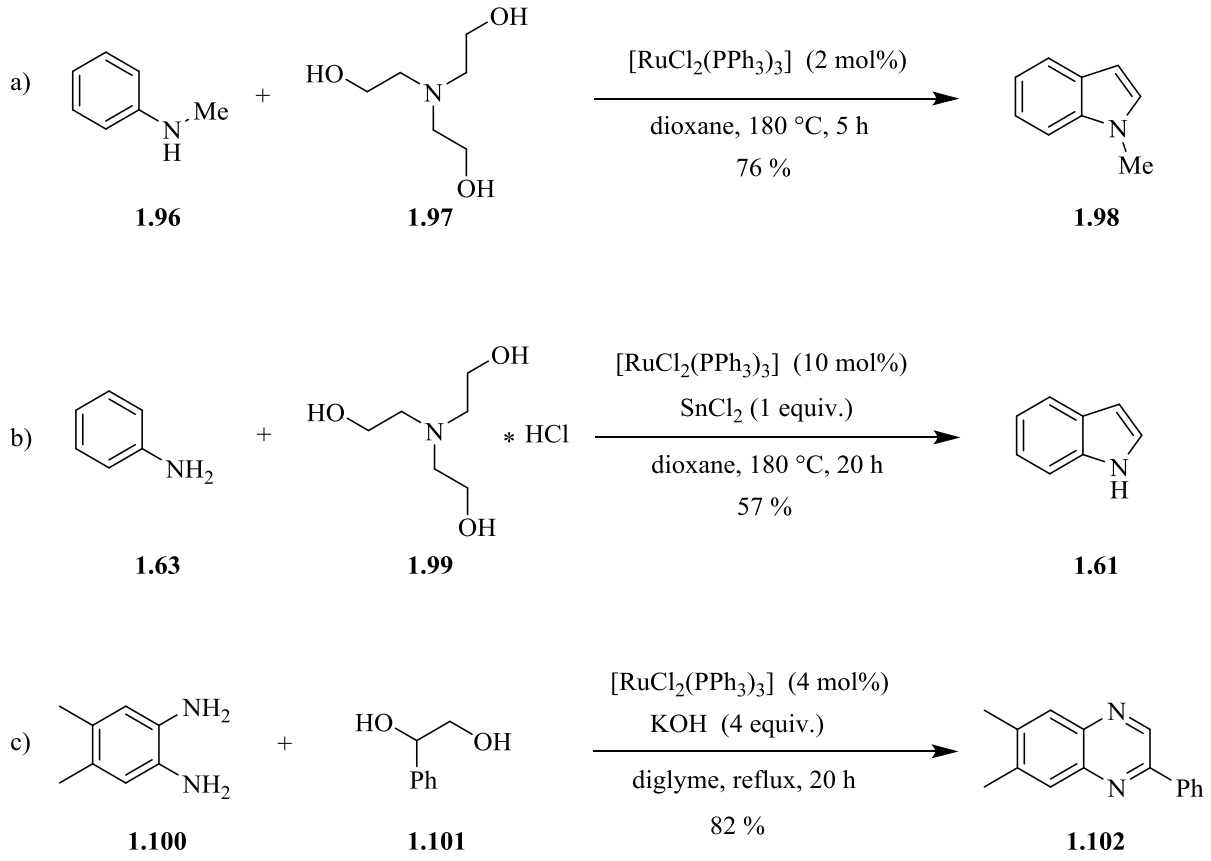
Scheme 1.45
The first synthesis of heterocycles using borrowing hydrogen by Watanabe

Later, Watanabe reported also the synthesis of indoles and quinolines by a reaction of diols with anilines (Scheme 1.46a-b)[14] and the cyclization of 2-aminophenethylalcohol to indole (Scheme 1.46c).[66] Other examples include the synthesis of benzoxazoles and benzimidazoles from aniline derivatives and primary alcohols (Scheme 1.46d),[67] the synthesis of 1,3-disubstituted 2,3-dihydroimidazol-2-ones from *N*,*N*'-disubstituted ureas (Scheme 1.46e),[68] and finally imidazol[1,2-a]pyridines starting from aminopyridines and diols (Scheme 1.46f).[69]



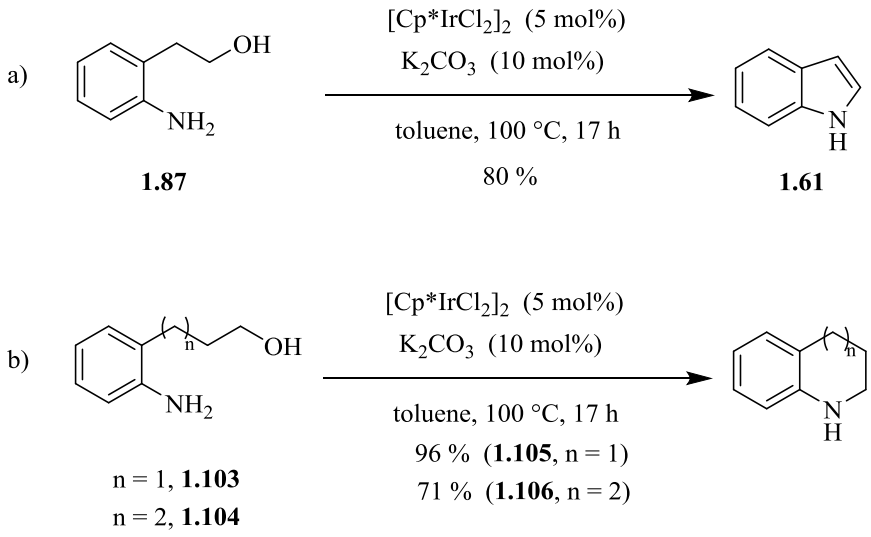
Scheme 1.46
First examples of heterocyclic synthesis using borrowing hydrogen strategy by Watanabe

Cho and co-workers reported ruthenium-catalyzed cyclization of anilines, such as **1.63** and **1.96**, with trialkanolamines (e.g. **1.97**) [70] and trialkanolammonium chlorides (e.g. **1.99**)[71] to give indoles, such as **1.61** and **1.98** (Scheme 1.47a-b). Furthermore, they introduced a new method for the synthesis of quinoxalines (such as compound **1.102**) using *o*-phenylenediamines (such as **1.100)** and vicinals diols (such as **1.101)** (Scheme 1.47c).[72]



Scheme 1.47
Synthesis of indoles and quinaxolines reported by Cho

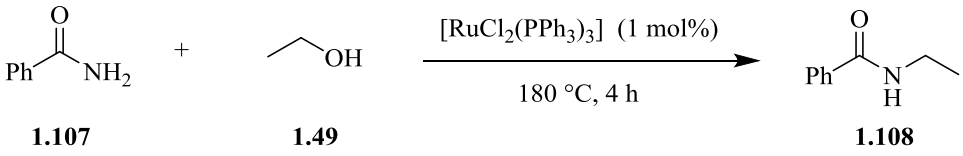
In 2002, Fujita *et al.*[73] cyclised 2-aminophenethyl alcohols to indoles using $[Cp^*IrCl_2]_2$. They synthesised a high variety of indoles including **1.61** from aminoalcohol **1.87** (Scheme 1.48a), without observing any indoline formation. With longer alkyl groups (C3-C4) between the aromatic ring and alcohol functionality, Fujita did not observe oxidative products such as quinoline or dihydroquinoline, but instead 1,2,3,4-tetrahydroquinoline **1.105** and 2,3,4,5-tetrahydro-1-benzazepine **1.106** were isolated in moderate to high yields (Scheme 1.48b).



Scheme 1.48
Synthesis of heterocycles by Fujita et al.

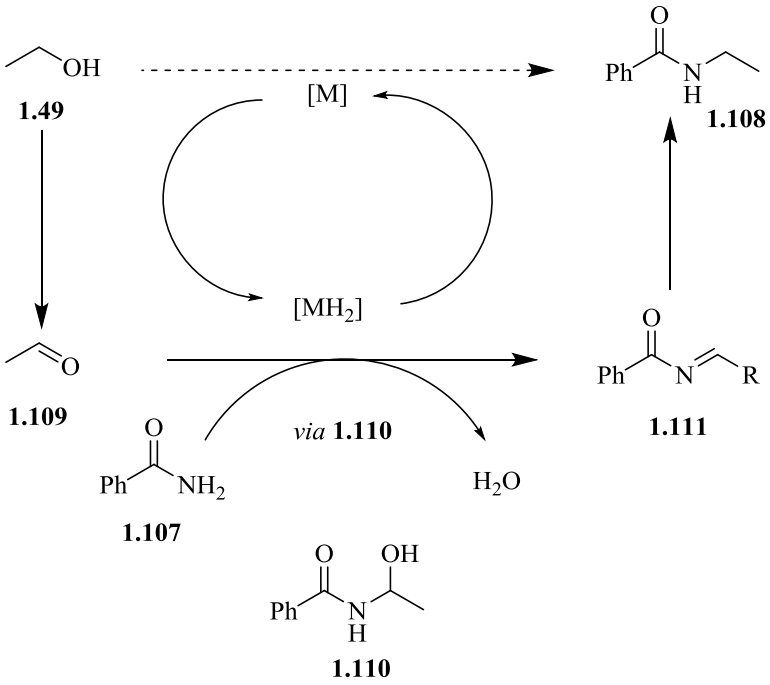
1.5.2.6 N-*Alkylation of Amides with Alcohols*

In 1983 Watanabe *et al.*[74] described the first ruthenium-catalyzed *N*-alkylation of amides using primary alcohols (Scheme 1.49).



Scheme 1.49
The first N-*alkylation of amides with alcohols by Watanabe*

The reaction pathway proceeds through oxidation of alcohol **1.49** to the corresponding aldehyde **1.109** catalysed by ruthenium complex. Next, aldehyde **1.109** can react with amide **1.107** to give *N*-acylamino alcohol **1.110**, which in turn undergoes dehydration. The dehydrated product **1.111** is hydrogenated by ruthenium hydride to give the corresponding alkylated amide (Scheme 1.50).

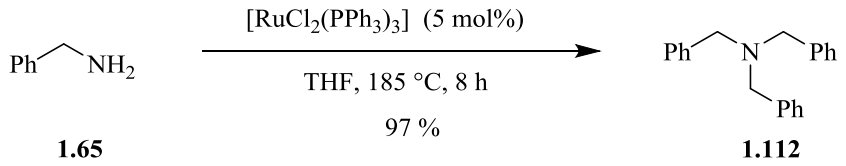


Scheme 1.50
Mechanism of N-*alkylation of amides with alcohols by borrowing hydrogen*

1.5.3 Borrowing Hydrogen in the Activation of Amines

As well as alcohols, amines can also be directly used as electrophiles exploiting a dehydrogenative oxidation pathway, giving the corresponding imines as key intermediates. In recent years several research groups have been interested in this reactivity, reporting a number of transformations of amines based on borrowing hydrogen methodology.

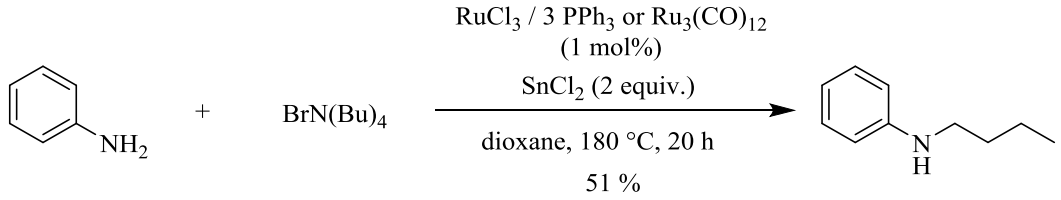
The first homogeneously catalysed homo-condensation of amines was reported by Porzi *et al.* [75] using $[RuCl_2(PPh_3)_3]$. Using this methodology they successfully converted primary amines into symmetrical tertiary amines, even if high temperatures were required (Scheme 1.51).



1.65 **1.112**

Scheme 1.51
The first self-condensation of amines by Porzi

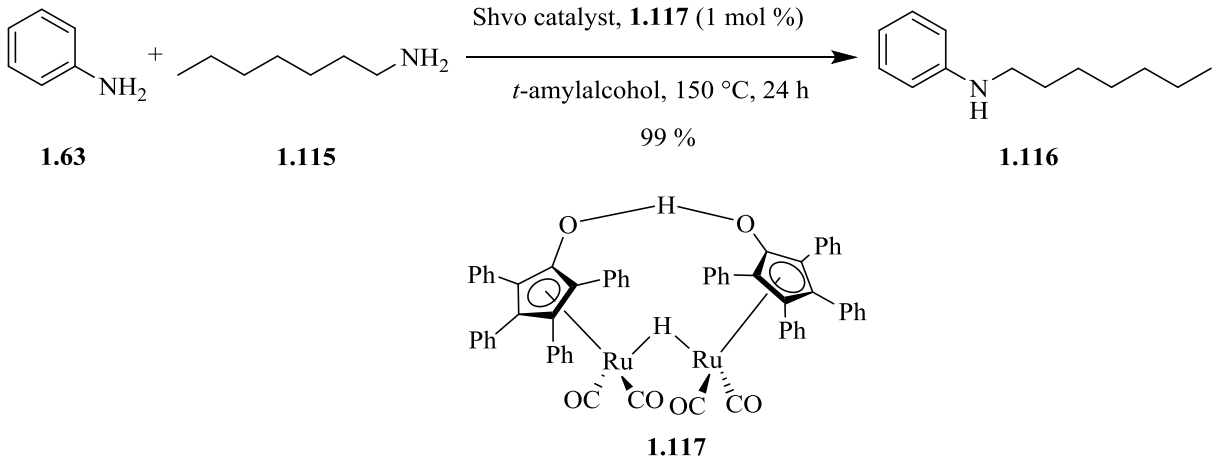
A way to exploit this intriguing reactivity is the alkylation of aryl amines with aliphatic amines. In 2001 Cho *et al.*[37] reported the selective *N*-monoalkylation of anilines with tetraalkylammonium halides (Scheme 1.52) using $RuCl_3/PPh_3$ or $[Ru_3(CO)_{12}]$ as catalysts in the presence of tin (II) chloride. Despite this breakthrough, substrate scope and yields were still quite limited.



1.63 **1.113** **1.114**

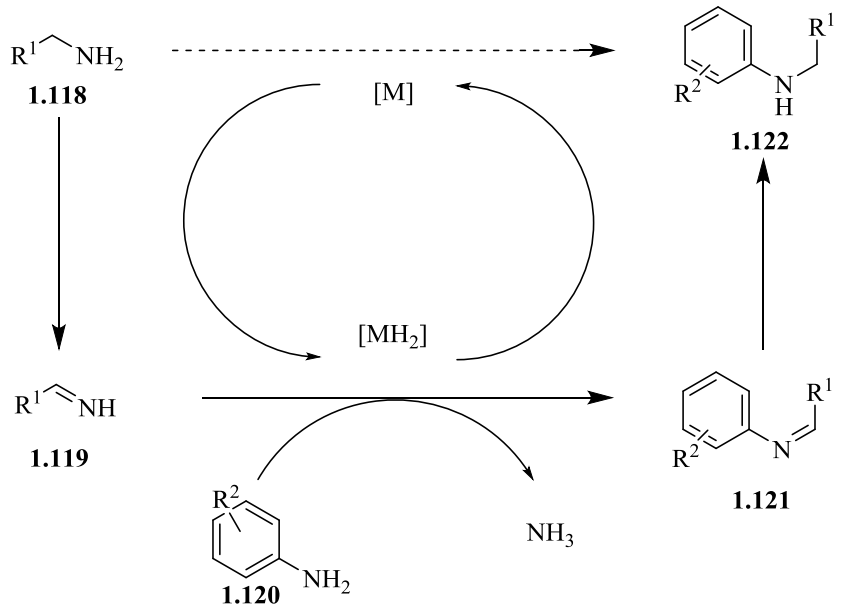
Scheme 1.52
Mono N*-alkylation of aniline with tetrabutylammonium bromide described by Cho*

In 2006, Beller and co-workers[76] extended the scope of *N*-alkylation of anilines with amines using Shvo catalyst. A variety of functionalised anilines were converted with a number of primary amines to the corresponding arylalkylamines in excellent yields, leaving ammonia as the only by-product (Scheme 1.53). In addition, Beller alkylated anilines with primary, secondary and tertiary amines, providing a strategy also for *N*-dealkylation of aliphatic amines.[77]



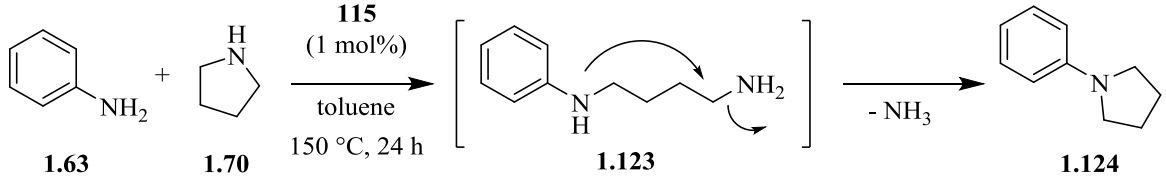
Scheme 1.53
Mono N-*alkylation of anilines using the Shvo catalyst by Beller*

This reaction, similarly to the amination of alcohols, occurs through a BH mechanism. In the first step, alkyl amine **1.118** is dehydrogenated to the corresponding imine **1.119**. After nucleophilic attack of aniline **1.120** and elimination of ammonia, the corresponding secondary imine **1.121** is hydrogenated to alkylated aniline **1.122** (Scheme 1.54).



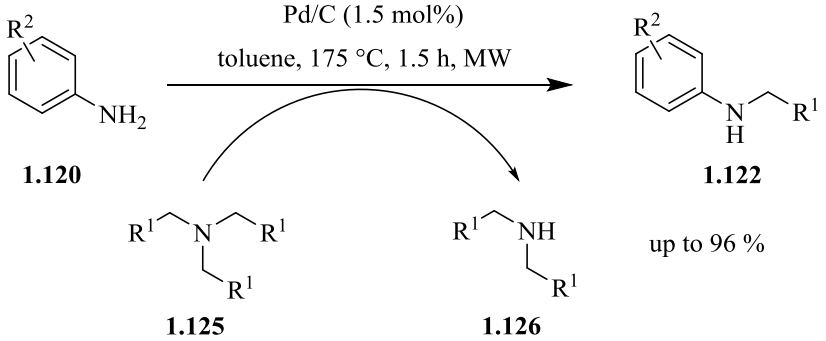
Scheme 1.54
Mechanism of N-*alkylation of anilines with amines*

In addition to noncyclic aliphatic amines, alkylation of aryl amines using cyclic aliphatic amines such as pyrrolidine **1.70** proceeds *via* borrowing hydrogen methodology in the presence of 1 mol% *Shvo* catalyst, leading to *N*-aryl-pyrrolidines (Scheme 1.55). [78]



Scheme 1.55
N-*alkylation of aniline with pyrrolidine using Shvo catalyst by Beller*

More recently, Porcheddu *et al*.[79] described the use of heterogeneous Pd/C for selective mono-*N*-alkylation of a broad number of anilines with tertiary amines (Scheme 1.56). This method, based on an easily recyclable heterogeneous catalyst, showed several fundamental improvements with respect to the previously reported processes: first, Pd/C is inexpensive and readily available; second, the catalyst can be recovered by simple filtration; and last an extremely low contamination of the product by residual palladium is expected. Furthermore, Pd/C does not require additional ligands that could become potential contaminants or produce unwanted side products.



Scheme 1.56
Mono N-*alkylation of anilines with tertiary amines catalysed by Pd/C by Porcheddu*

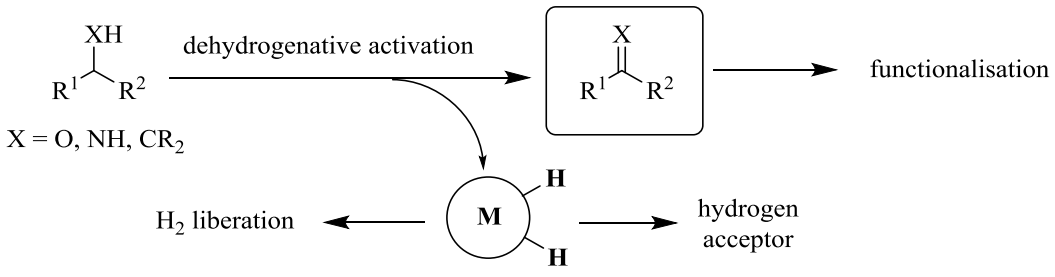
Microwave irradiation allowed to reduce the reaction times from 12 hours to 1.5 hours. Unfortunately, high temperatures were required (175 °C) and secondary amine is produced as a by-product, lowering the atom-economy of the process. It is worth to note that the catalyst could be recycled for up to five consecutive runs with no appreciable loss in the catalytic

activity. Shortly after, Taddei and co-workers[80] found that using Pd/C with a catalytic amount of acetic acid (10%) allowed to extend the scope of this transformation also to primary amines favouring the atom economy of the process.

1.6 Other Methods Based on Dehydrogenative Activation of Substrates

1.6.1 Introduction

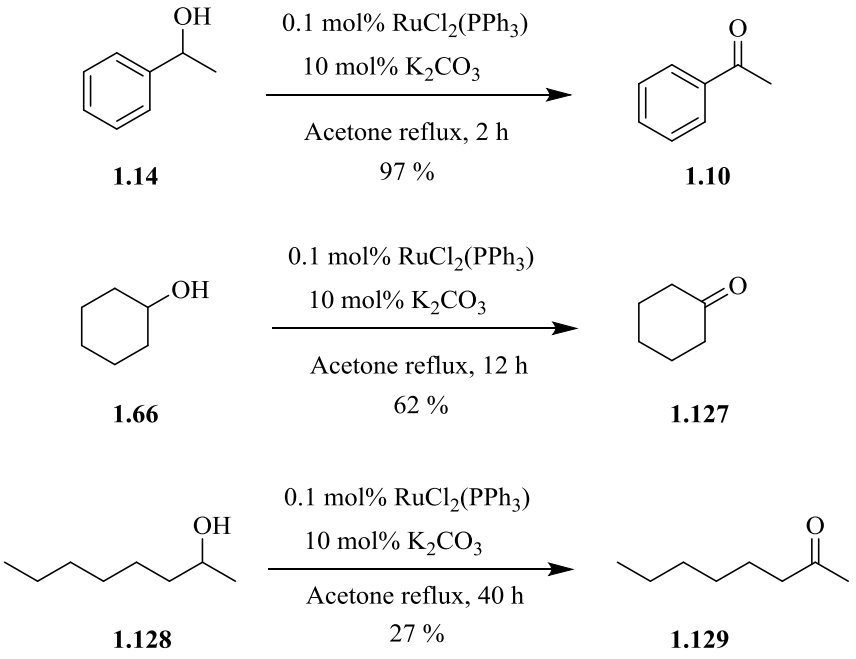
In borrowing hydrogen methodology, hydrogen taken from an unreactive substrate is returned to an intermediate derived from the substrate, and the overall process is redox-neutral. This is where the name of this strategy derives from. Parallel to BH, several synthetic methods based on a closely related strategy in which hydrogen gas from the substrate is released or transferred to a hydrogen acceptor have been developed (Scheme 1.57). Therefore, these methods, contrary to BH, involves a net oxidation and the transformation proceeds to give a product that has a higher oxidation state than the starting material. In each case, a less reactive species - such as an alkane, an alcohol or an amine - is converted to a more reactive one - an alkene, a carbonyl compound or an imine, respectively - that then reacts further in a tandem 'one-pot' procedure. The first step is catalysed by a transition-metal complex, while the following steps may or may not be catalysed, depending on the particular reaction. This strategy has been investigated extensively, and provides a very efficient, atom- and step-economic approach to valuable chemical scaffolds.



Scheme 1.57
Catalytic dehydrogenative activation

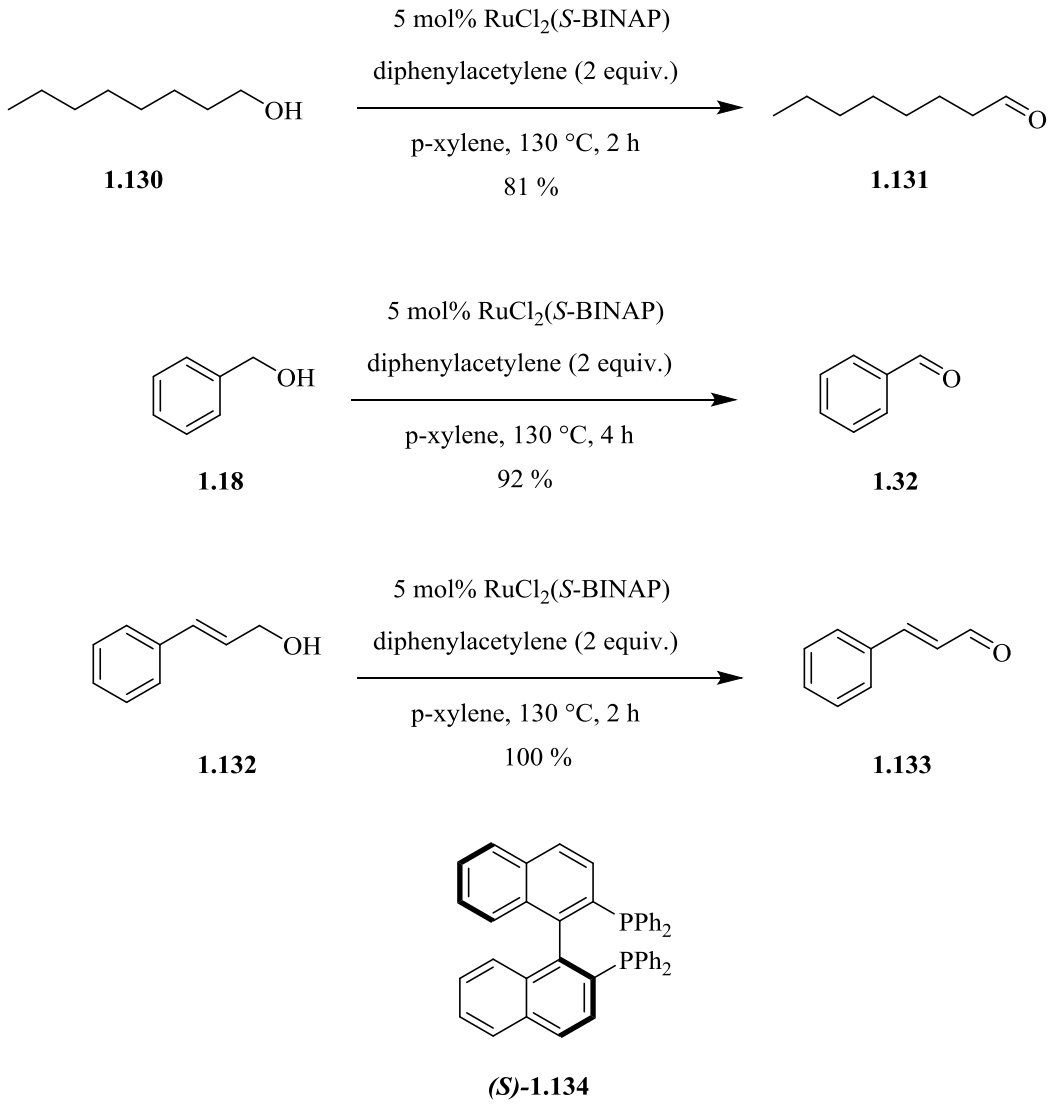
1.6.2 Dehydrogenative Alcohol Oxidation

The first homogeneous metal catalysed transfer hydrogenation for the oxidation of alcohols was reported by Wang and Bäckvall in 1992.[19] A number of aliphatic, benzylic and cyclic secondary alcohols, including 1-phenyethanol **1.14**, cyclohexanol **1.66** and 2-octanol **1.128**, were oxidised to the corresponding ketones using $RuCl_2(PPh_3)_3$ with K_2CO_3 in refluxing acetone (Scheme 1.58). The oxidation of primary alcohols was unsuccessful due to metal promoted decarbonylation of the product aldehydes and formation of an inactive metal carbonyl complex.



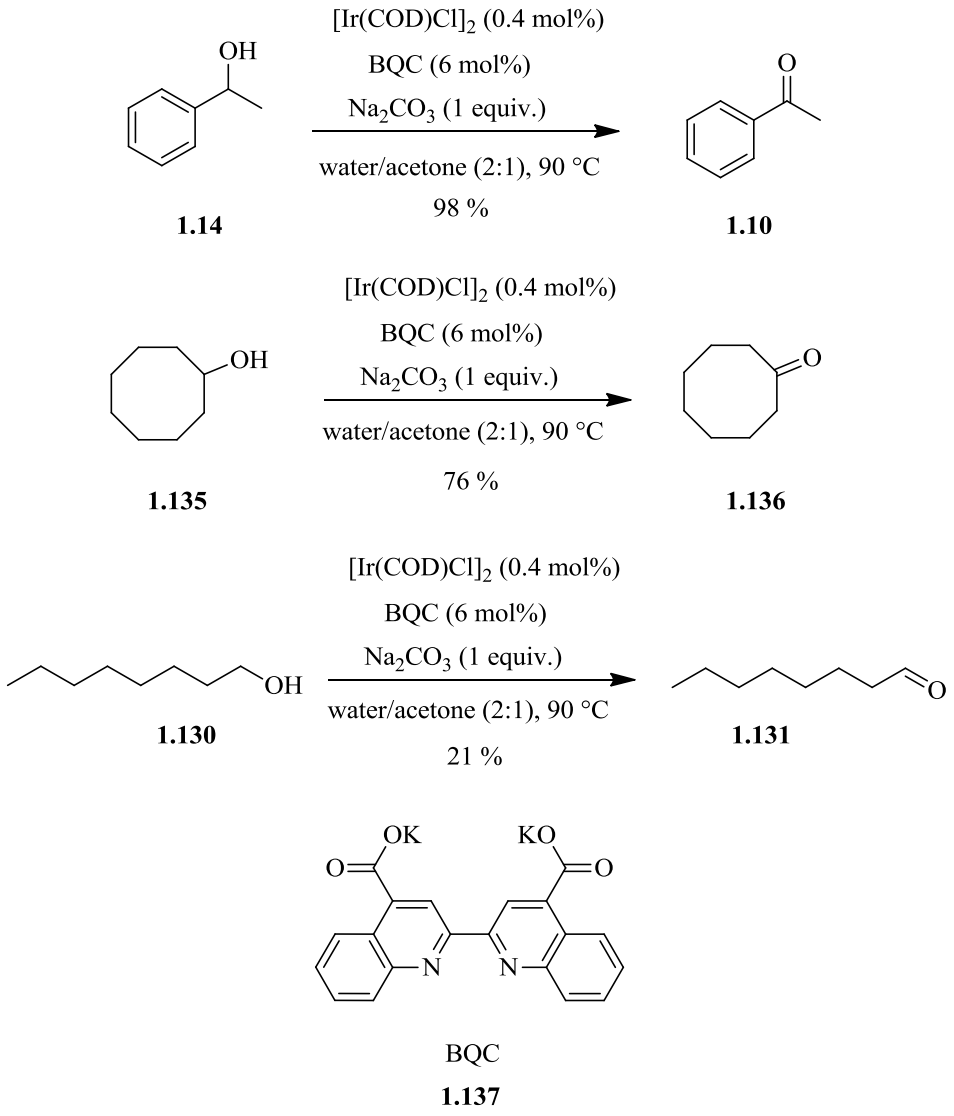
Scheme 1.58
Alcohol oxidation using a hydrogen acceptor

Oxidation of primary alcohols to aldehydes was achieved by Hulshof *et al*.[81] by heating substrates at 130 °C in *p*-xylene using $RuCl_2$(*S*-BINAP) as catalyst and diphenylacetylene as hydrogen acceptor (Scheme 1.59).



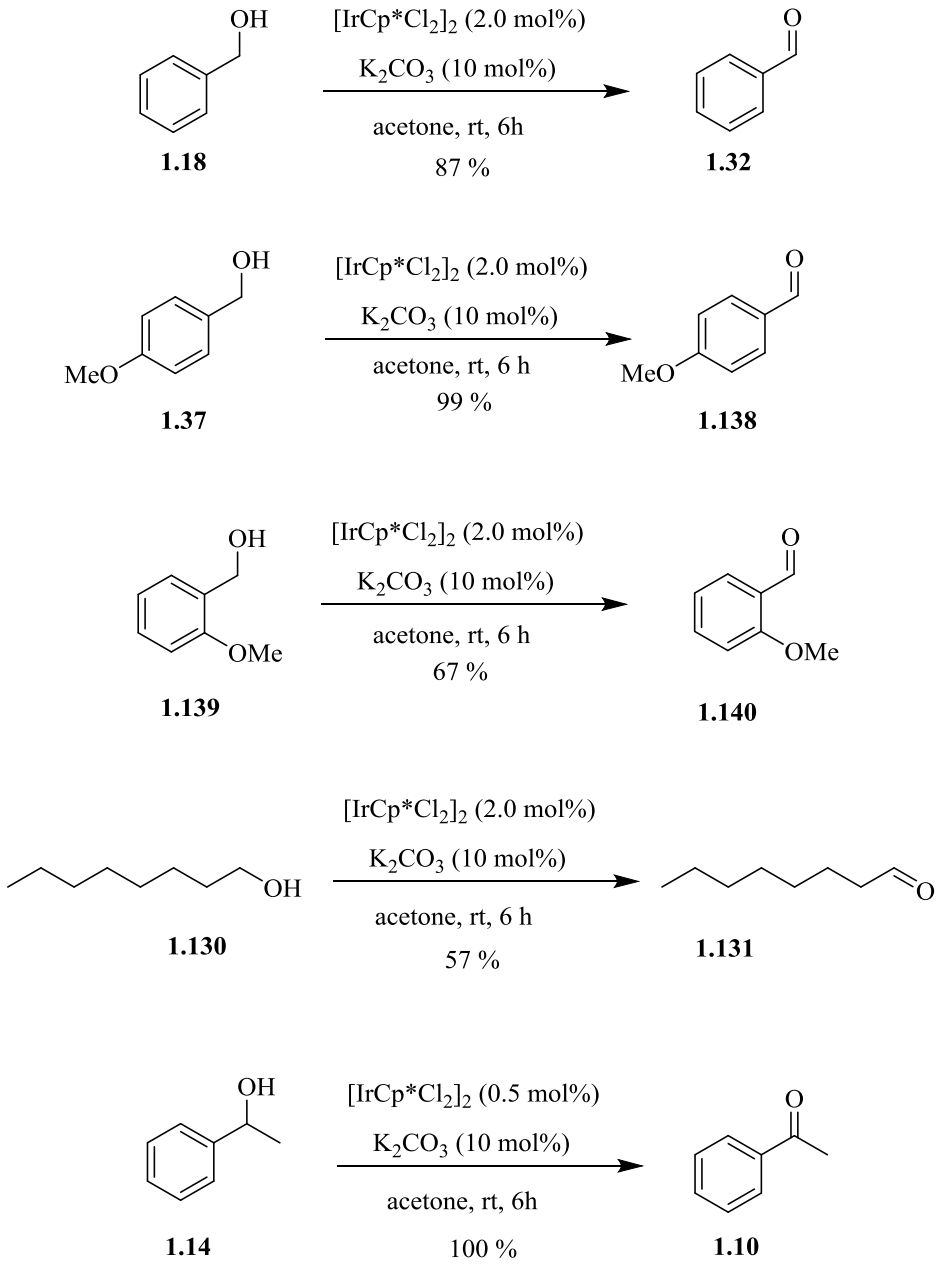
Scheme 1.59
Oxidation of primary alcohols by Hulshof

Iridium catalysts have also been used in the oxidation of both primary and secondary alcohols. In 2001 Ajjou[82] reported this reaction in aqueous media by using $[Ir(COD)Cl]_2$, 2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt (BQC) and Na_2CO_3 in the presence of acetone as hydrogen acceptor at 90 °C. A range of benzylic alcohols, long chain aliphatic alcohols (e. g. **1.130**) and cyclic secondary alcohols such as cyclooctanol **1.135** were oxidised in variable yields (Scheme 1.60).



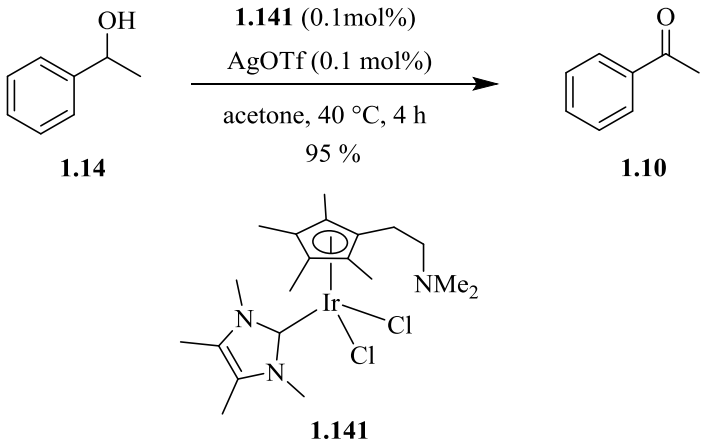
Scheme 1.60
Alcohol oxidation by Ajjou

In 2002 Fujita and co-workers[83] reported on the oxidation of primary and secondary alcohols with $[Cp^*IrCl_2]_2$ in the presence of K_2CO_3 and with acetone as both solvent and hydrogen acceptor. A range of substituted benzylic primary alcohols were oxidised in moderate to high conversion. Substrates bearing an electron-donating group in *para* position gave the highest conversions respect to those bearing electron-withdrawing groups or those bearing substituents at the *ortho* position, whereas aliphatic primary alcohols gave only moderate conversions. Secondary alcohols could also be efficiently oxidised, even with lower catalyst loadings (Scheme 1.61).



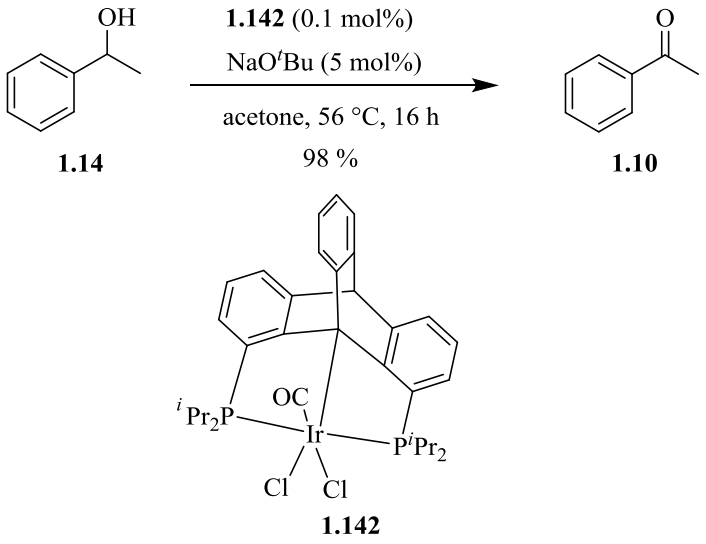
Scheme 1.61
*Oxidation of primary and secondary alcohols using [Cp*IrCl$_2$]$_2$*

In subsequent years, the same group discovered that the catalytic activity of Cp*Ir complexes in the Oppenauer-type oxidation of alcohols was considerably enhanced by introduction of *N*-heterocyclic carbene (NHC) ligands.[84] They showed that complex **1.141** bearing a pendant dimethylamino group (which acts as a basic site) allowed oxidation of 1-phenyethanol **1.14** in excellent yield without K_2CO_3 (Scheme 1.62).



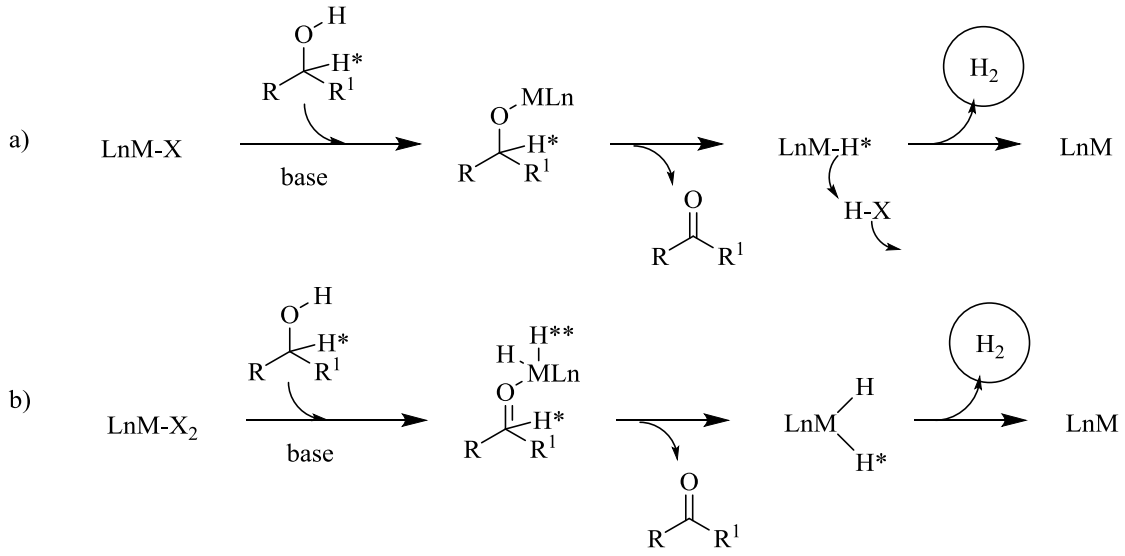
Scheme 1.62
Iridium NHC complex reported by Fujita for alcohol oxidation

An efficient PCP pincer iridium catalyst for the oxidation of benzylic secondary alcohols has been developed by Gelman and co-workers.[85] Using complex **1.142** (0.1 mol%) and KO*t*Bu (5 mol%) in refluxing acetone as both solvent and hydrogen acceptor, a range of benzylic alcohols were oxidised to acetophenone derivatives. 1-Phenylethanol was converted after 0.5 h in 92 % yield (Scheme 1.63). Apart from the strongly electron-withdrawing cyano group, electronic properties of substituents in the *para* position have little impact on the conversion.



Scheme 1.63
Oxidation of 1-phenylethanol with an Ir pincer complex

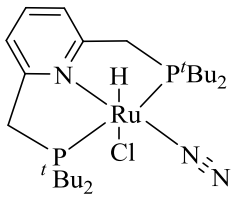
Undoubtedly the most interesting examples of alcohol oxidations are acceptorless and oxidant-free dehydrogenation reactions. These methods are based on a more atom-economical strategy in which molecular hydrogen can be effectively removed from the reaction mixture to drive the equilibrium toward the products. The considerable interest in this strategy comes from the possibility of using alcohols as bio-renewable feedstocks for generating valuable gaseous hydrogen for energy supply.[86] Unlike in hydrogen transfer where the hydrogen is delivered onto another organic substrate, in the case of acceptorless oxidation the hydrogen is released. If a monohydride mechanism is operating, a metal hydride species is first formed, followed by protonation by an acidic proton and subsequent hydrogen gas release (Scheme 1.64a). On the contrary, in the case of a metal dihydride mechanism, hydrogen generation occurs *via* reductive elimination (Scheme 1.64b).



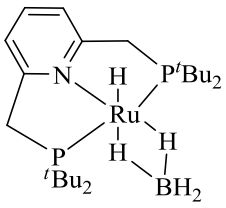
Scheme 1.64
Mechanism of hydrogen gas generation from an alcohol

Early examples of alcohol oxidation without hydrogen acceptor required the presence of an acid as a hydride ion acceptor.[87] Year 2004 presented a turning point in this field, when Milstein and co-workers[88] reported, for the first time, the use of electron-rich, bulky ruthenium PNP-type complexes as effective catalysts for dehydrogenation of secondary alcohols (Figure 1.2). Complex **1.143** was active in the oxidation of 1-phenylethanol **1.14** although catalyst activation with a base was needed (Scheme 1.65a-b). On the contrary, PNP- and PNN-type pincer complexes **1.144** and **1.145**, reported later by the same group, are active catalysts also

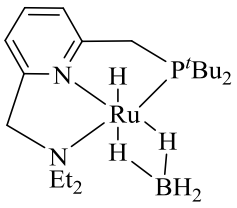
under neutral conditions and at lower loadings (Scheme 1.65c-d).[89]



1.143

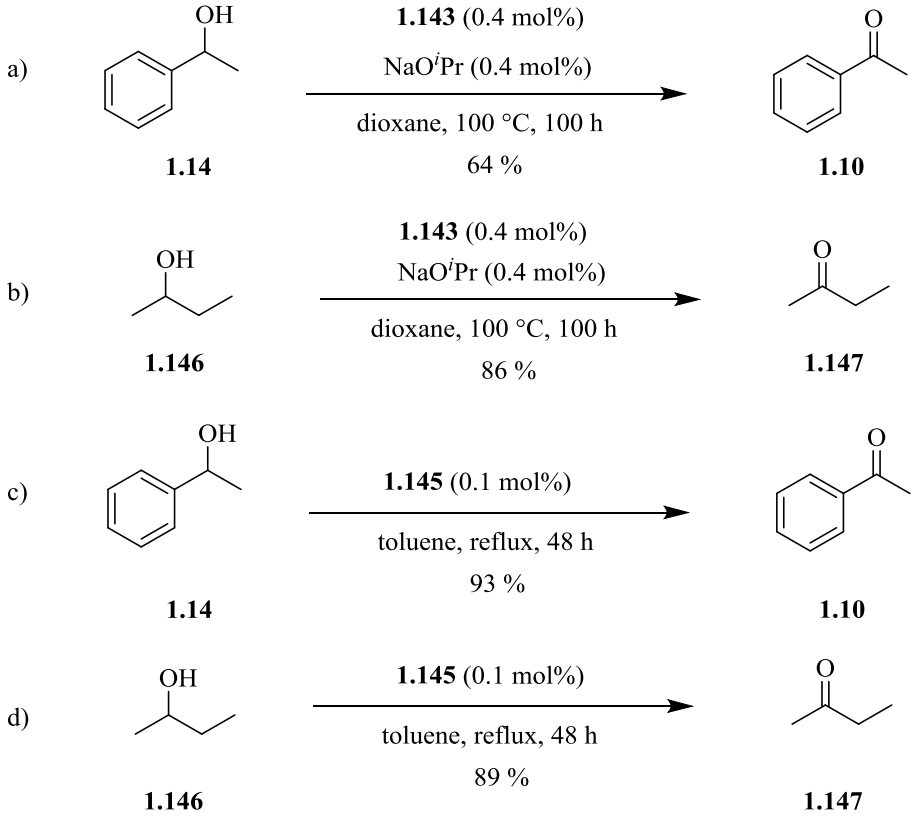


1.144



1.145

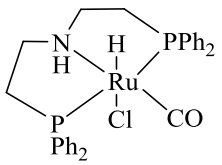
Figure 1.2
Ruthenium pincer complex used by Milstein



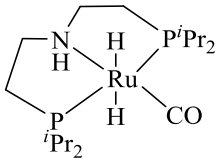
Scheme 1.65
Oxidation of secondary alcohol without hydrogen acceptor by Milstein

Beller and co-workers showed that combining ruthenium precursors [RuHCl(CO)(PPh_3)$_3$] and [RuH_2(CO)(PPh_3)$_3$] with PNP-type pincer ligands generates highly effective catalysts for hydrogen production from 2-propanol (Figure 1.3).[90] Complex **1.148** proved to be an efficient catalyst for dehydrogenation of 2-propanol at reflux. With 32 ppm of catalyst and 1.3

equivalents of NaO^{i}Pr relative to the catalyst, the turnover frequency was 1231 h^{-1} after 2 h. By tuning the substituents on the phosphines and using ruthenium precursor [$RuH_2(CO)(PPh_3)_3$], they improved significantly the rate of dehydrogenation of 2-propanol under neutral conditions: complex **1.149** gave a turnover frequency of 2048 h^{-1} after 2 h.



1.148



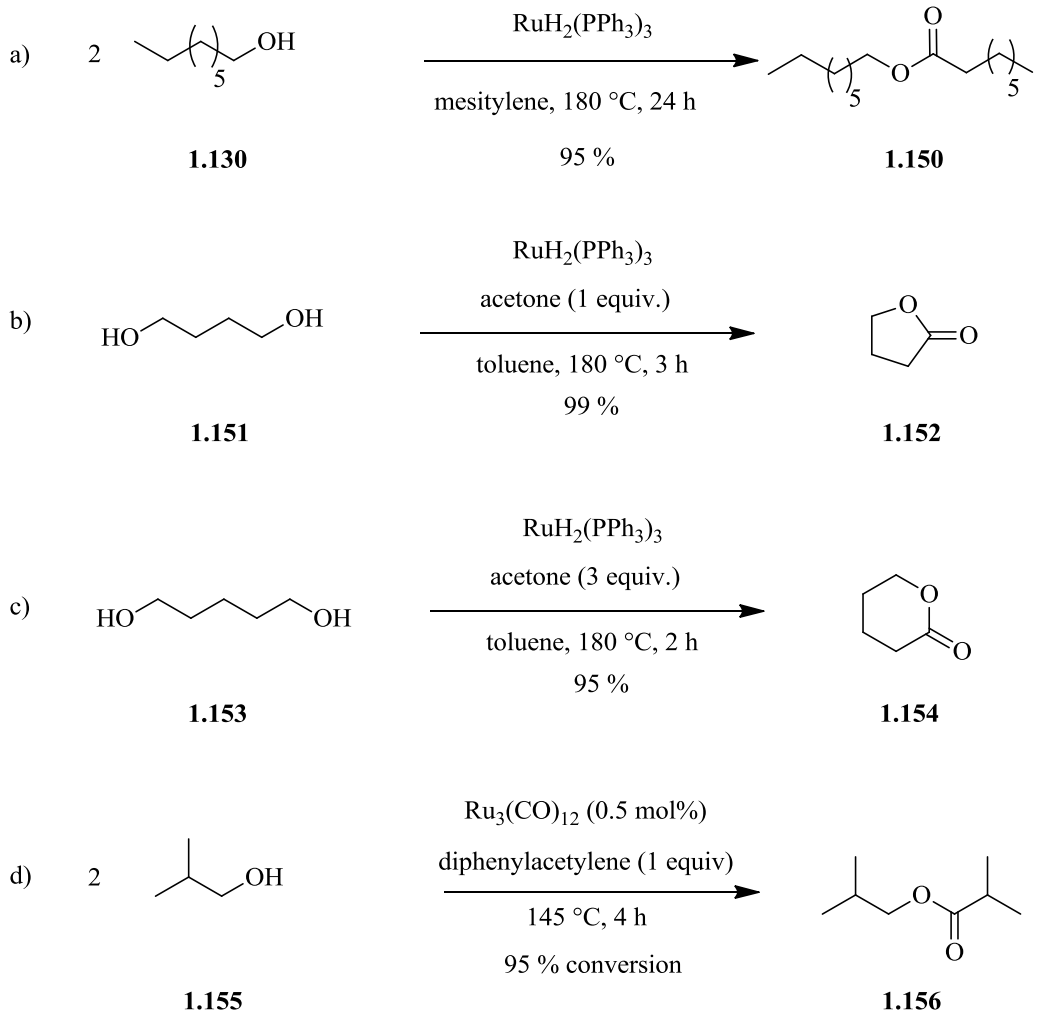
1.149

Figure 1.3
Beller's catalysts for hydrogen generation from 2-propanol

1.6.3 Synthesis of Esters via Dehydrogenative Coupling of Alcohols

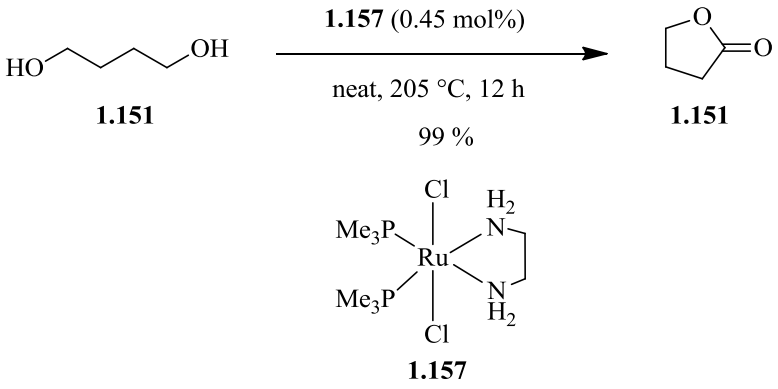
Esterification is one of the fundamental reactions in organic synthesis. Search for new environmentally friendly, atom-efficient methods for the synthesis of esters continues to be a challenge. An attractive approach is the direct catalytic transformation of alcohols to esters, without the use of the corresponding acids or acid-derivatives.

Murahashi and Shvo pioneereed a homogeneously catalysed dehydrogenative coupling of alcohols to form esters in 1980's.[91] In 1981 Murahashi reported a ruthenium catalysed transformation of alcohols to esters and lactones using $RuH_2(PPh_3)_3$ (Scheme 1.66a). The reaction conditions were harsh but, interestingly, a hydrogen acceptor was not needed and the reaction proceeded with hydrogen evolution. In addition, the method was applied to the synthesis of γ- and δ-lactones starting from 1,4- and 1,5-dioles, respectively (Scheme 1.66b-c). Lactonisation is greatly enhanced by transfer of hydrogen to an appropriate hydrogen acceptor such as acetone. Shortly after, Shvo described the same oxidative coupling of alcohols to give esters using $Ru_3(CO)_{12}$. In respect to Murahashi's system, in Shvo's case a hydrogen acceptor (such as an activated double bond) is needed. Linear and branched primary aliphatic alcohols as well as various benzylic alcohols were converted in good to excellent yields (Scheme 1.66d).



Scheme 1.66
First examples of esterification of alcohols

Lactone formation has also been performed using ruthenium bis-phosphine diamine complex **1.157**, that allows acceptorless dehydrogenation at elevated temperatures (Scheme 1.67).[92]



Scheme 1.67
Lactonisation of diols

In recent years, Milstein and co-workers reported the use of several rationally designed complexes, that are very active in oxidative esterification of alcohols (Figure 1.4).

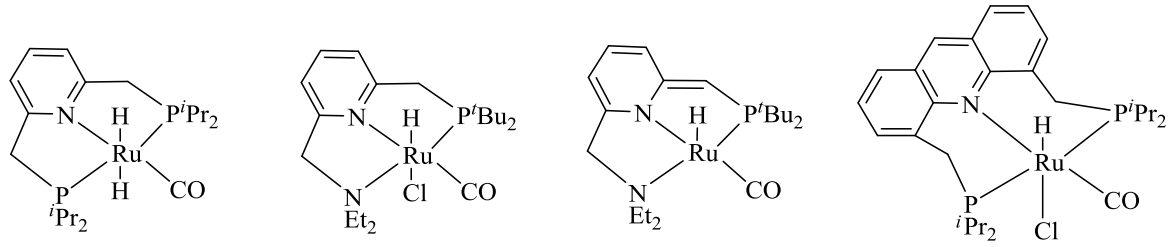
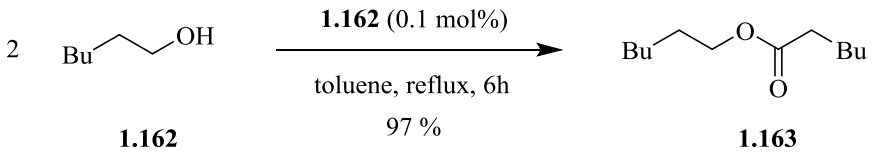


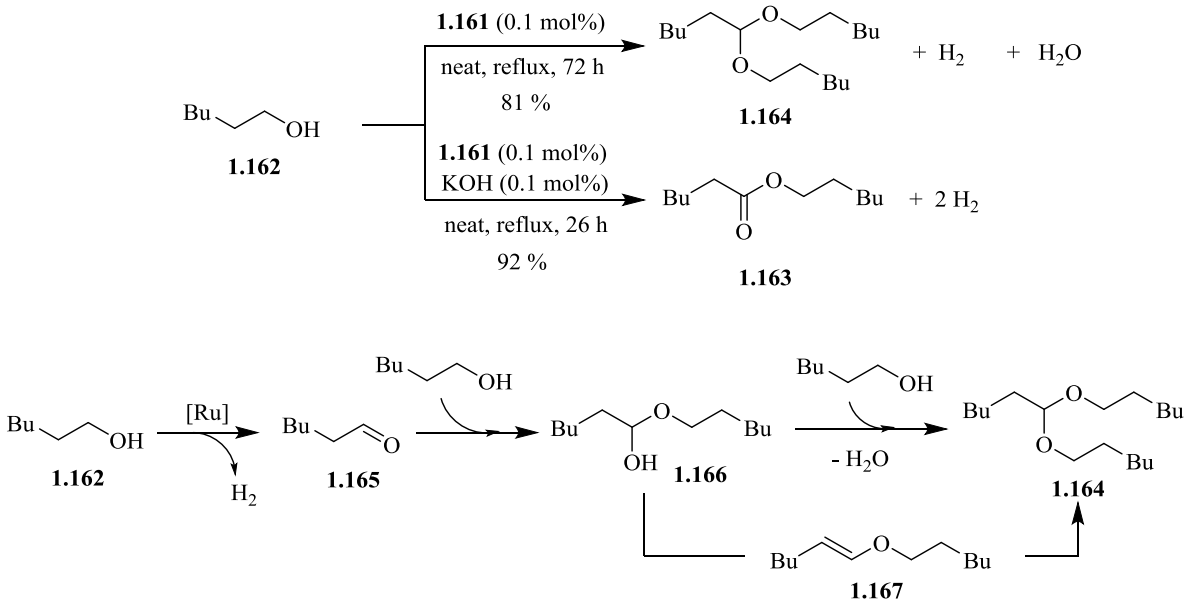
Figure 1.4
Milstein's catalysts used in dehydrogenative esterification of alcohols

Complex **1.158** catalysed dehydrogenative esterification of 1-hexanol **1.162** only in the presence of 1 equiv of KOH (relative to Ru) with discrete acitivities: after 24 h at 157 °C, 0.1 mol% of the complex had converted 67 % of 1-hexanol to hexyl hexanoate and H_2 under an argon flow. The analogous complex **1.159** bearing a hemilabile amine "arm" showed an improved activity: in the same reaction conditions, conversion of 1-hexanol increased to 91.5 %. Interestingly, the reaction temperature can be lowered to 115 °C in refluxing toluene, resulting in 94.5% yield of the ester after 24 h. Complex **1.160**, obtained by treating **1.159** with KO^{t}Bu, was found to be the best homogeneous catalyst in acceptorless dehydrogenative esterification of alcohols. When used as a catalyst without a base, ester yields of over 90% were obtained from the alcohols in relatively short reaction times (Scheme 1.68).



Scheme 1.68
Conversion of 1-hexanol to hexylhexanoate by Milstein

Also acridine catalyst **1.161** catalyses dehydeogenative coupling of alcohols to esters in the presence of a catalytic amount of base in refluxing solvent or under neat conditions. Interestingly, the same complex catalyses the conversion of alcohols into acetals in the absence of a base *via* a mechanism that may involve hemiacetal dehydration giving an enol ether, followed by alcohol addition to the double bond (Scheme 1.69).

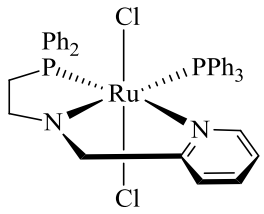


Scheme 1.69
Conversion of alcohols into acetals by Milstein

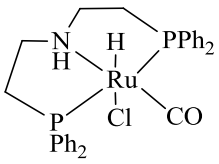
Esterification of ethanol is particularly interesting for two important reasons: (1) ethanol is a bio-renewable alcohol, and (2) the product of esterification of ethanol, ethyl acetate, is a widely used industrial bulk chemical.[93] With a world market of about 2.5 million tons per year,[94] ethyl acetate is largely used as solvent and is an important intermediate in the food industry, and for various customer applications such as glues, inks, and perfumes. Processes for the synthesis of ethyl acetate are primarily based on the use of petrochemical feedstocks. In

contrast, ethanol - an inexpensive starting material for ethyl acetate - is easily accessed from biomass and represents an important renewable building block.[95] To date, the acceptorless dehydrogenative synthesis of ethyl acetate from ethanol has been largely studied by using heterogeneous catalysts.[96] This reaction requires high temperatures (> 200 °C) and significant energy input, leading to moderate selectivity. Hence, yields up to only 56% have been achieved.

In 2012 Gusev and co-workers[93a] performed an extensive screening of various homogeneous ruthenium and osmium complexes, finding the air-stable complex **1.168** (Figure 1.5) a very active catalyst for the conversion of ethanol to ethyl acetate: 0.2 mol of refluxing ethanol was converted into ethyl acetate in 83 % conversion after 40 h, producing 17000 turnovers. The complex used can be prepared on a large scale from inexpensive and readily available starting materials. Catalyst **1.168** has unprecedented efficiency for acceptorless dehydrogenative coupling of ethanol under reflux.



1.168

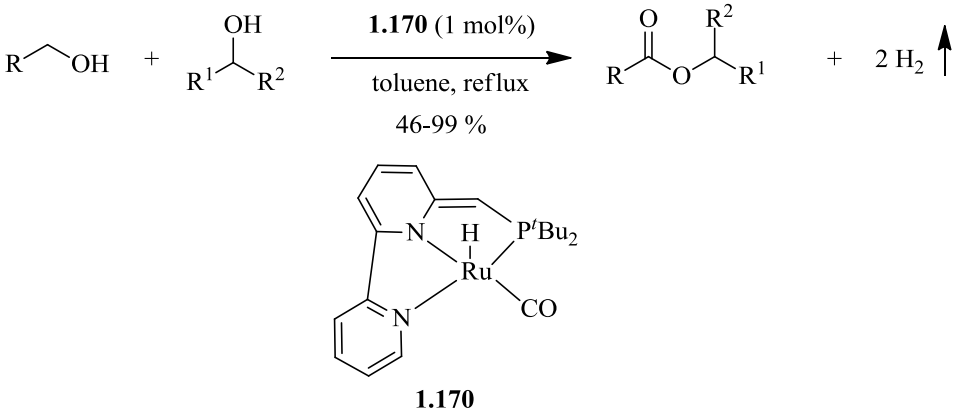


1.169

Figure 1.5
*Catalysts developed by Gusev (**1.168**) and Beller (**1.169**) for acceptorless dehydrogenative coupling of ethanol to ethyl acetate*

In 2012, Beller showed that ruthenium-based PNP pincer catalyst **1.169** efficiently catalysed the direct formation of ethyl acetate from ethanol in the presence of NaOEt as a base additive. Notably, neither solvent nor additional hydrogen acceptors are employed in this procedure. At low catalyst loading (50 ppm), high yields of ethyl acetate and excellent catalyst turnover frequencies (TOF = 1134 h^{-1}) were achieved. The authors demonstrated that the catalyst was active also at temperatures below reflux (60 °C), albeit with a lower performance.

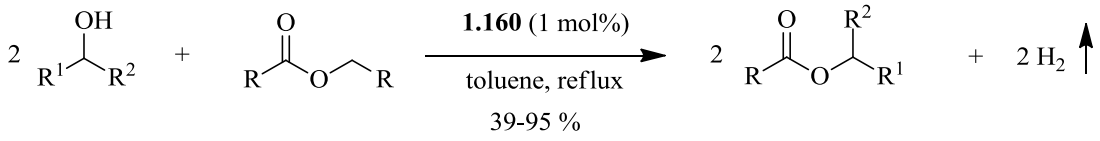
A more challenging dehydrogenative cross-coupling of primary and secondary alcohols to form mixed esters was achieved by Milstein, using the bipyridine-based dearomatised catalyst **1.170** (Scheme 1.70).[97] The synthesis of a variety of esters was achieved in high yields and good selectivites under neutral conditions (Scheme 1.70).



1.170

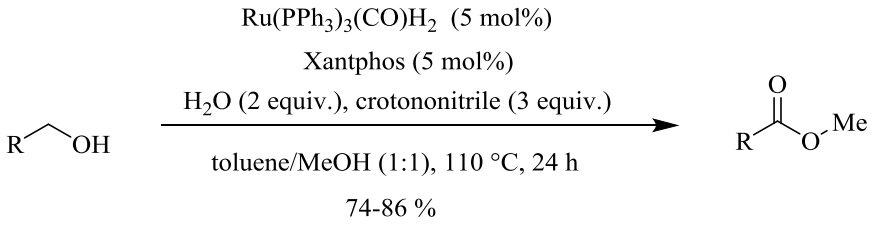
Scheme 1.70
Cross-dehydrogenative coupling of a primary and a secondary alcohols to form esters by Milstein

Milstein's group has also developed a distinct mode of transesterification, in which hydrogen gas is formed as a byproduct, rather than an alcohol as in conventional transesterifications.[98] In a reaction of symmetrical esters with 2 equivalents of secondary alcohols catalysed by complex **1.160** (Figure 1.4), both the acyl and alkoxy fragments of the substrate ester are incorporated into the product ester with liberation of hydrogen (Scheme 1.71). This cross-selectivity is a result of slower dehydrogenation of the secondary alcohol to the corresponding ketone, compared with the dehydrogenative coupling of the primary alcohol to ester.



Scheme 1.71
Transesterification with alcohols by Milstein

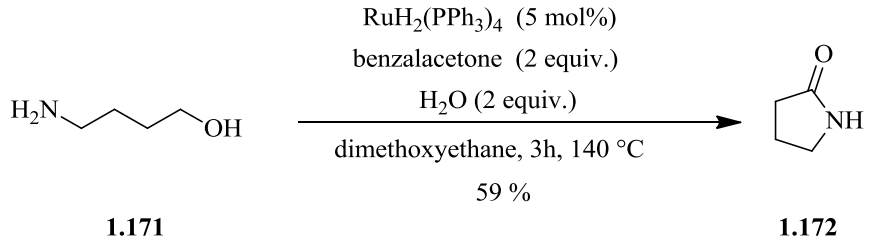
Williams and co-workers[99] described the synthesis of methyl esters from primary alcohols in the presence of methanol. $[Ru(PPh_3)_3(CO)H_2]$/Xantphos system showed a good activity in this reaction in the presence of crotononitrile as a hydrogen acceptor (Scheme 1.72).



Scheme 1.72
Oxidation of primary alcohols to methyl esters by hydrogen transfer by Williams

1.6.4 Synthesis of Amides via *Dehydrogenative Coupling of Alcohols with Amines*

Murahashi was the first to report the formation of an amide from an alcohol and an amine using $[RuH_2(PPh_3)_4]$ in the presence of a hydrogen acceptor (Scheme 1.73).[100] Five- and six-membered lactam rings were synthesised from amino alcohols in an intramolecular process. The addition of two equivalents of water to the reaction mixture was required to form the lactam product, whereas without water cyclic amines were formed.

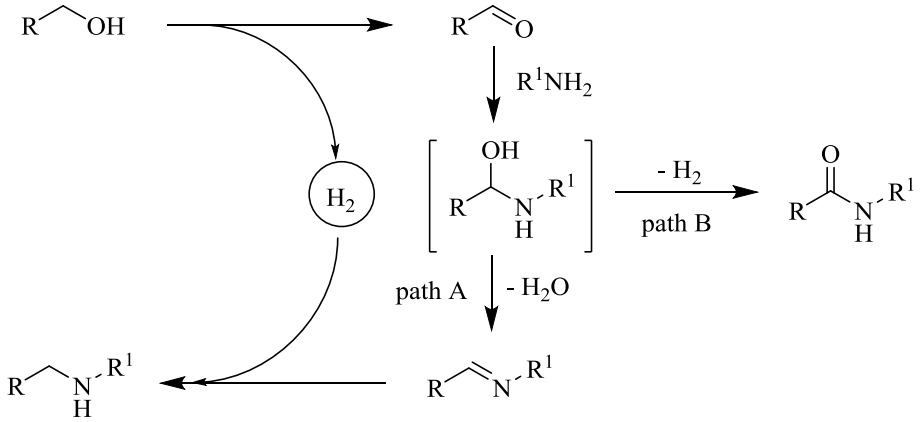


1.171 **1.172**

Scheme 1.73
Synthesis of lactames with aminoalcohols

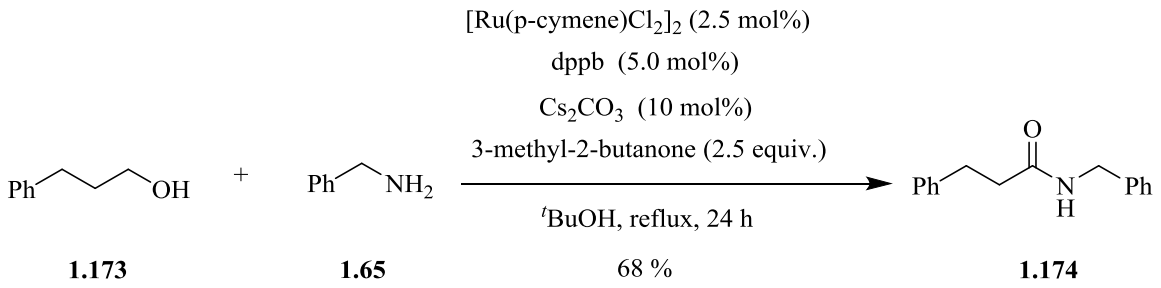
Both *N*-alkylation and amidation are thought to proceed through a hemiaminal intermediate. The presence of water is presumed to inhibit dehydration of the hemiaminal to generate the imine (Scheme 1.74 path A). Instead, the hemiaminal is irreversibly dehydrogenated, forming

an amide (Scheme 1.74 path B). It is currently unclear what properties predispose a complex for one pathway or the other.



Scheme 1.74
Mechanistic pathways towards amine (path A) and amides (path B) formation

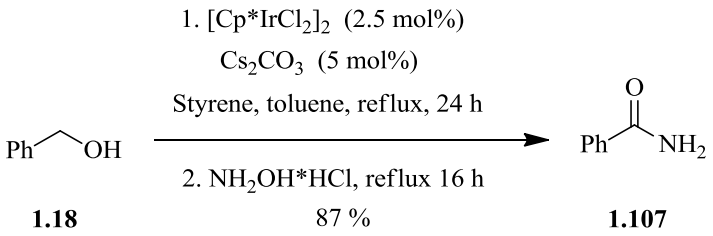
A similar approach was adopted by Williams and co-workers,[101] who reported the formation of amides from alcohols and amines in good yields using $[Ru(p\text{-cymene})Cl]_2$ in the presence of dppb and Cs_2CO_3 and a ketone as a hydrogen acceptor in refluxing *tert*-butanol (Scheme 1.75).



Scheme 1.75
Amidation of alcohols by Williams

With a related strategy Williams [102] converted alcohols into amides using hydroxylamine (Scheme 1.76). This reaction proceeds through a Beckmann rearrangement of an oxime intermediate. First, an alcohol is oxidized to the corresponding aldehyde in the presence of $[Cp^*IrCl_2]_2$ as catalyst and Cs_2CO_3 in refluxing toluene. A subsequent reaction of the aldehyde

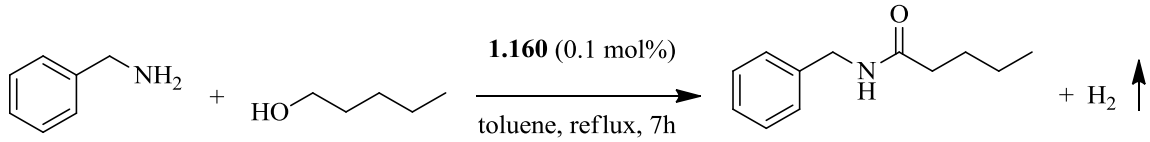
with hydroxylamine forms the oxime that then undergoes a rearrangement to the primary amide.



1.18 87 % **1.107**

Scheme 1.76
Williams approach to amides from alcohols

Milstein and co-workers[103] synthesised amides via dehydrogenatve coupling of alcohols and amines using using complex **1.160** (Figure 1.3) in the absence of a hydrogen acceptor. The same complex had previously been used also for dehydrogenative esterification of alcohols (Scheme 1.77). Hydrogen gas is evolved as the substrate is oxidised.



1.65 **1.47** 97 % **1.175**

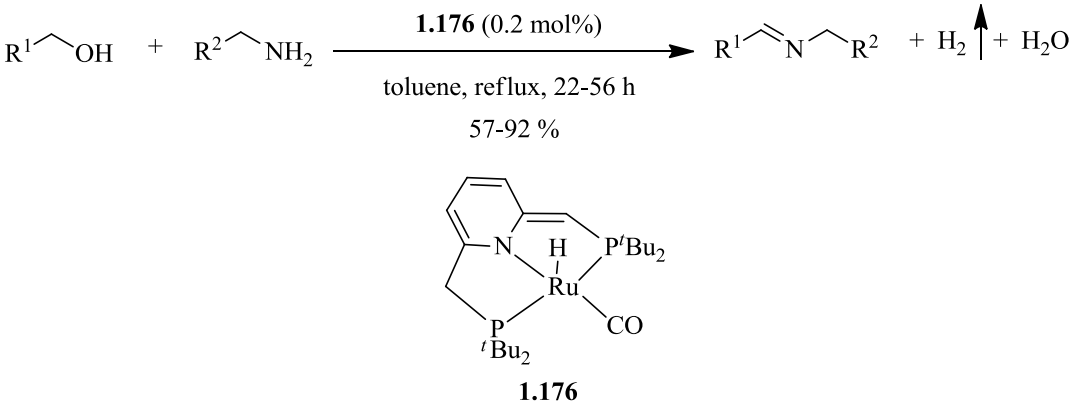
Scheme 1.77
Dehydrogenative amidation of alcohols with amines by Milstein

Aliphatic primary alcohols and primary and secondary amines were successfully used to form secondary and tertiary amides in excellent yields. The PNN-pincer ruthenium complex **1.160** employed works in the absence of a base or other catalyst activators. The authors think that the pincer ligand, which contains an unusual dearomatised ring, can alternatively aromatise and dearomatise during the catalytic cycle to facilitate the formation of hydrogen gas.

1.6.5 Combined Dehydrogenative-Dehydrative Coupling of Alcohols with Amines

In 2010 Milstein and co-workers[104] observed that RuPNP pincer complex **1.176** catalysed the dehydrogenative coupling of alcohols with amines leading preferentially to unexpectedly imine products instead of amides as previously observed using complex **1.160** (Scheme 1.78).

The catalyst was active under mild and neutral conditions and furnished the products in good yields, with formation of water and molecular hydrogen as the by-products.

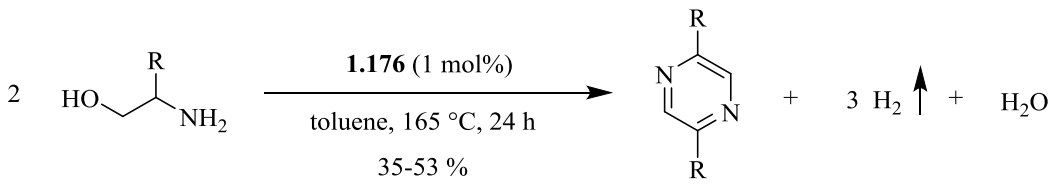


1.176

Scheme 1.78
Synthesis of imines from alcohols and amines by Milstein

A possible explanation of this observed selectivity towards imines instead of amides as in the case of complex **1.160** is that in the case of complex **1.176**, intermediate aldehyde dissociates from the metal complex, forming free hemiaminal in solution, whereas in the case of **1.160**, a coordinated aldehyde is attacked by the amine and no free hemiaminal is involved. It is believed that this difference may result from the hemilabile amine "arm" and higher steric hindrance in the complex **1.174**. As a consequence, the free hemiaminal eliminates water, providing a method for the synthesis of imines, with no subsequent hydrogenation to the corresponding amines.

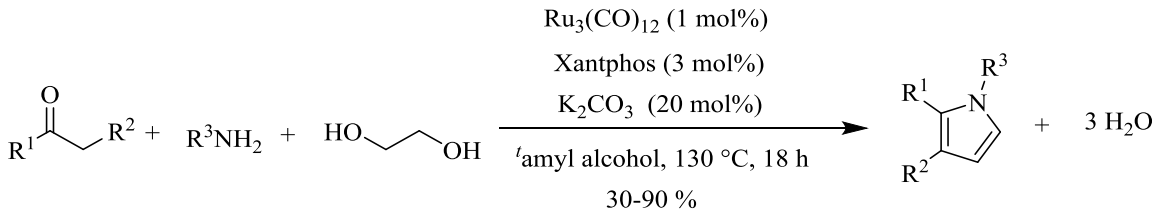
It is worth to note that this combination of dehydrogenation and dehydration has been also exploited in the synthesis of aromatic heterocycles, and very elegant methods have been developed in recent years for this important class of compounds. For example, amino alcohols were converted to pyrazines in moderate yields by Milstein who used complex **1.176** (Scheme 1.79).[105]



Scheme 1.79

Cyclisation of aminoalcohols to pyrazines by Milstein

An interesting synthetic approach to pyrroles based on alcohol dehydrogenation, imine formation and subsequent condensation was also reported by Beller and co-workers.[106] They developed a three-component synthesis using $Ru_3(CO)$ with an added diphosphine and a base for converting 1,2 diols, amines and ketones to a variety of functionalised pyrroles in good to very high yields (Scheme 1.80).



Scheme 1.80
A three component synthesis of pyrroles by Beller

1.7 Overview of the Work

Research conducted during my PhD and described in this thesis concerns the development of new environmentally friendly and atom-economic synthetic methodologies by applying hydrogen transfer strategy, focusing on the synthesis of important target molecules such as heterocycles and industrially valuable compounds.

In particular, given the high importance of heterocycles in several fields of chemistry and technology, we gave great focus on privileged structures such as indoles. A new and efficient strategy for indole synthesis *via* a ruthenium-catalysed cross-coupling of phenylhydrazines with alcohols has been developed as is described in Chapter 2 (*Organic Letters*, **2012**, *14*, 6112-6115). It is worth to note that indole skeleton is a privileged structure in drug design and discovery, and the availability of synthetic methodologies which make use of stable and readily available starting materials is highly desirable. Our method represents the first example described in the literature for indole synthesis starting from alcohols *via* a Fischer-type reaction. In a complementary work – aimed to significantly contribute to this field – we investigated the use of primary amines as pro-electrophiles in a "nature-inspired" protocol for the synthesis of indoles, using Pd/C as a heterogeneous catalyst as is described in Chapter 3 (*Advanced*

Synthesis and Catalysis, **2013**, *355*, 3002-3013).

Exploiting the know-how acquired in transfer hydrogenation strategies, we turned our attention on the synthesis of α,β-unsaturated aldehydes through a ruthenium-catalysed cross-dehydrogenative coupling between two different primary alcohols (Chapter 3), which can find potential application in the preparation of jasminaldehyde and its analogues, largely used in the fragrance industries (*Organic Letters*, **2014**, *16*, 2586-2589). We also extended this strategy to the synthesis of quinolines *via* cross-dehydrogenative coupling of alcohols and aminoarenes as described in Chapter 4 (*Advanced Synthesis and Catalysis*, DOI 10.1002/adsc.201400815).

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Chapter 2

Transition Metal Catalysed Cross-Coupling of Arylhydrazines with Alcohols and Amines: New Strategies for Indole Synthesis

2.1 Introduction

It was in 1866 when Baeyer, while studying the structure of the dye indigo, obtained a new compound that he called indole.[1] In 1869, Baeyer and Emmerling[2] proposed a correct formula for indole (Figure 2.1).

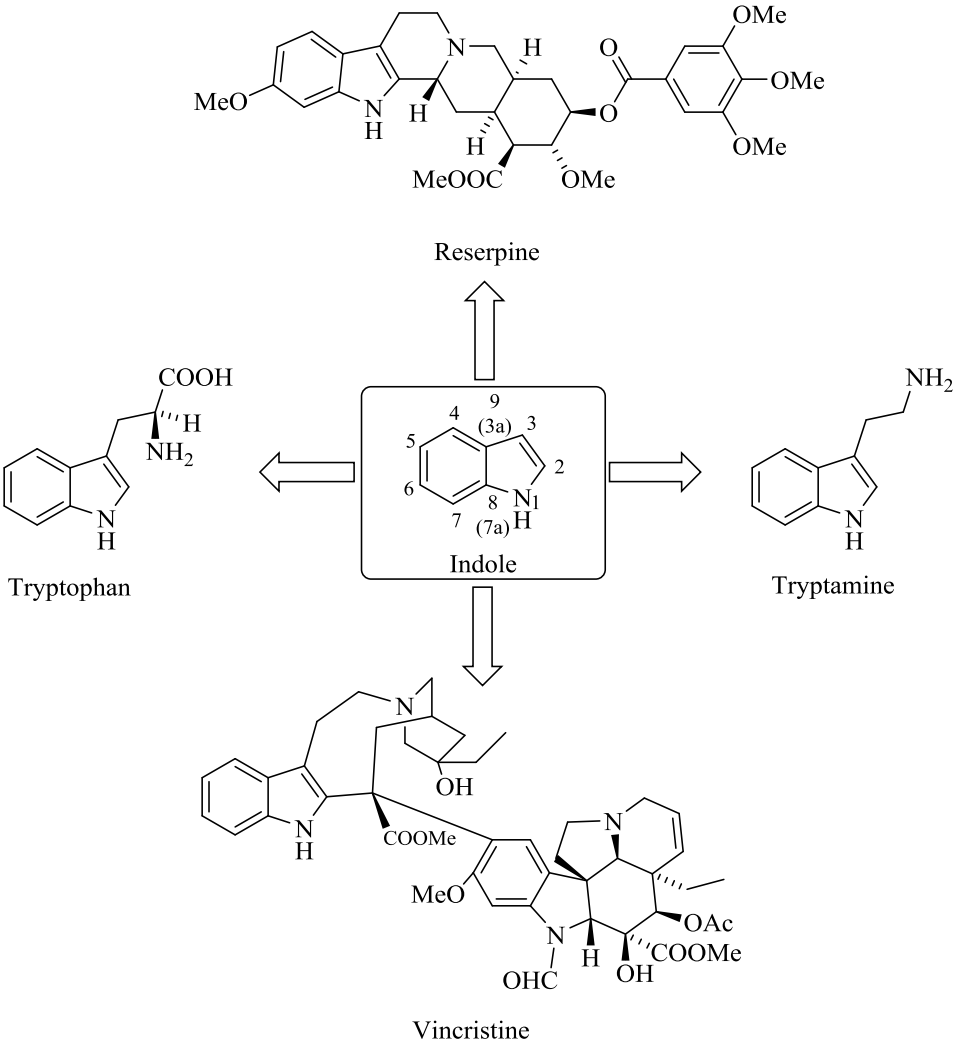


Figure 2.1
Indole ring and some naturally occurring indole derivatives

Interest in indole chemistry intensified from 1930s, when it became known that the indole nucleus is present in many important alkaloids, as well as in tryptophan and auxins. Two decades later, the alkaloid reserpine was introduced as one of the first drugs for the treatment of diseases of the central nervous system,[3] and shortly after, antitumor properties of indolyl

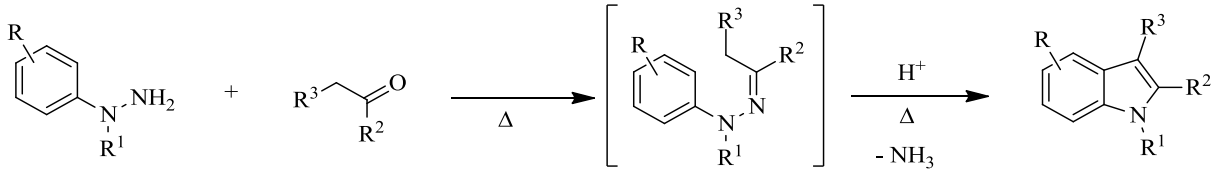
derivative vincristine were discovered.[4] Today, indole is considered a privileged structure not only for its widespread occurrence in natural compounds, but also for its ubiquitous presence as a core scaffold in pharmaceuticals, agrochemicals, and functional materials.[5]

Due to its importance, indole is now the focus of an extremely extensive and fervent research area, and continues to inspire synthetic and medicinal chemists with an increasing interest. However, there is still a strong demand for versatile, mild and efficient syntheses that permit both structural diversity and complexity. Current trends in indole synthesis focus on the development of new catalytic methods enabling the use of environmentally friendly reagents and conditions (minimisation of waste, energy saving, etc.).

2.2 Traditional Methods for Indole Synthesis

2.2.1 Fischer Indole Synthesis

This methodology was described for the first time in 1883 by Emil Fischer.[6] It is one of the oldest methods for preparing indoles, and also one of the most versatile and common approaches to this heterocycle due to its operational simplicity.[7] Indole is obtained by heating an enolisable phenylhydrazone in acidic conditions. Phenylhydrazones in turn can be prepared by reacting phenylhydrazines with enolisable aldehydes or ketones (Scheme 2.1).

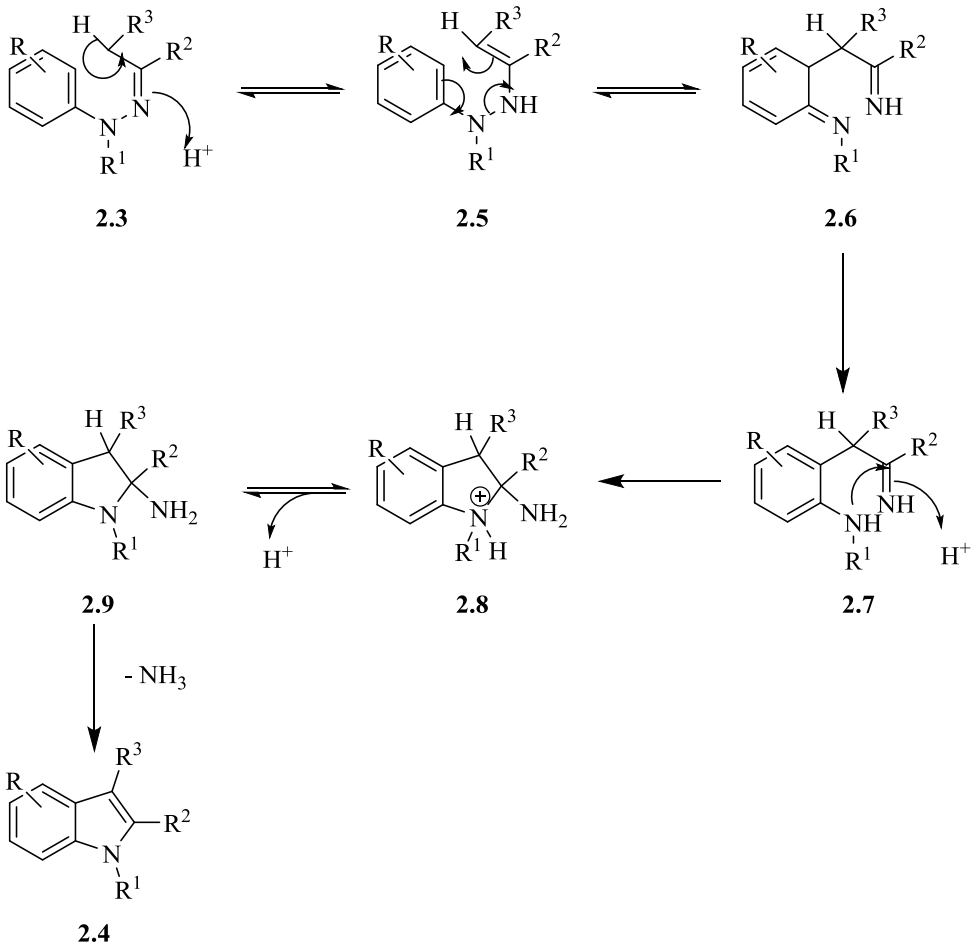


2.1 **2.2** **2.3** **2.4**

Scheme 2.1
The Fischer indole synthesis

The mechanism of this reaction is depicted in Scheme 2.2.[8] Under acidic conditions phenylhydrazone **2.3** isomerises to the respective enamine or ene-hydrazine **2.5**. After protonation, a cyclic [3,3]-sigmatropic rearrangement occurs, producing imine **2.6**. Imine **2.7** forms cyclic aminal **2.9**, which under acid catalysis eliminates NH_3, resulting in the

energetically favorable aromatic indole **2.4**. Isotopic labelling studies showed that the aryl nitrogen of the starting phenylhydrazine is incorporated into the resulting indole.[9] Tautomerisation of 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.

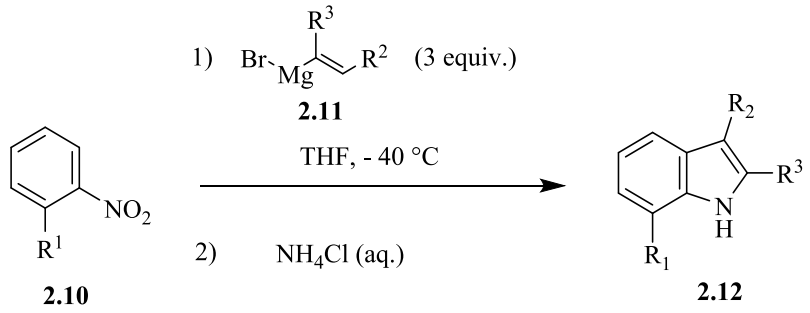


Scheme 2.2
Mechanism of Fischer cyclisation

2.2.2 Bartoli Indole Synthesis

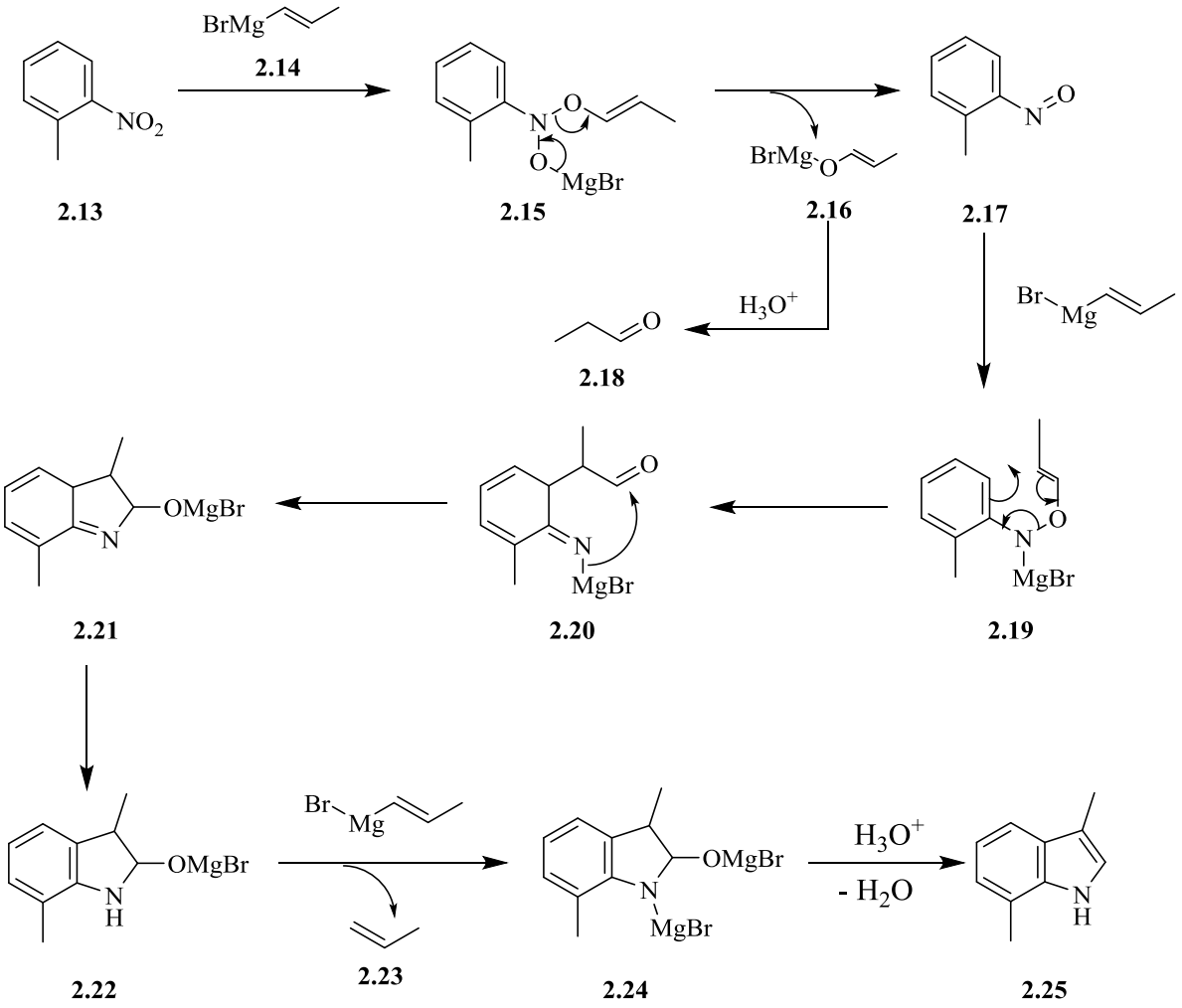
Discovered in 1989, Bartoli indole synthesis is the reaction between *ortho*-substituted nitroarenes with vinyl Grignard reagents to form substituted indoles (Scheme 2.3).[10] This method employs simple and readily available starting materials, and has rapidly become the shortest and most flexible route to 7-substituted indoles, as classical indole syntheses generally

fail in their preparation. The limiting factor of the Bartoli indole synthesis is the necessity of an *ortho*-substituent on the aromatic ring because *o*,*o*- unsubstituted nitroarenes follow a completely different pathway when reacting with vinyl Grignard reagents.



Scheme 2.3
Bartoli indole synthesis

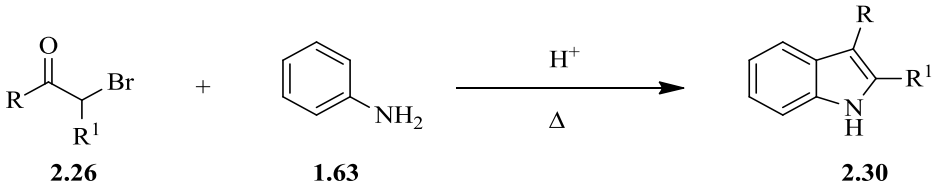
The mechanism illustrated in Scheme 2.4 refers to the reaction between *o*-nitrotoluene **2.13** and propenyl Grignard **2.14** to form 3,7-dimethylindole **2.25**. The reaction begins by the addition of the Grignard reagent **2.14** onto nitroarene **2.13** to form intermediate **2.15**, which spontaneously decomposes to form nitrosoarene **2.17** and magnesium salt **2.16**. Reaction of nitrosoarene **2.17** with a second equivalent of the Grignard reagent **2.14** forms intermediate **2.19**. The steric bulk of the *ortho* group causes a [3,3]-sigmatropic rearrangement forming the intermediate **2.20**. Cyclisation and tautomerisation give intermediate **2.22**, which will react with a third equivalent of the Grignard reagent **2.14** to give a dimagnesium indole salt **2.24**. In the final step H_2O is eliminated and indole **2.25** is formed.



Scheme 2.4
Mechanism of Bartoli indole synthesis

2.2.3 Bischler Indole Synthesis

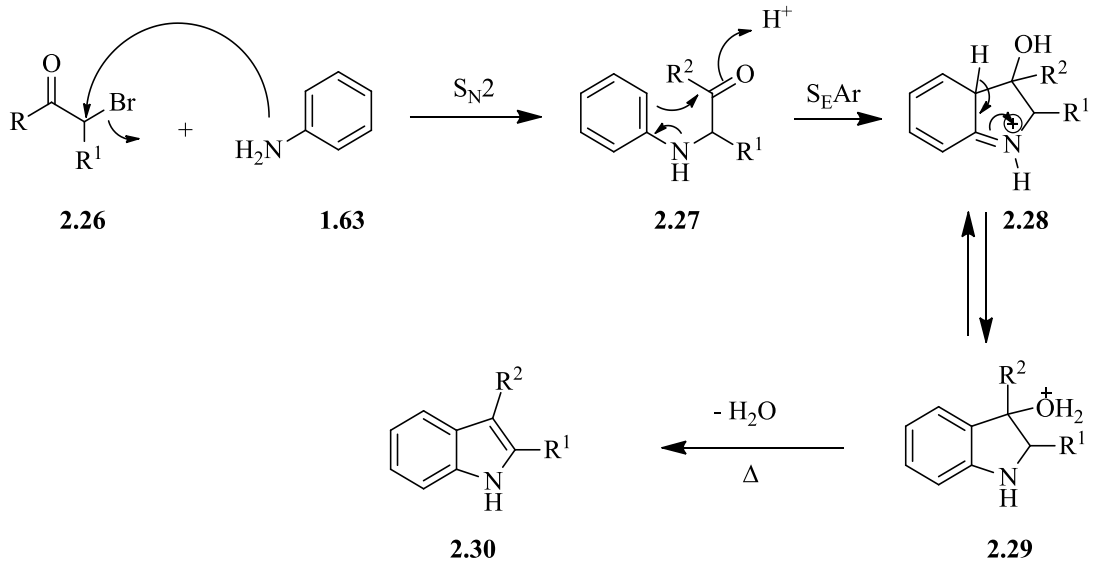
Starting materials for Bischler synthesis are α-bromo-ketones and anilines (Scheme 2.5).[11] In spite of its long history, this classical reaction has received relatively little attention in comparison with other methods for indole synthesis, perhaps owing to the harsh reaction conditions that it requires.



2.26 **1.63** **2.30**

Scheme 2.5
Bischler indole synthesis

Reaction begins with a nucleophilic substitution of aniline **1.63** with α-bromo-ketone **2.26** to form intermediate **2.27**, which under acidic conditions undergoes an aromatic electrophilic substitution to give non-aromatic intermediate **2.28** in equilibrium with **2.29**. In the final step elimination of H_2O and aromatisation give the final indole **2.30** (Scheme 2.6).



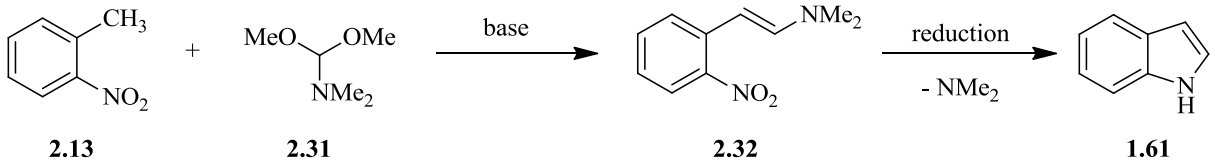
2.26 **1.63** **2.27** **2.28** **2.29** **2.30**

Scheme 2.6
Mechanism of Bischler indole synthesis

2.2.4 Leimgruber-Batcho Indole Synthesis

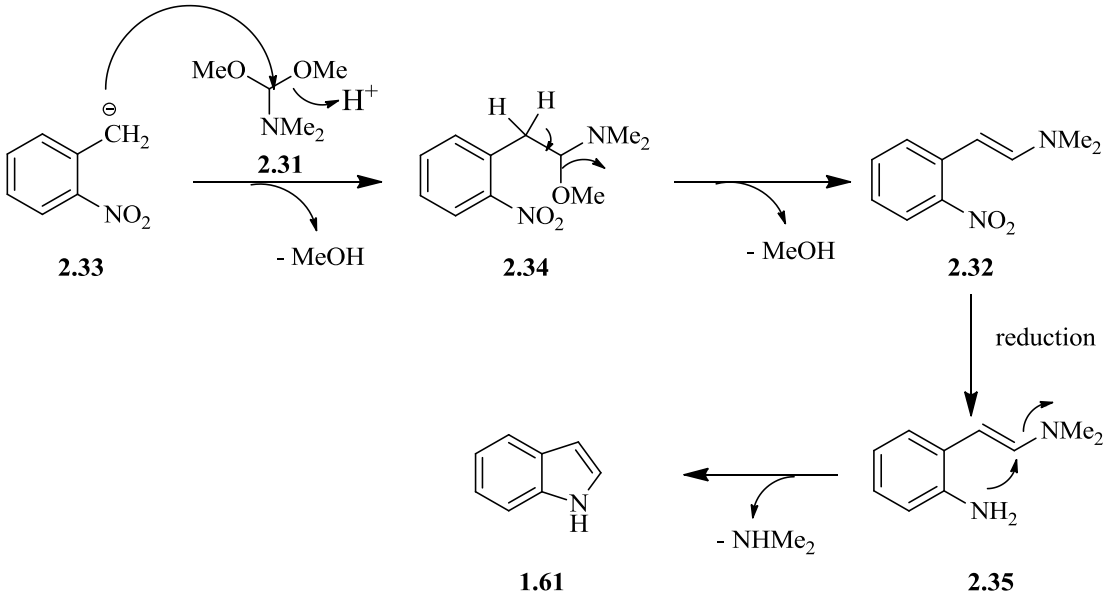
This reaction was first reported by Batcho and Leimgruber in 1971. It is a general, mild, two-step process that consists of the condensation between substituted *o*-nitrotoluene **2.13** and *N*,*N*-dimethylformamide dimethyl acetal **2.31** to give an *o*-nitrophenylacetaldehyde enamine **2.32**, and the subsequent reductive cyclisation to furnish the indole **1.61** (Scheme 2.7). A base

is required in order to generate the nucleophilic carbanione **2.33**. Various reagents have been reported to reduce the nitro group, and combination of hydrazine hydrate-Raney Nickel for the reductive cyclisation has been found to give high yield. This reaction has been applied for the synthesis of indoles with various substituents on the benzene ring.



2.13 **2.31** **2.32** **1.61**

Scheme 2.7
Leimgruber-Batcho indole synthesis

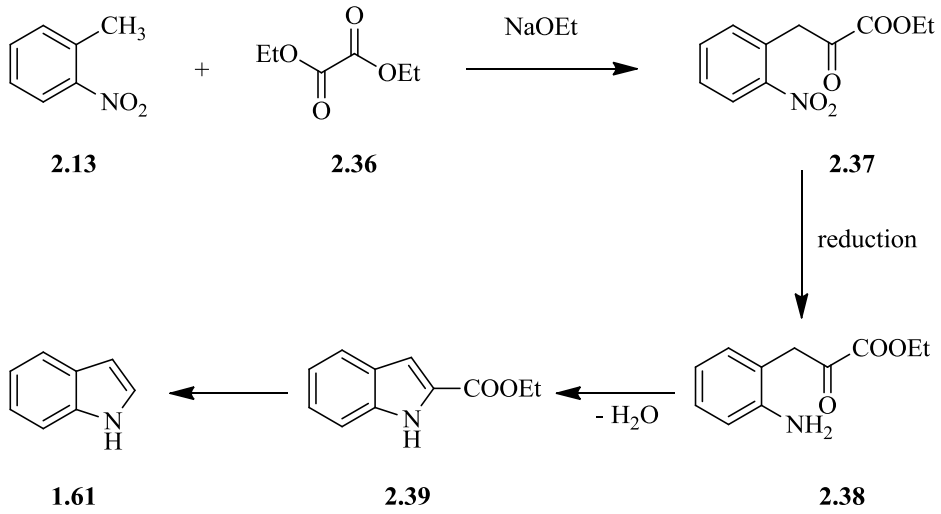


2.33 **2.34** **2.32** **1.61** **2.35**

Scheme 2.8
Mechanism of Leimgruber-Batcho synthesis

2.2.5 Reissert Indole Synthesis

Reissert indole synthesis involves a reaction between *ortho*-nitrotoluene **2.13** and diethyl oxalate **2.36**, and the subsequent reduction of nitro group followed by cyclisation-aromatisation, as illustrated in Scheme 2.9.[12]



Scheme 2.9
Reissert indole synthesis

In the first step, a base is required in order to generate a nucleophilic carbanione. The reductive cyclisation of **2.37** can be carried out with zinc in acetic acid, giving indole **2.39**. If desired, **2.39** can be decarboxylated by heating to give indole **1.61**.

2.3 Ru Catalysed Cross-Dehydrogenative Coupling of Alcohols with Arylhydrazines: a New Entry to Indole Synthesis

2.3.1 Introduction

Among the diverse approaches that have been developed for preparing indole derivatives, the Fischer synthesis is the oldest method and still today remains the most powerful and widely employed one due to its versatility and operational simplicity.[7, 13] Substrates for this reaction are *N*-aryl hydrazones that are converted into the corresponding indole via an acid-catalysed [3+3] sigmatropic rearrangement and subsequent elimination of ammonia. Since the discovery of the Fischer indole synthesis, a large number of modifications have been reported, greatly improving the original method and providing several advantages and applications. The most obvious improvements concerned the discovery of efficient catalysts to promote the cyclisation of arylhydrazones under milder conditions, and various protocols have been developed using

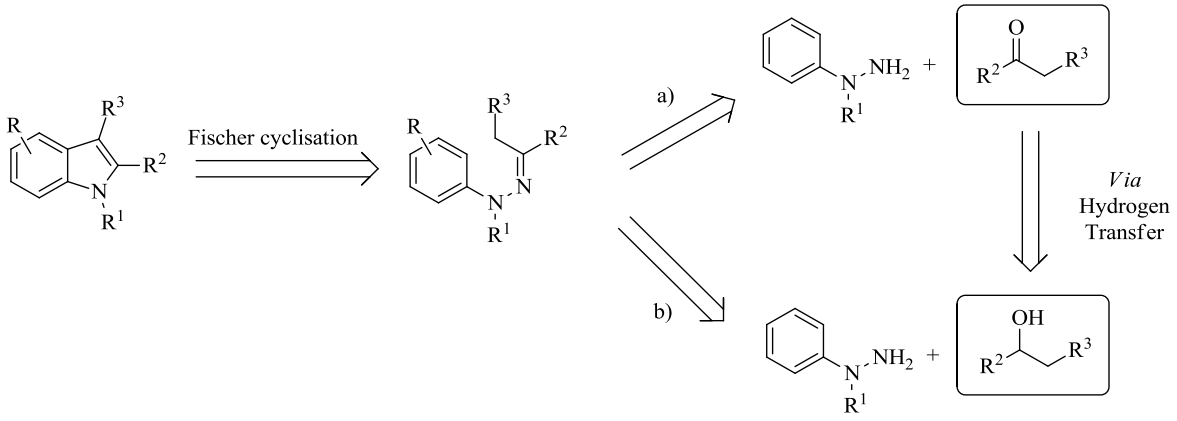
different Lewis acids,[14] Bronsted acids,[15] solid acids,[16] and acidic ionic liquids.[17]

Another subject that has been extensively studied over the years regards the development of straightforward and efficient strategies for obtaining *N*-arylhydrazone precursors. A number of methods are available,[18] the most common being the condensation of an aldehyde or a ketone with an *N*-arylhydrazine. Several drawbacks derive from the common instability and toxicity of hydrazines. In order to overcome this issue a prominent development was introduced in recent times by Buchwald[19] who used aryl halides instead of arylhydrazines to access the key *N*-arylhydrazone intermediate, which then undergoes a conventional Fischer cyclisation by a treatment with an acid. Aryl halides are inexpensive, less toxic and more readily available than arylhydrazines commonly used in the classical approach.

On the other hand, despite its versatility, the Fischer indole reaction with aldehydes constitutes a two-step procedure (hydrazone formation and cyclisation), which sometimes proceeds in a low yield. In fact, aldehydes are labile to oxidation, aldol reactions and polymerisation, and these side reactions severely limit the conversion into the final indole product.[20] Therefore, aldehydes are often protected as acetals, that are hydrolysed *in situ* during hydrazone formation.[21] Other attractive alternatives are protection of the aldehyde as a bisulfite or as an aminal.[22] In order to circumvent the limitations related to the use of aldehydes and to avoid the need of additional protection steps, Campos *et al.*[15c] proposed an elegant solution using substituted enol ethers and enol lactones as substitutes for the aldehyde component in the Fischer indole reaction. Also Beller and co-workers[23] investigated this field. They exploited the coupling of arylhydrazines with terminal alkynes to form intermediate arylhydrazones and, after cyclisation, the corresponding indoles. Alternative approaches regarded the formation of reactive aldehydes *in situ* from suitable precursors. This strategy has been described by Eilbracht *et al.*[20a] who developed a novel approach to indoles from olefins *via* a tandem hydroformylation/Fischer indole synthesis.

Despite these advancements, the development of general, practical and efficient methods for the preparation of functionalised indoles from simple and easily accessible starting materials remains an active research field, as this is a critical goal for pharmaceutical and chemical industries. During the course of our studies on transfer hydrogenation reactions and heterocycle synthesis we became intrigued by the possibility of using primary alcohols as aldehyde equivalents in the Fischer indole reaction (Scheme 2.10). In accordance with hydrogen auto-transfer principles, the indole synthesis should proceed through a domino reaction sequence.

First the alcohol is oxidised *in situ* into the corresponding aldehyde or ketone *via* a metal-promoted hydrogen transfer to a hydrogen acceptor, and subsequently the reactive aldehyde condenses with an arylhydrazine present in the reaction mixture, giving the corresponding arylhydrazones that is finally converted into an indole under appropriate acidic conditions. In this way sensitive carbonyl compounds can be generated *in situ* with high efficiency starting from alcohols. The carbonyl compounds should be present in a minimal concentration at any given time of the reaction since they are consumed as soon as they are formed. This strategy should provide a viable solution for minimising both unwanted side reactions and tedious purifications.[24] In this kind of a synthetic protocol alcohols play a dual role: they are not only a masked and stable form of aldehydes, but also cheap and widely available starting materials. With these considerations in mind we were confident that suitable conditions could be developed in order to generate the hydrazone from the aryl hydrazine and the alcohol *in situ*, and to catalyse the [3 + 3] rearrangement in the same pot. We envisaged the possibility that the same transition metal complex could promote both transformations through a dual catalysis mechanism. Alternatively, a cooperative catalysis of a transition metal complex with an acidic catalyst should be the key strategy to obtain the target indole.



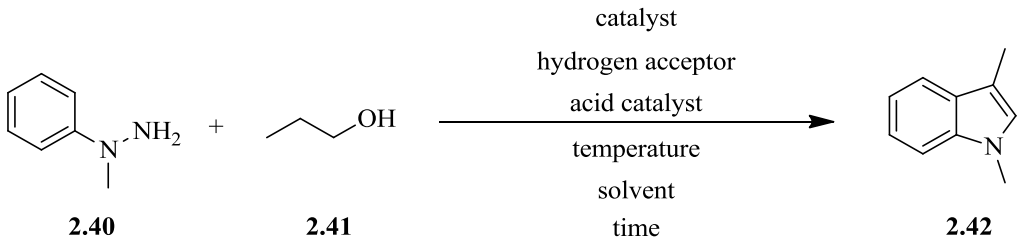
a) Classical approach to indoles

b) Hydrogen transfer based approach to indoles

Scheme 2.10
Protocol for indole synthesis from alcohols and phenylidrazines

2.3.2 Results and Discussion

We chose the reaction of *N*-methyl-*N*-phenylhydrazine **2.40** with 1-propanol **2.41** as a model transformation for optimising the reaction conditions (Scheme 2.11). In carrying out our optimisation studies, we focused our attention on several reaction parameters, including the choice of the metal catalyst, the hydrogen acceptor and the acid required for Fischer cyclisation, in addition to reaction temperature, solvent and reaction time.



Scheme 2.11
Model reaction used for procedure optimisation

Work began by examining different Pd, Rh, Ir, and Ru based complexes, which were the most successfully and widely used catalytic systems in the *N*-alkylation of amines by alcohols *via* borrowing hydrogen methodology (Table 2.1).[25] Our preliminary results showed that palladium-based catalysts were not active in this reaction. We observed negligible conversion of 1-propanol **2.41** after heating reagents in toluene at 150 °C overnight in the presence of crotononitrile as hydrogen acceptor and H_2SO_4 as acid catalyst (Table 2.1, entries 1 and 2). Using the same reaction conditions, we also tested a variety of rhodium-based complexes that showed only a moderate activity, giving the final indole product **2.42** in low yields (Table 2.1, entries 3-5). Therefore, we focused our attention on several ruthenium- and iridium-based catalysts (Table 2.1, entries 6-10). Interestingly, the reaction carried out using $[Cp^*IrCl_2]_2$ resulted in the formation of indole **2.42** in a moderately improved yield (Table 2.1, entry 6), whereas the most significant improvement was observed using ruthenium cluster $[Ru_3(CO)_{12}]$ (Table 2.1, entry 10). After our preliminary studies, $[Ru_3(CO)_{12}]$ was identified as the most active catalyst in the reaction of arylhydrazine **2.40** with alcohol **2.41**, giving 1,3-dimethyl indole **2.42** in moderate yield after heating reagents in the presence of crotononitrile and H_2SO_4 at 150° in toluene overnight (Table 1, entry 10).

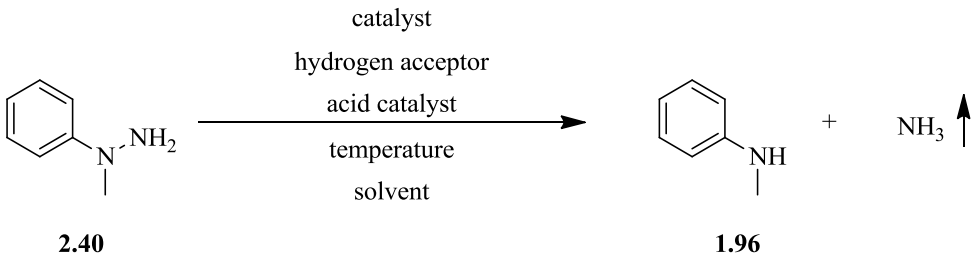
Table 2.1 *Catalyst screening for the reaction between* ***2.40*** *and* ***2.41***

Entry	Catalyst (5 mol%)	Solvent	Temperature (°C)	Acid	Yield (%)[a]
1	$Pd(PPh_3)_4$	toluene	150	H_2SO_4	-
2	$PdCl_2(PPh_3)_2$	toluene	150	H_2SO_4	-
3	$RhCl(PPh_3)_3$	toluene	150	H_2SO_4	7
4	$RhH(CO)(PPh_3)_3$	toluene	150	H_2SO_4	12
5	$Rh(acac)_3$	toluene	150	H_2SO_4	15
6	$[Cp^*IrCl_2]_2$	toluene	150	H_2SO_4	35
7	$[RuCl_2(p\text{-cymene})]_2$	toluene	150	H_2SO_4	18
8	$RuHCl(CO)(PPh_3)_3$	toluene	150	H_2SO_4	15
9	$RuCl_2(PPh_3)_3$	toluene	150	H_2SO_4	11
10	$Ru_3(CO)_{12}$	toluene	150	H_2SO_4	53

Reactions were carried out in a closed vial inserted in a preheated oil bath at the stated temperature: N-*Methyl*-N-*phenylhydrazine (1 mmol), 1-propanol (1 mmol), crotononitrile (1 mmol), catalyst (5 mol %), acid additive (1 mmol), toluene (2.5 mL), under Ar, 150 °C, overnight.* [a] *Yield of isolated pure product.*

Unfortunately, yields were limited by the N-N bond breakage of arylhydrazine **2.40**, a side-reaction leading to the formation of compound **1.96** as a main by-product (Scheme 2.12). Therefore, in order to further improve this cross-coupling of alcohols with arylhydrazines, we studied the reaction of *N*-methyl phenylhydrazine **2.40** with 1-propanol **2.41** in the presence of various phosphine ligands. The use of phosphine-based ligands has already been reported as effective strategy for improving the catalytic activity of $Ru_3(CO)_{12}$ in hydrogen transfer based amination of alcohols.[25c, d, f] Interestingly, we observed that the addition of some phosphine ligands not only greatly improved the performance of the catalyst, but also determined a different product distribution (indole *vs* aniline), depending on the particular ligand used (Table 2.2). We could observe that some phosphines favoured the N-N bond breakage, leading to a lower indole/aniline ratio (Table 2.2, entries 3 and 4). On the other hand, the reaction resulted in a higher indole/aniline ratio when phosphine ligands such as dppp, DavePhos, PCy_3 and BIPHEP were used (Table 2.2, entries 5, 7-9). BIPHEP gave us the best results, avoiding completely the formation of aniline by-product. Using $Ru_3(CO)_{12}$ (5 mol%) and BIPHEP (15

mol%), *N*-methyl-*N*-phenylhydrazine **2.40** and 1-propanol **2.41** were converted into indole **2.42** in 77 % yield (Table 2.3, entry 1).



Scheme 2.12
Degradation of N-*methy*-N-*phenylhydrazine under reaction conditions*

Table 2.2 *The influence of various phosphine ligands on the indolisation reaction*

Entry	Catalyst (5 mol%)	Phosphine (15 mol%)	Acid	Ratio[a] 2.42/1.96
1	$Ru_3(CO)_{12}$	-	H_2SO_4	5:5
2	$Ru_3(CO)_{12}$	PPh_3	H_2SO_4	5:5
3	$Ru_3(CO)_{12}$	P(*o*-Tol)$_3$	H_2SO_4	2:8
4	$Ru_3(CO)_{12}$	P[$Me_3(C_6H_2]_3$	H_2SO_4	0:10
5	$Ru_3(CO)_{12}$	dppp	H_2SO_4	6:4
6	$Ru_3(CO)_{12}$	Xantphos	H_2SO_4	5:5
7	$Ru_3(CO)_{12}$	PCy_3	H_2SO_4	9:1
8	$Ru_3(CO)_{12}$	DavePhos	H_2SO_4	8:2
9	$Ru_3(CO)_{12}$	BIPHEP	H_2SO_4	10:0

Reactions were carried out in a closed vial inserted in a preheated oil bath at the stated temperature: N-*Methyl*-N-*phenylhydrazine (1 mmol), 1-propanol (1 mmol), crotononitrile (1 mmol), catalyst (5 mol %), phosphine (15 mol%) acid (1 mmol), toluene (2.5 mL), under Ar, 150 °C, overnight.* [a]*Determined by GC/MS*

In order to minimise the catalyst loading, we performed a series of experiments lowering the amount of $Ru_3(CO)_{12}$ from 5 mol% to 1 mol% (Table 2.3, entries 1-3). We found 2 mol% of $Ru_3(CO)_{12}$ as the optimal catalyst concentration, whereas lower loadings caused a sharp drop in the final yield (Table 2.3, entry 3). Next, we studied the influence of different solvents on the

reaction outcome. We observed slightly lower yields changing the solvent from toluene to CPME or 1,4-dioxane (Table 2.3, entries 4 and 5), whereas with TAA indole yield increased up to 84 % (Table 2.3, entry 6).

Table 2.3 *Optimisation of the reaction conditions*

Entry	Catalyst (mol%)	Phosphine (mol%)	Solvent	Temp. (°C)	Acid	Yield (%)[a]
1	$Ru_3(CO)_{12}$ (5)	BIPHEP (15)	Toluene	150	H_2SO_4	77
2	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	Toluene	150	H_2SO_4	75
3	$Ru_3(CO)_{12}$ (1)	BIPHEP (3)	Toluene	150	H_2SO_4	61
4	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	CPME[b]	150	H_2SO_4	69
5	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	1,4-dioxane	150	H_2SO_4	65
6	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA[c]	150	H_2SO_4	84
7	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	150	AcOH	81
8	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	150	$ZnCl_2$	89
9	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	150	$ZnCl_2$	92[d]
10	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	130	$ZnCl_2$	93[d]
11	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	170	$ZnCl_2$	90[d]
12	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	100	$ZnCl_2$	22[d]
13	$Ru_3(CO)_{12}$ (2)	BIPHEP (6)	TAA	130	$ZnCl_2$	-[e]

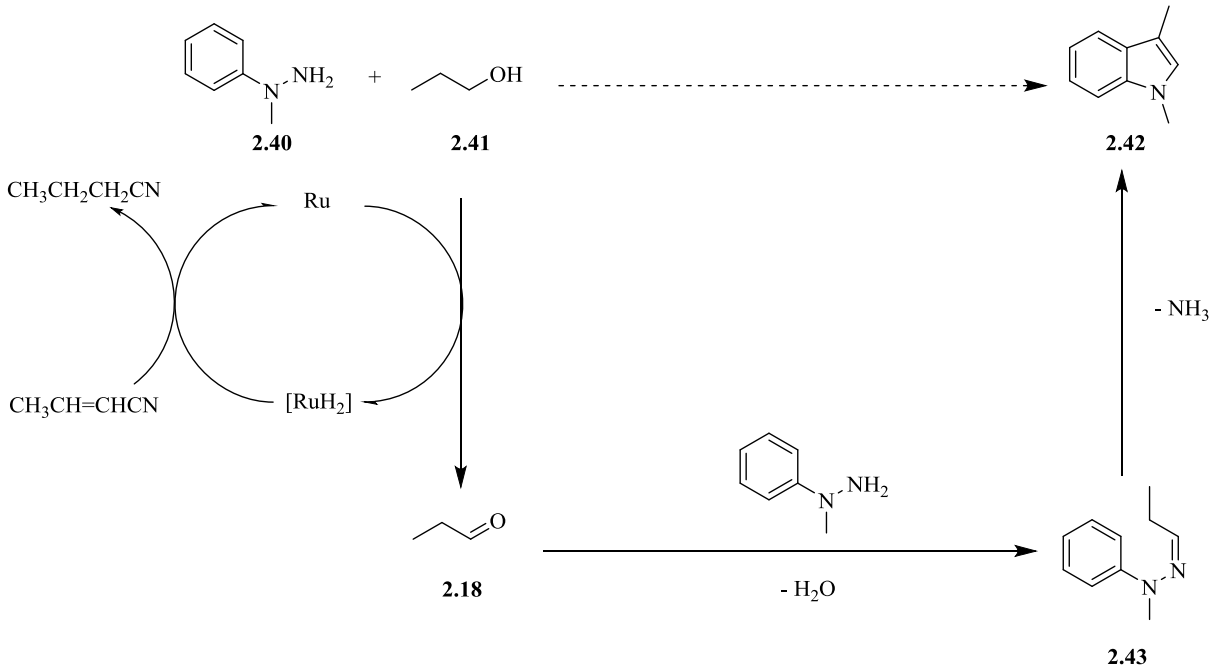
Reactions were carried out in a closed vial inserted in a preheated oil bath at the stated temperature: N-*Methyl*-N-*phenylhydrazine (1 mmol), 1-propanol (1 mmol), crotononitrile (1 mmol), acid additive (1 mmol), toluene (2.5 mL), under Ar. [a]Yield of isolated pure product. [b]CPME = cyclopentyl methyl ether. [c]TAA =* tert-*amyl alcohol (2-methyl-2-butanol). [d]Reaction performed under microwave dielectric heating for 3 h. [e]Reaction performed without hydrogen acceptor.*

To find the best conditions for promoting the Fischer cyclisation of phenylhydrazone intermediate, we turned our attention to screening several acid catalysts. Among the various acids tested (Table 2.3, entries 6-8), $ZnCl_2$ gave the final product in 89 % yield.

With a reliable method in hand, we decided to study the pilot reaction under microwave dielectric irradiation (MWI). Interestingly, we observed a complete conversion of reagents into the final product after only 3 hours with an increased yield of 92 % (Table 2.3, entry 9). The

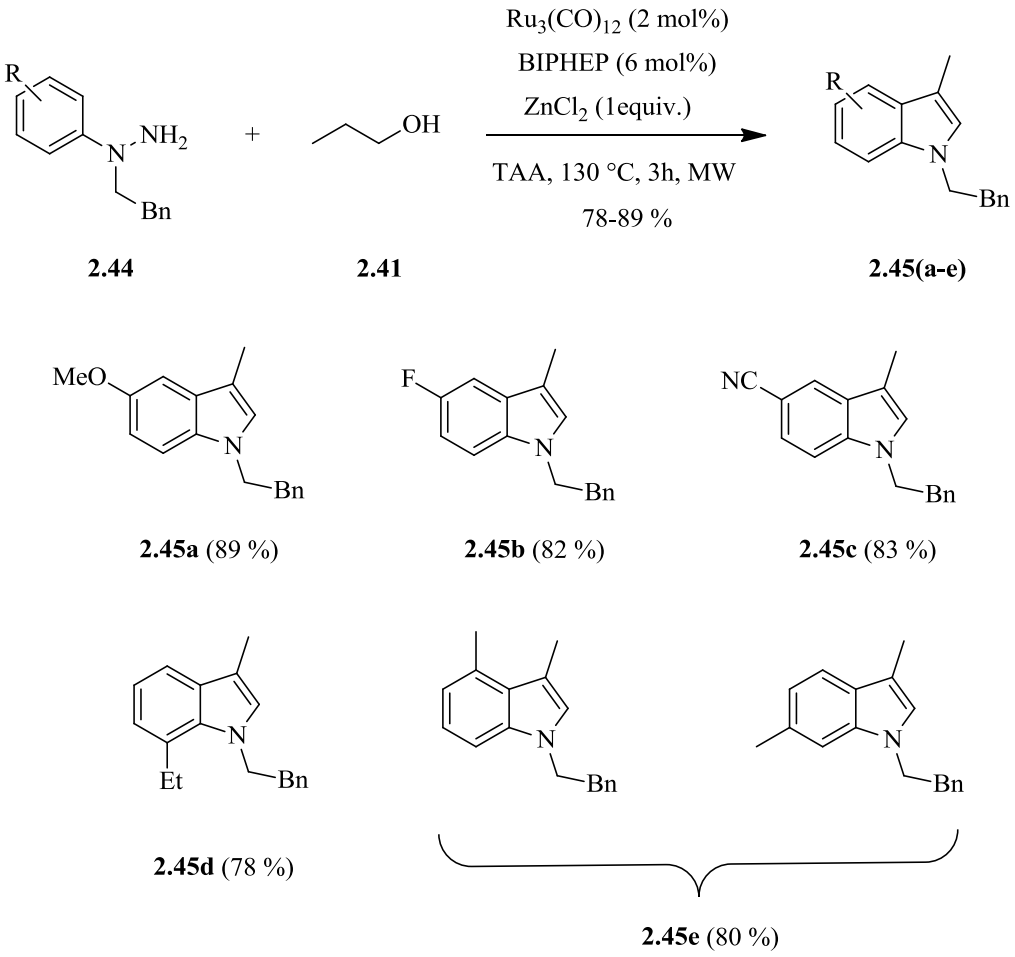
reaction temperature could also be lowered down to 130 °C without observing significant variations in indole yield (Table 2.3, entry 10). Lower temperatures resulted in a limited conversion of substrates, and therefore in very low yield (Table 2.3, entry 12). Conversely, conducting the reaction at temperatures higher than 150 °C did not lead to improvement (Table 2.3, entry 11).

At this point we reasoned on the mechanism of this transformation and on the role of the hydrogen acceptor. In principle, several olefins could be used as hydrogen scavengers. Two reasons brought us to choose crotononitrile as hydrogen acceptor: it is an activated olefin, and both the alkene and its hydrogenated product are volatile. It is important to note that we observed no conversion of substrates **2.40** and **2.41** and no formation of indole **2.42** in the absence of crotononitrile (Table 2.3, entry 13). Therefore, we hypothesised that the presence of a hydrogen acceptor (at least 1.0 equiv. respect to alcohol) was necessary for regenerating the active catalytic species (Scheme 2.13). On the basis of our experiments and previously published mechanisms,[26] we could outline a possible reaction pathway for the transformation of *N*-methyl-*N*-phenylhydrazine **2.40** and 1-propanol **2.41** into indole **2.42** in the presence of $Ru_3(CO)_{12}$, as described in Scheme 2.13. We believe that the reactions may proceed *via* an initial oxidation of alcohol **2.41** into the corresponding carbonyl compound **2.18** by formal transfer of a hydrogen molecule to crotononitrile with concomitant regeneration of the catalyst. The *in situ* generated carbonyl compound **2.18**, in the presence of arylhydrazine, is immediately converted into the corresponding hydrazone **2.43**. The subsequent acid catalysed aromatic [3 + 3] sigmatropic rearrangement gives the desired indole ring **2.42**. To verify this mechanism the hydrazone intermediate was isolated in the reaction performed without acid catalyst.



Scheme 2.13
A possible reaction mechanism

Once an efficient method for the catalytic conversion of 1-propanol **2.41** into *N*-methyl-3-methylindole **2.42** was developed, we proceeded by investigating the scope and limitations of our protocol. We extended the reaction to variously substituted arylhydrazines and a number of primary and secondary alcohols. First we studied the influence of substituents on the aromatic ring of arylhydrazine. Therefore, the reaction of 1-propanol with various commercially available aryl hydrazines was explored (Scheme 2.14). We successfully converted all tested arylhydrazines into the corresponding indoles in high yields. In general, both electron-donating and electron-withdrawing groups on the aryl ring were tolerated, without significant impact on the yield (**2.45a-e** in Scheme 2.14). As expected, a *meta* substituted phenylhydrazine led to an approximately equimolar mixture of both regioisomers **2.45e** in 80% overall yield (Scheme 2.14).



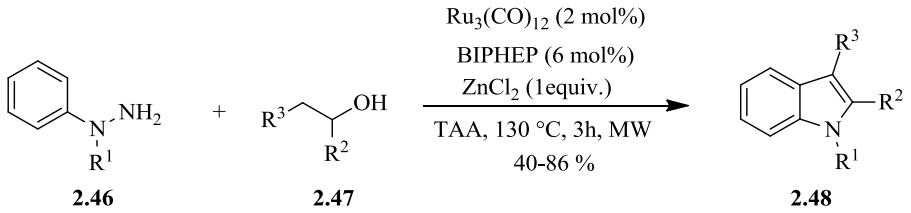
Scheme 2.14
Synthesis of indoles by reaction of differently substituted arylhydrazines with 1-propanol

Encouraged by these results, we decided to extend the reaction to different primary and secondary alcohols. Varying the alcohol substrates allowed us to obtain indoles that are differently substituted at C-2 and C-3 positions. In addition to 1-propanol, also higher aliphatic primary alcohols 1-hexanol and 1-octanol were successfully converted into indoles **2.48a** and **2.48b** in 78 % and 71 % yields, respectively. Interestingly, the presence of an aromatic or heteroaromatic ring on the aliphatic chain was well tolerated, and corresponding indoles were obtained in yields ranging from 67% to 86 % (Scheme 2.15, indoles **2.48c-g**). Although this reaction was compatible with various substituents on the nitrogen atom of arylhydrazine, yields decreased drastically when we used NH-free arylhydrazines as substrates (Scheme 2.15, indoles **2.48m-o**). This may be due to a lower stability of NH-phenylhydrazines respect to *N*-substituted ones in the reaction conditions used, since a significant formation of gaseous ammonia was

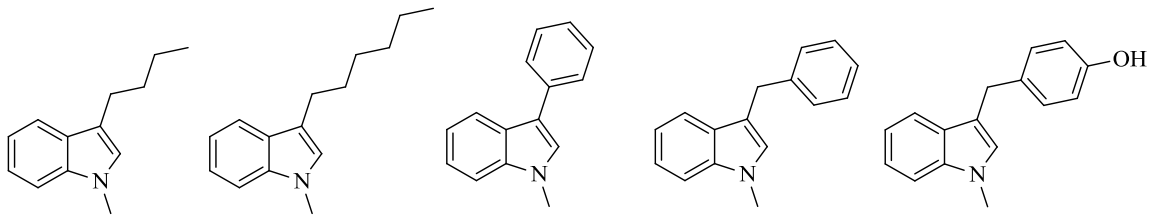
observed during the reaction.

Apart from primary alcohols, we also investigated the transformation of several secondary alcohols using the same reaction conditions. It is worth noting that also secondary alcohols, both linear and cyclic, were converted into the corresponding 2,3-disubstituted indoles in moderate to high yields (Scheme 2.15, indoles **2.48p-v**). 2-hydroxyalkanes gave exclusively the indole derived from cyclisation on the more highly substituted side of the corresponding hydrazones (Scheme 2.15, indoles **2.48p-q** and **2.48s**), whereas unsymmetrical secondary alcohol 3-heptanol led to the corresponding indole as a 65/35 mixture of two regioisomers (Scheme 2.15, indoles **2.48r**).

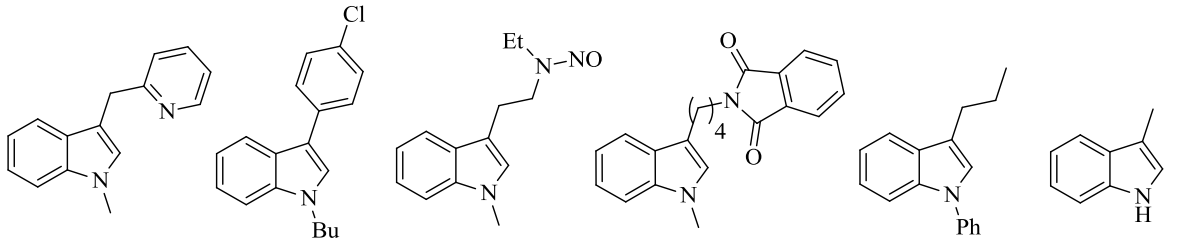
Applying this method for converting several end-chain functionalised primary and secondary alcohols allowed us to discover the true potential of this procedure. All of the functionalised alcohols we tested gave the corresponding indoles in moderate to good yields (Scheme 2.15, indoles **2.48h**, **2.48i**, **2.40u-v**).



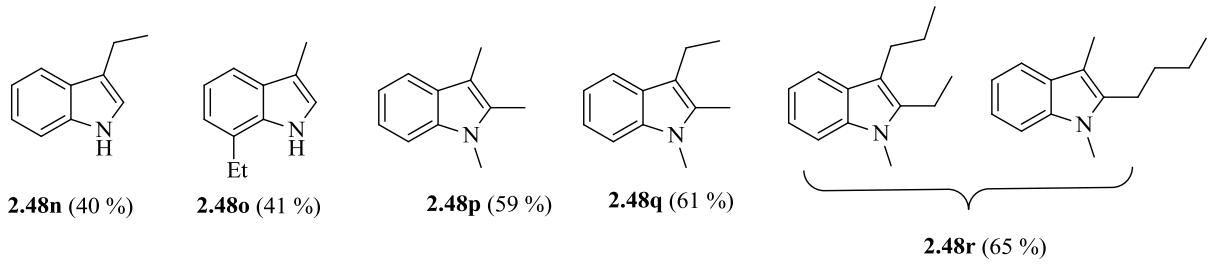
2.46 **2.47** **2.48**



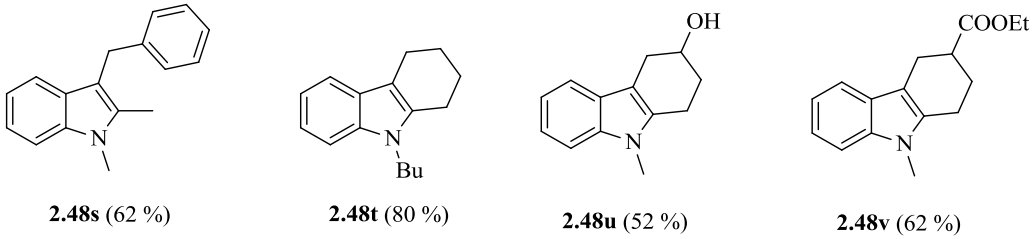
2.48a (78 %) **2.48b** (71 %) **2.48c** (76 %) **2.48d** (86 %) **2.48e** (83 %)



2.48f (67 %) **2.48g** (80 %) **2.48h** (86 %) **2.48i** (75 %) **2.48l** (73 %) **2.48m** (43 %)



2.48n (40 %) **2.48o** (41 %) **2.48p** (59 %) **2.48q** (61 %) **2.48r** (65 %)



2.48s (62 %) **2.48t** (80 %) **2.48u** (52 %) **2.48v** (62 %)

Scheme 2.15
Indole library synthesised through reaction of arylhydrazines with alcohols

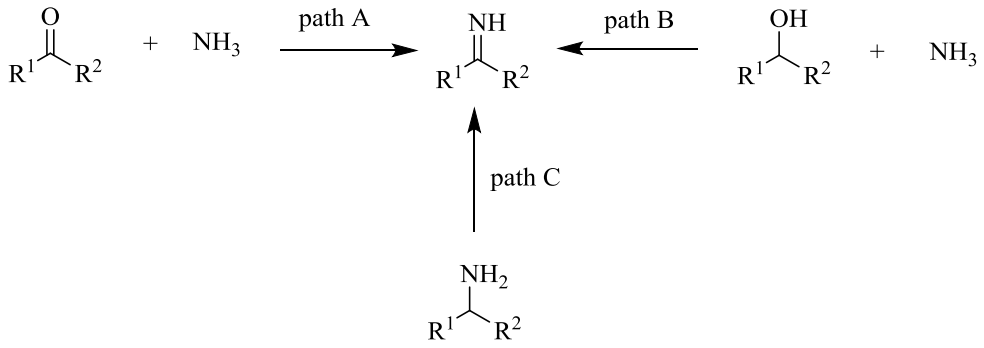
2.3.3 Conclusions

We have developed an efficient alternative to the classical Fischer indole synthesis that provides a straightforward and fast method for obtaining functionalised indoles in good to excellent yields starting from alcohols instead of aldehydes, and by using hydrogen transfer as activation strategy. Given the low cost and wide variety of commercially available alcohols, their use as starting materials in indole synthesis is highly attractive. In addition, alcohols are more stable than aldehydes, easy to handle and can be stored for a longer time. The possibility to easily introduce on the indole ring additional functional groups is a prominent advantage of this method because it provides access to valuable structures, that in turn can be subsequently modified in order to increase the molecular diversity around the indole core. The compatibility of microwave irradiation with the used catalytic system allowed to significantly increases the reaction rates, while also enhancing the final indole yields.

2.4 *Pd/C-Catalysed Dehydrogenative Generation of Imines from Amines. Application to Indole Synthesis* Via *Cross-Dehydrogenative Coupling of Amines with Arylhydrazines*

2.4.1 Introduction

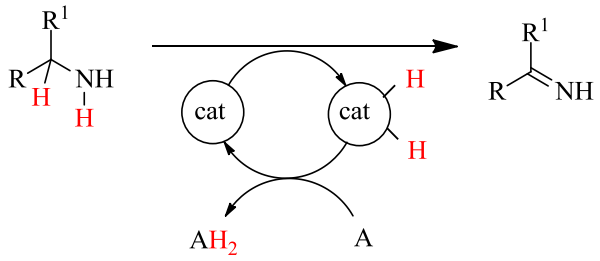
Imines are key intermediates in the elaboration of different functional groups in organic chemistry, as well as major building blocks in the construction of nitrogen-containing molecules.[12, 27] The imine group itself is also present in many natural and pharmaceutically relevant molecules with activity across diverse biological targets.[28] 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 (Scheme 2.16 path A).[29] Imines can also be prepared by a temporary oxidation of alcohols to aldehydes or ketones in the presence of amines *via* a dehydrogenative process (Scheme 2.16 path B).[30] However, the most direct approach to imines is amine dehydrogenation, that transforms primary (and secondary) amines into the corresponding imines (Scheme 2.16, path C).[31] Although common in nature, this process has been rarely applied in organic synthesis.



Scheme 2.16
Different strategies for preparing imines

In the early 80's, Murahashi[32] pioneered imine formation by amine dehydrogenation with Pd black. Lately, the interest was focused on secondary and tertiary amine oxidation under homogeneous catalysis using ligand stabilised Ru, Rh and Ir complexes in alkylation of arylamines with aliphatic ones.[33] More recently, Porcheddu *et al*.[33e, 34] reported a dehydrogenative method for using amines in alkylation of anilines and benzimidazole synthesis under hydrogen transfer conditions.

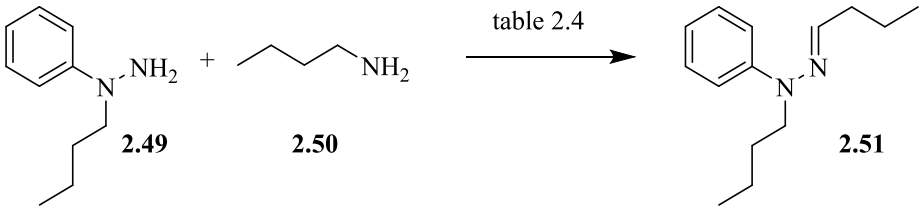
We wanted to evaluate the possibility of using imines generated *in situ* from amines as intermediates in the synthesis of indoles. In theory, imines can act as electrophilic coupling partners in the reaction with phenylhydrazines to give phenylhydrazones. This should allow us to develop a new and efficient approach to the construction of indole skeleton using readily available and stable amines as starting materials. As outlined before, the most attractive route to convert 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 2.17).



Scheme 2.17
Metal catalysed dehydrogenation of an amine to imine (A = Acceptor)

2.4.2 Results and Discussion

We began our investigation studying the reaction between butylamine **2.50** and 1-butyl-1-phenylhydrazine **2.49** in the presence of different catalysts and crotononitrile as hydrogen acceptor (Scheme 2.18).



Scheme 2.18
The pilot reaction for optimisation of the reaction conditions

First, we carried out an extensive screening of various catalytic systems, performing reactions in toluene at 170 °C for 12 h (Table 2.4). We observed no reaction using most ruthenium complexes (Table 2.4, entries 1-6), apart from Shvo catalyst, which provided phenylhydrazone **2.51** in low yield (Table 2.4, entry 7). On the contrary, palladium- and iridium-based catalysts showed good catalytic activity under the same reaction conditions (Table 2.4, entries 8-14). In particular, we observed the best results in terms of yield and purity using palladium, which was preferred to iridium owing to its higher stability and relatively low cost. Among several palladium catalysts tested, Pd/C (10% wt, 5 % mol) was found to be the best for this reaction (Table 2.4 entry 14), along with $Pd(OH)_2$ and palladium black (Table 2.4, entries 12 and 13). Further optimisation studies focused on catalyst loading, reagent ratio,

reaction temperature and solvent. Interestingly, increasing catalyst concentration shortened reaction times significantly without influencing the yields (Table 2.5 entry 2), whereas lower catalyst loading than 5 mol% led to lower reaction yields (Table 2.5 entry 1).

Subsequently, we studied the effect of variation of reagent ratio on the final yield (Table 2.5 entries 3-5). Unfortunately, lowering arylhydrazine/amine ratio resulted in a significant decrease of the final yield, and dibutylamine derived from homocoupling of butylamine was observed as the major by-product. We reasoned that excess hydrazine was required in order to suppress the homocoupling of amine, allowing an almost quantitative conversion of amine into arylhydrazone.

Table 2.4 *Catalyst screening for the cross-dehydrogenative coupling of* ***2.49*** *with* ***2.50***

Entry	Catalyst (mol%)	Ratio 2.50/2.49	Solvent	Temp. (°C)	Yield (%)[a]
1	$Ru_3(CO)_{12}$ (5)	1/3	Toluene	170	-
2	$RuCl_3$ (5)	1/3	Toluene	170	-
3	$RuCl_2(PPh_3)_3$ (5)	1/3	Toluene	170	-
4	$[Ru(p\text{-}cymene)Cl_2]_2$ (5)	1/3	Toluene	170	-
5	$RuH_2(PPh_3)_4$ (5)	1/3	Toluene	170	-
6	Ru/C (5)	1/3	Toluene	170	-
7	Shvo (5)	1/3	Toluene	170	41
8	$[Cp^*IrCl_2]_2$ (5)	1/3	Toluene	170	57
9	$Pd(PPh_3)_4$ (5)	1/3	Toluene	170	21
10	$Pd(OAc)_2$ (5)	1/3	Toluene	170	85
11	Pd NPc (5)	1/3	Toluene	170	39
12	Pd black (5)	1/3	Toluene	170	95
13	$Pd(OH)_2/C$ (5)	1/3	Toluene	170	96
14	Pd/C (5)	1/3	Toluene	170	98

Reactions were carried out in a closed vial inserted in a preheated oil bath 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.*

We also performed a solvent screening. Toluene gave the best results, whereas with more polar solvents, such as water or *tert*-amyl alcohol, yields decreased (Table 2.4, entries 6-8). It is worth noting that the reaction could also be conducted without solvent (neat), giving in a remarkably high yield (90 %, Table 2.4, entry 9).

Table 2.4 *Optimisation of reaction conditions for the cross-dehydrogenative coupling of* ***2.49*** *with* ***2.50***

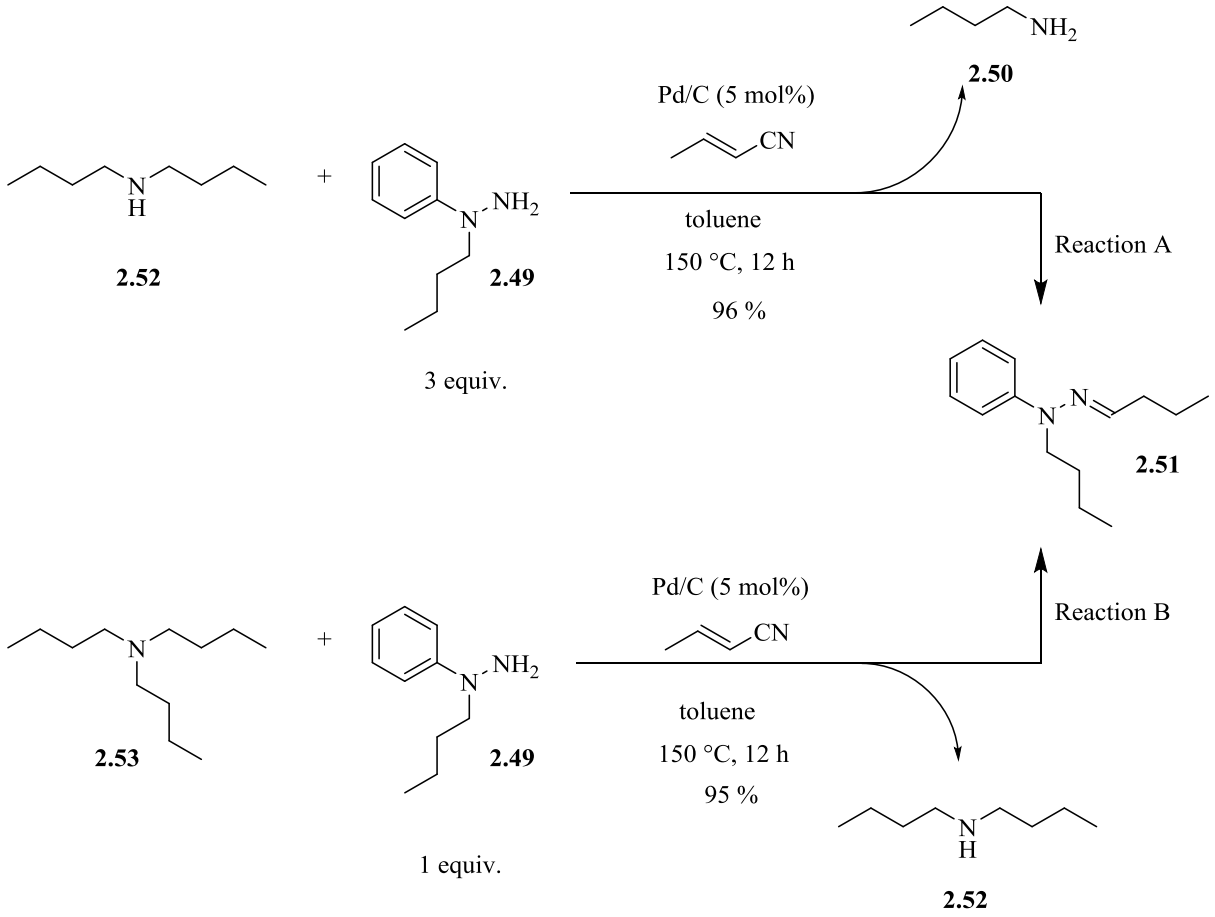
Entry	Catalyst (mol%)	Ratio 2.50/2.49	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	Pd/C (2)	1/3	Toluene	170	12	78
2	Pd/C (50)	1/3	Toluene	170	3	91
3	Pd/C (5)	1/2	Toluene	170	12	78
4	Pd/C (5)	1/1	Toluene	170	12	45
5	Pd/C (5)	2/1	Toluene	170	12	35
6	Pd/C (5)	1/3	H_2O	170	12	70
7	Pd/C (5)	1/3	TAA[b]	170	12	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 closed vial inserted in a preheated oil bath 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.*

Finally, the influence of the reaction temperature was investigated. We observed that temperature could be lowered down to 150 °C without affecting the conversion or yield (Table 2.4 entry 12). Unfortunately, the temperature could not be lowered further because at 130 °C the formation of the hydrazone was significantly reduced (Table 2.4, entries 11-12).

With optimisation of the procedure completed, we wanted to see whether the reaction could also be performed with secondary and tertiary amines. Therefore, we studied the reaction of 1-butyl-1-phenylhydrazine **2.49** with tributylamine **2.53** and dibutylamine **2.52** (Scheme 2.19).

Interestingly, using dibutylamine instead of butylamine, the formation of hydrazone **2.51** was achieved under the same reaction conditions (Scheme 2.19, Reaction A). It is worth noting that, when tributylamine was employed as the starting reagent, only one equivalent of hydrazine was required to get complete conversion of hydrazine (Scheme 2.19, 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.

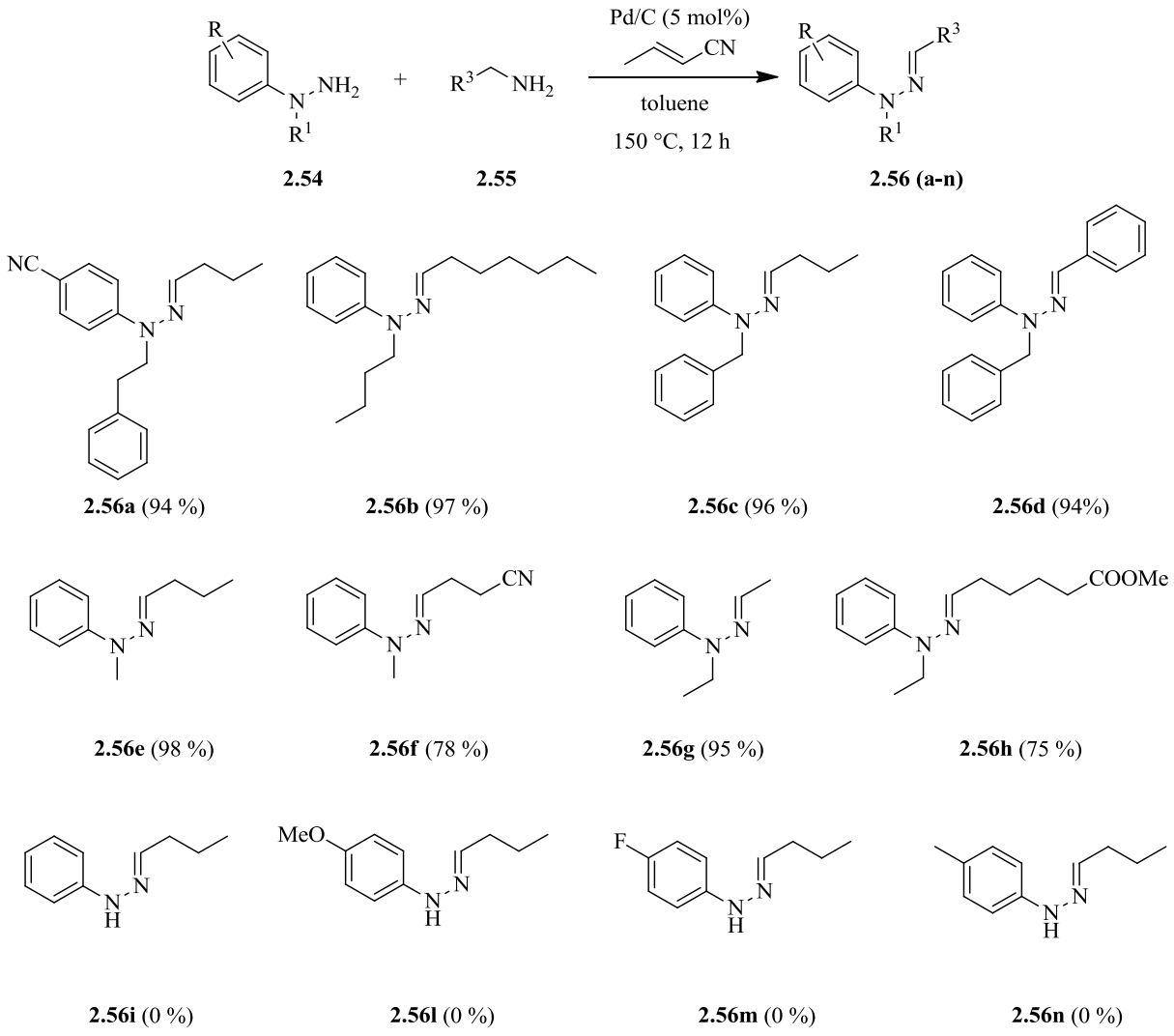


Scheme 2.19
*Synthesis of phenylhydrazone **2.51** using dibutylamine **2.52** and tributylamine **2.53***

Although the overall atom economy of the process based on the tertiary amine is comparable with the reaction with primary amines (one molecule of secondary amine *vs* two molecules of hydrazine lost), we decided to investigate primary amines as cross-coupling partners further, due to their larger availability.

We tested the scope of our method by applying the optimised procedure to other amines

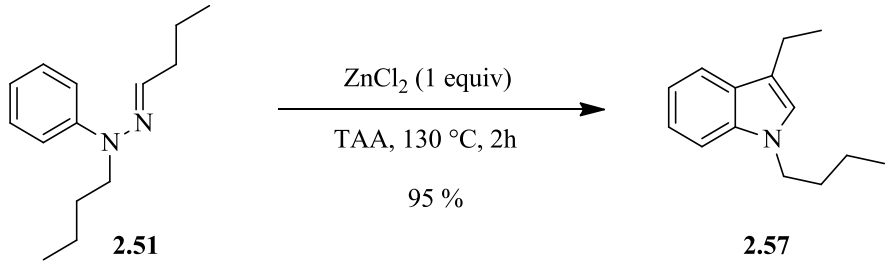
and 1-alkyl-1-arylhydrazines, observing that the corresponding arylhydrazones were obtained in very high yields (Scheme 2.20, products **2.56a-h**). Unfortunately, the use of NH-phenylhydrazines in this reaction was not possible due to a rapid decomposition of substrate with formation of aryldiazene (ArN=NH) and further loss of nitrogen, and formation of by-products (Scheme 2.20, products **2.56i-n**).[35]



Scheme 2.20
Synthesis of arylhydrazones from amines and phenylhydrazines

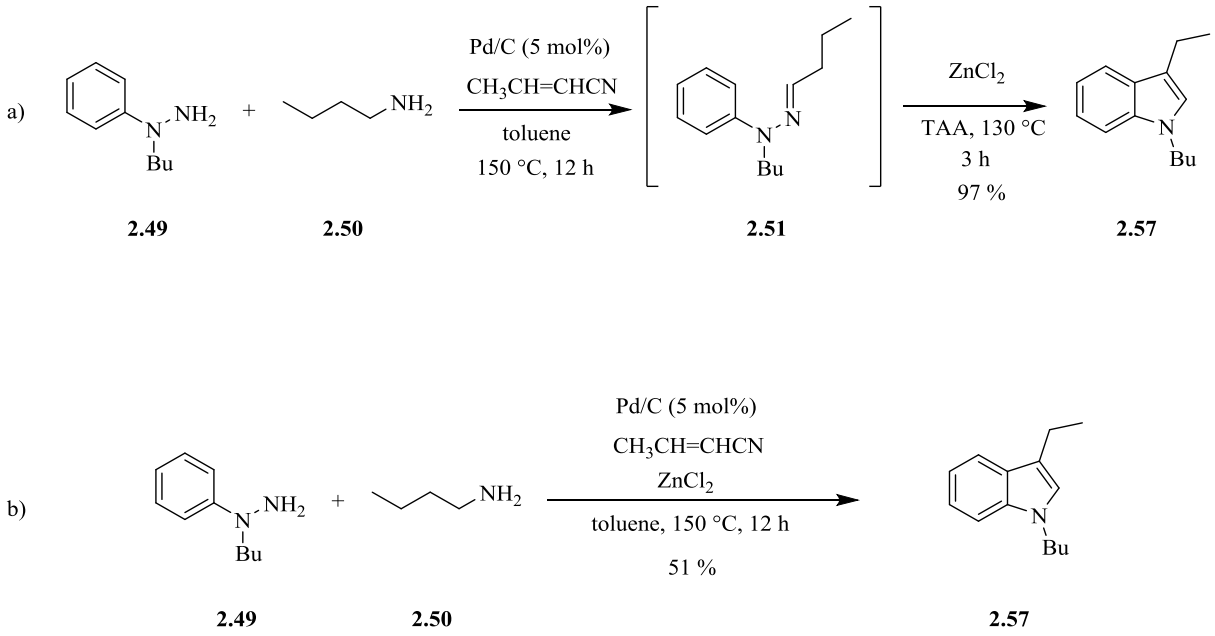
We decided to explore the possibility of combining the preparation of phenylhydrazones from amines with an additional transformation to access more complex molecules. Focusing our interest on indoles, we attempted a novel synthesis of these herocycles exploiting the

Fischer methodology because of its fascinating combination of wide versatility and experimental simplicity.[36] We treated the previously prepared 1-buty-1-phenylhydrazone **2.51** under acidic conditions for promoting a [3,3]-sigmatropic cyclisation. Using 1 equivalent of $ZnCl_2$ in 2-methyl-2-butanol (*tert*-amyl alcohol) at 130 °C for 2 h, the corresponding 1-butyl-3-ethyl-1*H*-indole **2.57** was obtained in 95 % yield (Scheme 2.21).



Scheme 2.21
Cyclisation of arylhydrazone to indole under acidic conditions

Subsequently, we tried to prepare indole **2.57** through a one-pot two-step procedure, involving first a Pd/C catalysed synthesis of arylhydrazone **2.51** and then a Fischer cyclisation to obtain the desired product **2.57**. After the first step, Pd/C could be easily removed by filtration, and phenylhydrazone **2.51** was directly subjected to Fischer-indolisation reaction by addition of the acid catalyst, which triggers the 3,3-sigmatropic rearrangement. We were pleased to see that this two-step procedure gave indole **2.57** in very high yield (Scheme 2.22a). Not yet satisfied, we have also investigated the possibility of performing both transformations in one step by adding $ZnCl_2$ in the first step (Scheme 2.22b). Unfortunately, using this direct approach we obtained indole **3** in only 51% yield. It is important to note that control experiments confirmed that no reaction took place in the absence of Pd/C, and no cyclisation of hydrazone without $ZnCl_2$.

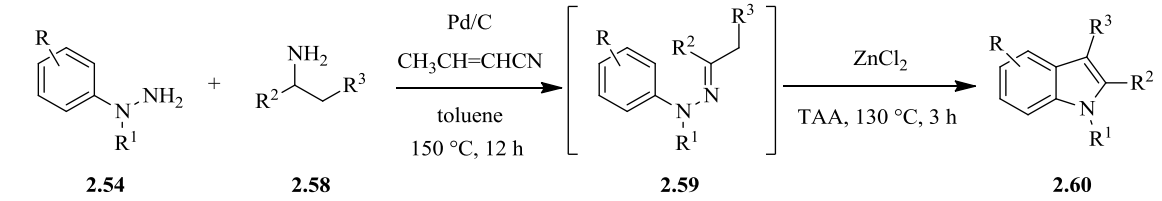


Scheme 2.22
*Synthesis of indole **2.57** through an one-pot two-step procedure (a), and one-step procedure (b)*

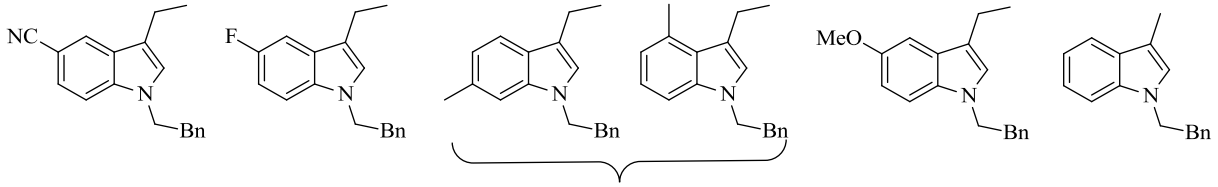
Therefore, we decided to attempt the synthesis of a small library of indoles using the two-step protocol. The results obtained are summarised in Scheme 2.23. In most cases, the 3,3-sigmatropic rearrangement was complete in less than 3 hours. A wide variety of both electron-withdrawing and electron-donating substituents on the aryl moiety were well tolerated, suggesting that electronic effects did not hamper the reaction progress (Scheme 2.23, indoles **2.60a-d**). With a *meta*-substituted phenylhydrazine, a mixture of the corresponding 4- and 6-substituted indole was obtained, as expected (Scheme 2.23, indoles **2.60c**). We explored this unusual amine based Fischer indolisation process by combining a set of commercially available phenylhydrazines with an array of different amines. As reported in Scheme 2.23, the developed reaction showed a wide scope across a range of structurally varied amines, providing the corresponding indoles in good to excellent yields (Scheme 2.23, compounds **2.60m-z**). Long-chain aliphatic amines were suitable substrates (Scheme 2.23, compounds **2.60m),** as well as amines bearing both an aromatic and an aliphatic ring (Scheme 2.23, compounds **2.60n-p** and **2.48t**). Particularly noteworthy is the fact that cross-coupling between tryptamine and 1-butyl-1-phenylhydrazine occurred under standard conditions, allowing the preparation of an interesting unsymmetrical 3,3'-bis-indole **2.60p** (Scheme 2.23), 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 **2.60q** and **2.60r** in good yields as single regioisomers. This protocol proved to be also compatible with the presence, on the amine skeleton, of several different functional groups, such as -OH, -OMe, -CO_2Me, affording compounds **2.60s-z** in 65–86 % yield. These additional functional groups provide further opportunities for subsequent chemical manipulations to increase the molecular diversity and complexity on the indole ring.

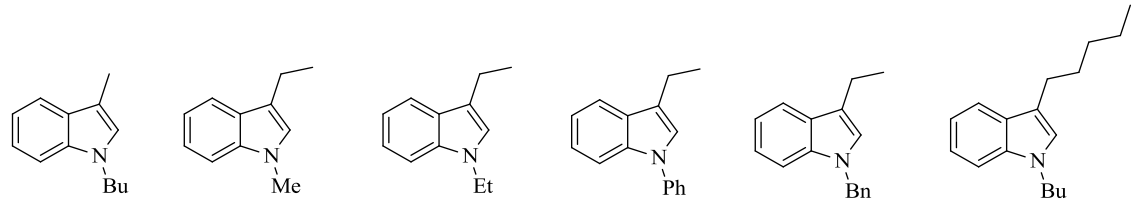
Although this procedure is generally applicable, the only concern regards the possibility to obtain indoles with a free NH group, that seemed inaccessible by this route. Classical NH protecting groups (Cbz, Boc, Ac, etc) described for arylhydrazines in the literature have been found incompatible with the reaction conditions.[37] However, when 1-benzyl-1-phenylhydrazine was reacted with propyl amine, butylamine or phenethylamine, the corresponding 1-benzyl indoles were obtained in good yields (> 80 %). The indoles with a free NH group (Scheme 7, indoles **2.48m**, **2.48n** and **2.71**) were then easily obtained in good yields by debenzylation,[38] *via* treatment with ^{t}BuOK/DMSO and oxygen at room temperature for 20 min. Since *N*-1-benzyl-1-phenylhydrazine **2.61** is cheap and commercially available, the *N*-debenzylation step fit very well in our synthetic protocol without additional changes to the initial procedure (Scheme 2.24).



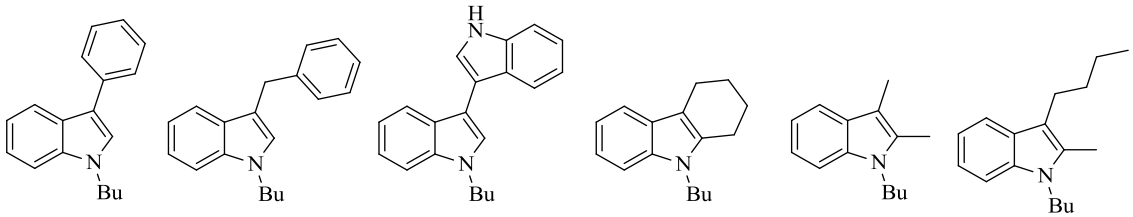
2.54 **2.58** **2.59** **2.60**



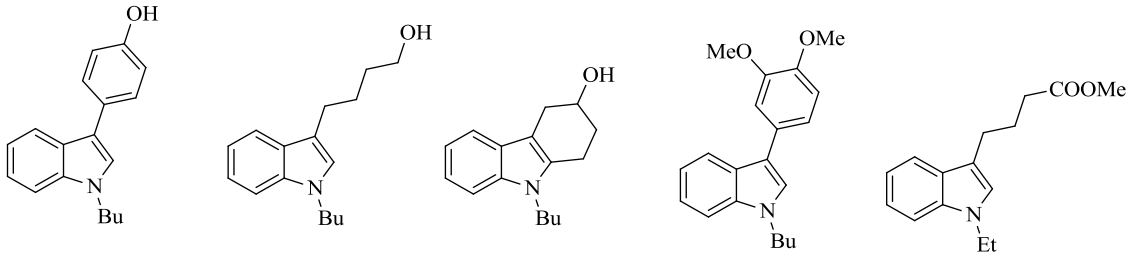
2.60a (86 %) **2.60b** (90 %) **2.60c** (92 %) **2.60d** (93 %) **2.60e** (94 %)



2.60f (95 %) **2.60g** (96 %) **2.60h** (97 %) **2.60i** (57 %) **2.60l** (85 %) **2.60m** (90 %)

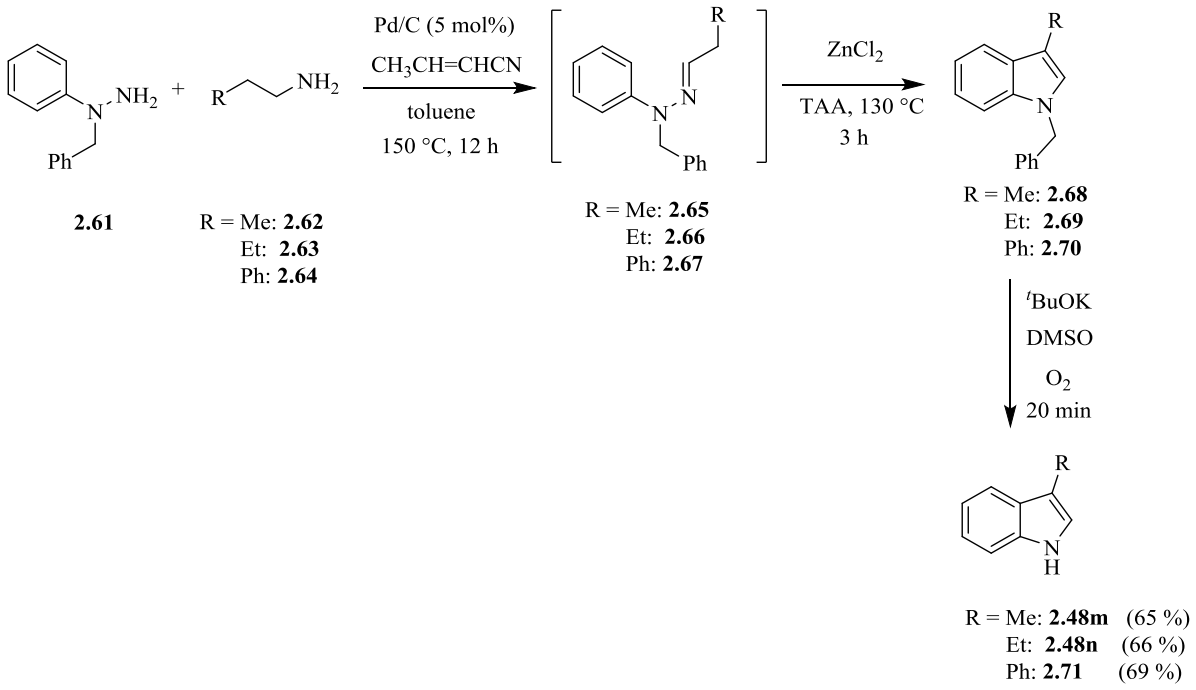


2.60n (80 %) **2.60o** (83 %) **2.60p** (48 %) **2.48t** (81 %) **2.60q** (86 %) **2.60r** (84 %)



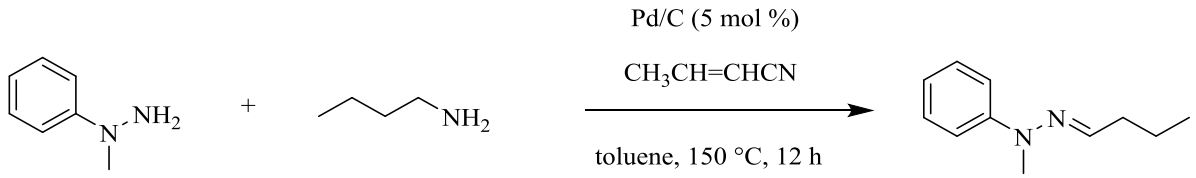
2.60s (82 %) **2.60t** (85 %) **2.60u** (75 %) **2.60v** (86 %) **2.60z** (65 %)

Scheme 2.23
Domino one-pot two-step synthesis of indoles by reaction of arylhydrazines with amines



Scheme 2.24
Synthesis of NH-indoles combining our procedure with a debenzylation strategy

Finally, the possibility of effective recycling of the Pd/C catalyst was evaluated on the reaction of 1-methyl-1-phenylhydrazine with butylamine. The separation of the catalyst was carried out after the first step. The reaction mixture containing the hydrazone in toluene was filtered, and 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 at least five consecutive reactions could be run without noticeable decrease in activity (Scheme 2.25). To verify the heterogeneous nature of the catalytic process, we carried out several leaching studies.[39] "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 negligible amounts of Pd was detected in solution.



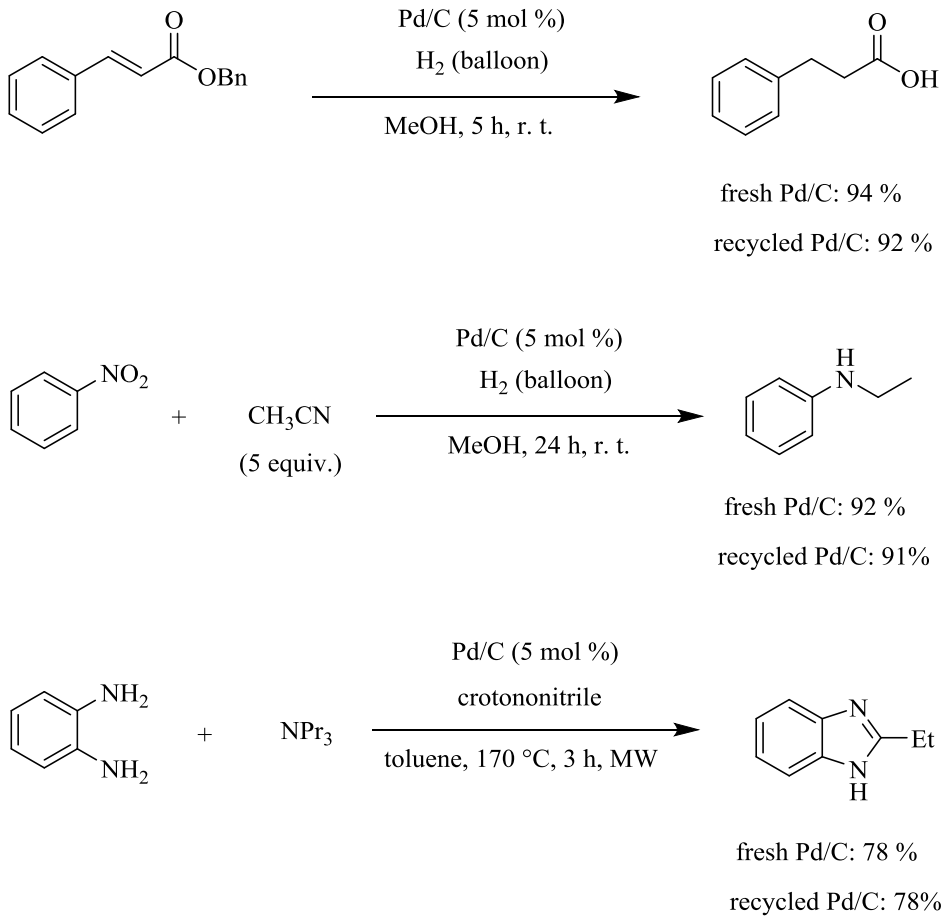
2.54e **2.50** **2.56e**

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

[a] isolated yield

Scheme 2.25
Catalyst recycling experiments

As the use of a heterogeneous catalyst in the hydrogen transfer process is a qualifying point of our process, we decided also to investigate whether the recycled catalyst could be used in other catalytic processes. Three different Pd/C catalysed reactions were explored comparing results obtained both with recycled and fresh Pd/C (Scheme 2.25).[40] We were pleased to observe no significant difference in terms of yields and purities between the two catalytic procedures.



Scheme 2.26
Palladium-catalysed processes investigated both with fresh and recycled catalyst

2.4.3 Conclusions

Chemical transformations involving primary amines are of great importance in biology and chemistry because the amino functionality is present in a vast majority of biomolecules, pharmaceuticals, and chemical precursors used in the synthesis of many important target molecules.[41] Following our interest in the development of new methodologies for indole ring, we have achieved a direct transformation of primary amines into arylhydrazones by reaction with arylhydrazines under transfer hydrogenation conditions. The application of 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.

2.5 General Conclusions

The implementation of atom-economic and direct methods for indole syntheses still remains a demanding goal. We have reported two novel protocols for the synthesis of 2-substituted and 2,3-disubstituted indoles, both based on the classical Fischer cyclisation, which proved to be a powerful tool for obtaining functionalised indole rings. Even if both of these methods are fairly general in terms of substrates, they often complement each other in terms of suitable starting materials, as in most cases one hits the mark where the other one fails.

In the cross-dehydrogenative coupling of arylhydrazines with alcohols, the homogeneous catalytic system $Ru_3(CO)_{12}$/BIPHEP promoted the reaction giving the formation of reactive aldehydes *in situ*. The catalyst proved to be active at moderate temperatures (130 °C) allowing the reaction to go to completion in only 3 h under microwave irradiation. On the contrary, in the case of the reaction of phenylhydrazines with amines harsher reaction conditions (150 °C) and longer reaction times (12 h) were needed. Here, application of microwave dielectric heating in order to speed up the reaction was problematic due to the strong interaction between MW and the metal catalyst, causing explosion risks and related safety issues. The possibility to easily recover and recycle the catalyst was a concrete feature of this protocol, which encourages its application on a large scale. On the contrary, this option is not feasible when using homogeneous $Ru_3(CO)_{12}$/BIPHEP catalytic system.

Interestingly, the reaction between phenylhydrazines and alcohols could be carried-out using stoichiometric amounts of both substrates, making this method very appealing from the economic point of view. Unfortunately, this was not possible when using amines. In fact, a self-condensation of primary amines occurred as a major side reaction, and this forced to use an excess of phenylhydrazine.

The atom-economy of both processes was limited by the necessity to use a hydrogen acceptor to promote the reaction. Our investigation on the possibility to avoid the use of hydrogen acceptor showed that this was not possible in the case of the reaction of alcohols with arylhydrazines. In fact, negligible conversion of substrates was detected when the reactions were carried out in the absence of crotononitrile. We hypothesised that the hydrogen acceptor was mandatory with the $Ru_3(CO)_{12}$/BIPHEP catalytic system to re-oxidise the catalyst and complete the catalytic cycle. Further investigations should allow to identify different catalytic systems able to perform the same transformation without the need of the hydrogen acceptor,

thus improving the overall process. On the contrary, more encouraging results were observed carrying out the reaction of amines with arylhydrazines in the absence of crotononitrile. The product was formed in moderate yield but, again, considerable improvements may be achieved if particular means are adopted for efficiently removing hydrogen from the reaction mixture.

The practicality of the two methods can also be analysed. Both reactions were easy to perform and did not require any post-reaction workup apart from the filtration of the catalyst when using Pd/C. The only difference regards the possibility to perform the reaction of arylhydrazines with alcohols in one single step leading directly to indole product. On the contrary, the same reaction performed with amines instead of alcohols gave comparable results only with a two-step (one-pot) procedure. Both reactions could also be stopped at the hydrazone step, thus making both protocols suitable not only for indole synthesis but also for the preparation of arylhydrazones.

Both methods were characterised by a general scope of substrates, including variously substituted arylhydrazines and functionalised alcohols and amines. Although the reactions were successfully applied to various arylhydrazines differently substituted both on the phenyl ring and on the arylic nitrogen (N1) atom, we encountered problems when the reaction was performed with NH-free arylhydrazines to obtain NH-free indoles. In fact, only low yields of the desired indole were achieved when using alcohols and $Ru_3(CO)_{12}$/BIPHEP, and no product at all was formed when using amines and Pd/C. In the latter case, degradation of arylhydrazines occurred very quickly, during the first minutes of the reaction. We attributed this to the harsher temperatures and to an increased lability of NH-arylhydrazines in the presence of palladium.

Regarding the electrophilic coupling partner (alcohol and amine), we tested the reaction of arylhydrazines with a wide variety of alcohols and amines observing a good compatibility of several functional groups on the aliphatic chain of the alcohol/amine. This allowed us to obtain a wide library of functionalised indoles. The synthesis of indoles containing an amino group on the C-3 position of the ring was achieved in good yields by the Ru-catalysed procedure using aminoalcohols with the amino group protected as a phtaloyl. Interestingly, also diols were compatible substrates, but only if the two hydroxyl groups were on a cyclic structure. However, the most suitable procedure for obtaining an indole ring bearing a hydroxyl substituent on C-2 or C-3 position was using the appropriate aminoalcohol and Pd-catalysed reaction. In fact, the palladium catalyst has shown an excellent selectivity towards the oxidation of the amino group, leaving intact the hydroxyl group. Therefore, the two methods described in this chapter are in

this case complementary. If we want to obtain an indole bearing an OH-group on C-2/C-3 positions the most suitable and convenient method is the Pd-catalysed procedure, whereas if our target is an indole with an amino group we should prefer the Ru-catalysed method. Also phenol groups on the aliphatic chain of primary and secondary alcohols or primary and secondary amines are compatible with both methods.

In conclusion, we have developed two distinct methods for the synthesis of indole derivatives combining the classical Fischer cyclisation with the principles of hydrogen transfer. Both synthetic protocols are characterised by environmental compatibility, discrete atom-efficiency, and cheap and easily accessible starting materials. All these features highlight the potential value in industrial applications. In addition, the introduction of functional groups in the indole molecules expands the scope of use of the latter in organic synthesis and the combination of the indole ring with other functional groups can lead to novel compounds with unique physical and chemical properties.

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Chapter 3

Synthesis of Cinnamaldehyde Derivatives through a One-Pot Dehydrogenative Cross-Coupling of Primary Alcohols

3.1 Introduction

α,β-Unsaturated aldehydes are important starting materials and intermediates in the synthesis of a large number of fine chemicals, particularly in the field of flavour and fragrance chemistry,[1] and pharmaceuticals.[2] Despite their ubiquity and utility in organic chemistry, the synthesis of α,β-unsaturated carbonyl compounds is often a tedious and sometimes a challenging transformation. Cinnamaldehyde and its derivatives are a prominent class of naturally occurring α,β-unsaturated aldehydes, widely used in food and cosmetic industries.[3] Cinnamaldehyde is the main component of cassia oil and cinnamon bark oil, and is used as a flavouring in foods and beverages to impart a cinnamon flavour. Other important properties are its antimicrobial and antifungal activities.[4] In addition, several derivatives of cinnamaldehyde are commercially useful. To name a few examples, dihydrocinnamyl and cinnamyl alcohols, which occur naturally and are produced by hydrogenation of cinnamaldehyde, are used to confer the fragrances of hyacinth and lilac, and jasminaldehyde and α-hexylcinnamaldehyde which are important commercial fragrances.

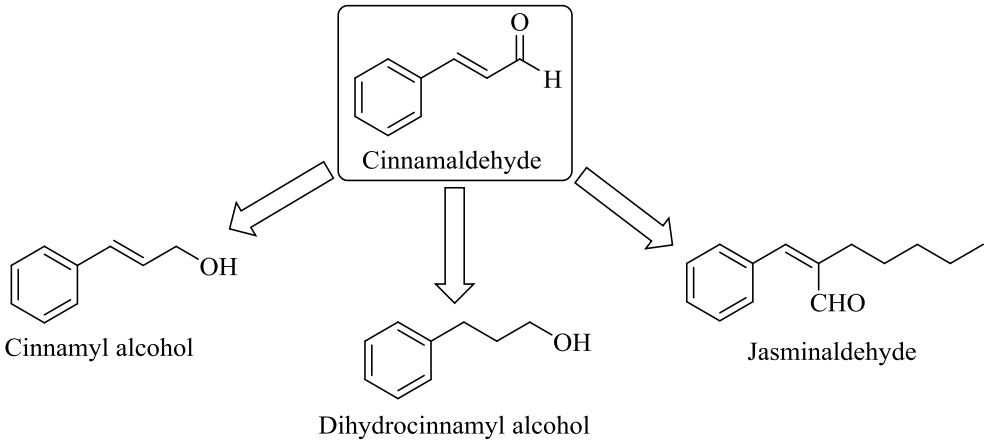
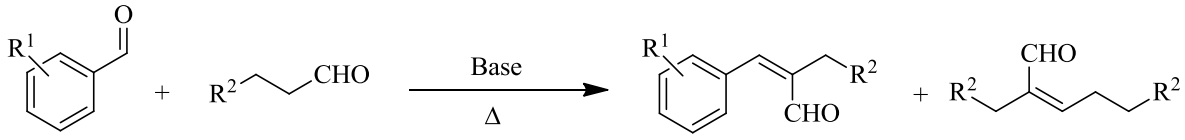


Figure 3.1
Cinnamaldehyde and some derivatives

The most common and relevant strategy for preparing cinnamaldehyde derivatives such as jasminaldehyde and its analogues at both small and industrial scales is a cross aldol condensation reaction between aromatic aldehydes and aliphatic aldehydes by using excess amounts of homogeneous alkaline catalysts (NaOH or KOH).[5] The reaction is invariably accompanied by self-condensation of the aliphatic aldehyde, which forms the major by-product

of this transformation (Scheme 3.1). In addition the reaction suffers from the propensity of aldehydes to polymerise, leading to a number of undesired by-products. A valid strategy for controlling selectivity and suppressing self-condensation is to keep low the concentration of the aliphatic aldehyde by using a high benzaldehyde concentration. The disadvantages of such a process include expensive separation procedures, corrosion hazard, and environmental problems due to the use of alkali metal hydroxides. In order to facilitate purification, it is necessary to minimise the self-condensation reaction by using a selective catalyst and appropriate operating parameters.



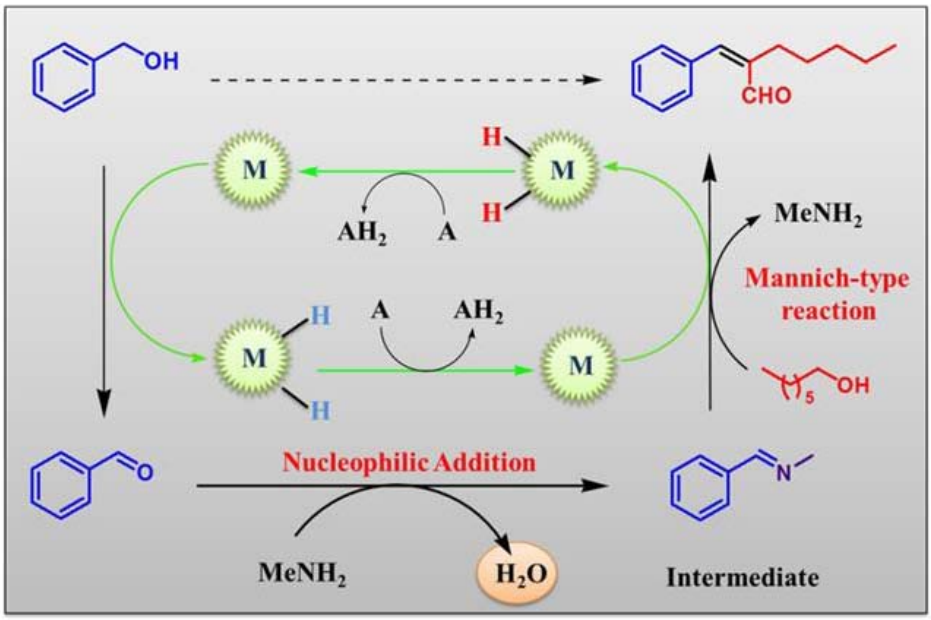
Scheme 3.1
The aldol condensation between an aromatic aldehyde with an aliphatic aldehyde

During recent years, the industrially relevant reaction of heptanal with benzaldehyde to give jasminaldehyde has attracted considerable attention.[6] Much interest has been given to the development of heterogeneous bi-functional catalysts that act exploiting a synergistic cooperation of both the weak acid sites and basic sites in promoting this reaction.[7] Several studies demonstrated that the role of the weak acid sites is the activation of benzaldehyde by protonation of the carbonyl group, which favours the attack of the enolate heptanal intermediate generated on basic sites.[7]

With the aim of significantly contributing to this field, we studied an alternative route to jasminaldehyde and its analogue compounds by exploring the possibility of generating reactive aldehydes *in situ* from inexpensive, readily accessible and more stable precursors such as alcohols. To achieve this goal, we designed a new catalytic protocol based on HT strategy. We investigated a domino process in which the starting alcohols are catalytically converted into the corresponding aldehydes, that are, in turn, readily transformed by an *in situ* reaction as soon as they are formed. In this way, the concentration of the sensitive aldehydes is low at any given moment of the process, limiting side reactions. In our hypothesis, this strategy should bring a significant progress in the efficiency and selectivity of the process, minimising the self-condensation of aldehydes and their polymerisation.

3.2 Synthesis of Cinnamaldehyde Derivatives via Dehydrogenative Cross-Coupling of Primary Alcohols

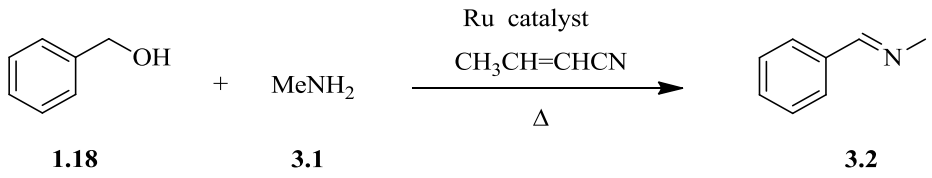
Following our interest in hydrogen transfer (HT) strategies, we focused our attention on the development of a synthetic protocol for a rapid access to α,β-unsaturated aldehydes, through the cross-dehydrogenative coupling of two different primary alcohols behaving as latent aldehydes. We designed a cascade reaction where a non enolisable aldehyde is first generated *in situ* by the removal of a hydrogen molecule from an alcohol, and then temporarily trapped as an imine. The following Mannich-type condensation between the imine species and the other transient aldehyde should give us the target compounds (Scheme 3.2).[8]



Scheme 3.2
A domino strategy for the synthesis of cinnamaldehydes

3.2.1 Results and Discussion

Work began by looking at the reaction between benzyl alcohol **1.18** and methylamine **3.1** for establishing the optimal reaction conditions for generating the intermediate imine **3.2** (Scheme 3.3).



Scheme 3.3
Conversion of benzyl alcohol into the corresponding N-*methylimine*

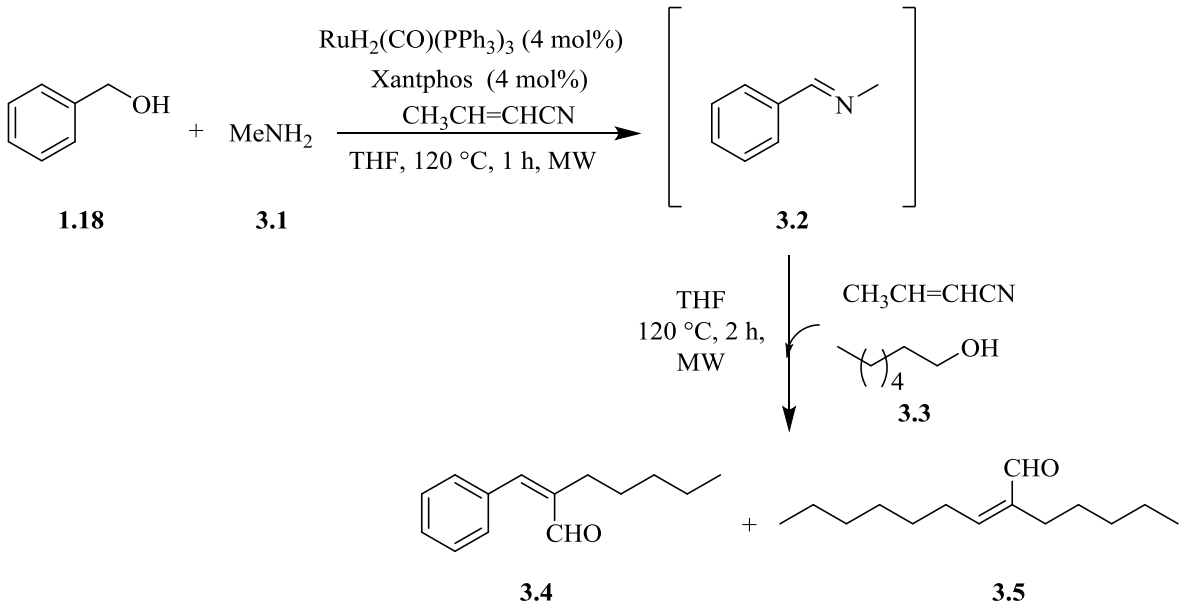
We evaluated the performance of a range of ruthenium-based catalytic systems (Table 3.1, entries 1-4). Although we did not observe significant differences in the activity of different catalysts, $RuH_2CO(PPh_3)_3$ gave a slightly better yield than the others (Table 3.1, entry 4). Unfortunately, when catalyst loading was decreased to 3 mol% we noticed a significant drop in the yield. Therefore, we decided to proceed our optimisation studies using 4 mol% of catalyst. A temperature screening showed that the reaction can also be carried out at lower temperatures than 150 °C. Lowering temperature down to 120 °C had no effect on the reaction outcome (Table 3.1, entry 6), whereas at 110 °C a slight decrease in the yield was observed (Table 3.1, entry 7). To further increase the efficiency of the catalyst we screened several phosphine ligands (Table 3.1, entries 8-11). As expected the use of ligands resulted in a noticeable improvement, and we found the combination of $RuH_2CO(PPh_3)_3$ (4 mol %) with phosphine ligand Xantphos (4 mol %) as the most active catalytic system in performing the oxidative conversion of benzyl alcohol **1.18** into imine **3.2** by hydrogen transfer in the presence of a hydrogen acceptor (Table 3.1, entry 11). Interestingly, microwave (MW) dielectric heating sped up this transformation, cutting down the reaction times from 24 h to only 1 h (Table 3.1 compare entries 11 and 12). If the reaction was carried out in the absence of hydrogen acceptor, the major product detected was *N*-methylbenzylamine, deriving from the reduction of imine **3.2**. Therefore, hydrogen acceptor was mandatory in this step in order to prevent the reduction of imine.

Table 3.1 *Optimisation of the reaction conditions for imine formation*

Entry	Catalyst (5 mol%)	Ligand (5 mol%)	Solvent	Temperature (°C)	Time (h)	Yield[a]
1	$RuHCl(CO)(PPh_3)_3$	-	THF	150	24	54
2	$[RuCl_2(p\text{-cymene})]_2$	-	THF	150	24	49
3	$Ru_3(CO)_{12}$	-	THF	150	24	52
4	$RuH_2(CO)(PPh_3)_3$	-	THF	150	24	63
5	$RuH_2(CO)(PPh_3)_3$	-	THF	150	24	49[b]
6	$RuH_2(CO)(PPh_3)_3$	-	THF	120	24	61
7	$RuH_2(CO)(PPh_3)_3$	-	THF	110	24	50
8	$RuH_2(CO)(PPh_3)_3$	PCy_3[c]	THF	120	24	83
9	$RuH_2(CO)(PPh_3)_3$	CataCXium[d]	THF	120	24	74
10	$RuH_2(CO)(PPh_3)_3$	Dppf[e]	THF	120	24	81
11	$RuH_2(CO)(PPh_3)_3$	Xantphos[f]	THF	120	24	97
12	$RuH_2(CO)(PPh_3)_3$	Xantphos	THF	120	1	97[g]

Reaction conditions: benzyl alcohol (1.0 mmol), methylamine (1.3 mmol), crotononitrile (1.1 mmol), catalyst (4 mol%) in THF (2.0 mL) at the indicated temperature for 24 h. Unless otherwise specified, the reactions were carried out in a closed vessel inserted in a preheated oil bath. [a]Yield determined by ^1H NMR spectroscopic analysis with an internal standard. [b]The catalyst loading has been reduced to 3 mol%. [c]4 mol % of ligand tricyclohexylphosphine have been added. [d]4 mol% of cataCXium (Di-adamantylalkylphosphine) have been used. [e]4 mol % of dppf [1,1'-Bis(diphenylphosphino)ferrocene] has been used. [f]4 mol % of Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) have been used. [g]Reaction performed under microwave dielectric heating at 120 °C for 1h.

At this point, we turned our attention on the synthesis of cinnamaldehyde derivatives by reaction of imine **3.2** with primary alcohols. First, we investigated whether the same catalytic system used for imine synthesis could also promote the dehydrogenative cross-coupling of 1-heptanol **3.3** with the previously prepared imine, to give the corresponding α,β-unsaturated aldehydes **3.4** (Scheme 3.4). Therefore, once the formation of **3.2** was achieved, we added to the same reaction mixture 1 equivalent of heptanol **3.3** and 1.1 equivalent of crotononitrile, and the resulting reaction mixture was then heated under MW irradiation at 120 °C for 2 h (Scheme 3.4). After the reaction was run, we observed a complete conversion of 1-heptanol to form the desired product **3.4**, along with product **3.5**, deriving from self-condensation of alcohol **3.3**, in a 60:40 ratio (Table 3.2, entry 1).



Scheme 3.4
One-pot two-step protocol for the synthesis of jasminaldehyde

In order to suppress or minimise the undesired self-condensation reaction and improve the chemoselectivity, we carried out a series of experiments by adjusting the imine to 1-heptanol ratio (Table 3.2, entries 2-4). The reaction performed using 0.5 equivalents of 1-heptanol **3.3** respect to imine **3.2** resulted in an improved selectivity towards the desired cross-coupling product **3.4** (table 3.2, entry 2), whereas further increasing the imine concentration had no significant impact on selectivity (Table 3.2, entries 3-4). On the other hand, experiments carried out using excess of alcohol **3.3** showed that the target product could be obtained in comparable yields only using 3 equivalents of 1-heptanol. In this case, a very complex reaction mixture and difficult purifications made the process unattractive. When evaluating the effects of acid additives on chemoselectivity of this reaction (Table 3.2, entries 5-12), we found that the addition of 100 mg of silica gel allowed us to further improve chemoselectivity up to 85% (Table 3.2, entry 11). The role of crotononitrile in this second step must also be pointed out: in addition to favouring the oxidation of 1-heptanol, it is needed to prevent the imine from behaving as hydrogen acceptor, and to avoid the over-reduction of the α,β-unsaturated aldehydes formed.

Table 3.2 *Optimisation of the second step (Mannich-type reaction of **3.3** with **3.2**)*

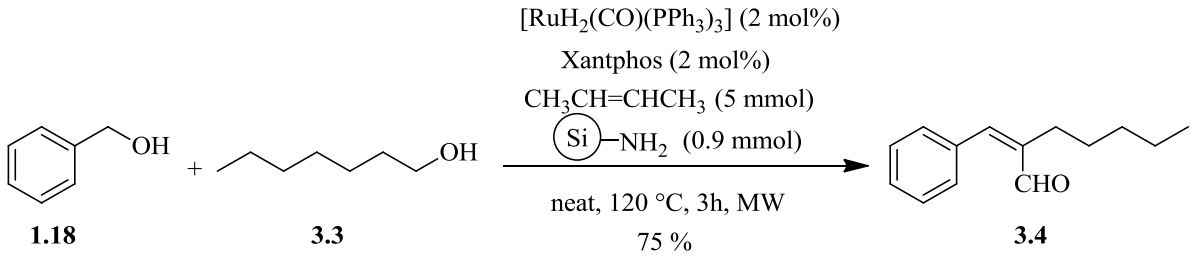
Entry	3.2 (mmol)	3.3 (mmol)	Additive	Ratio 3.4/3.5[a]
1	1	1	-	60:40
2	2	1	-	75:25
3	3	1	-	77:23
4	5	1	-	76:24
5	2	1	*p*TsOH	78:22
6	2	1	CH_3COOH	80:20
7	2	1	^tBuCOOH	81:19
8	2	1	CH_3CH_2COOH	82:18
9	2	1	CH_3CH_2COOH	83:17
10	2	1	Silica gel (50 mg)	82:18
11	2	1	Silica gel (100 mg)	85:15
12	2	1	Silica gel (150 mg)	86:14

Reactions carried out using $RuH_2(CO)(PPh_3)_3$ (4 mol%), Xantphos (4 mol%) in THF at 120 °C under MW irradiation for 2 h. [a]Ratio determined by ^1H NMR spectroscopic analysis.

Having optimised both reaction steps, we attempted the overall transformation in a one-step procedure (Scheme 3.5). Using 2 mmol of benzyl alcohol, 1 mmol of 1-heptanol and 2 mmol of methylamine the desired product **3.4** was detected in the reaction mixture in a very low amount because conversion of 1-heptanol was moderate, even after a prolonged reaction time (Table 3.3, entries 1-2). However, reducing the amount of methylamine from 2 mmol down to 0.5 mmol yielded 40% of α,β-unsaturated aldehyde **3.4** (Table 3.3, entry 3). We hypothesised that amine excess might inhibit or reduce the activity of the metal complex. Unfortunately, lowering $MeNH_2$ amount below 0.5 mmol gave the product in lower yields. (Table 3.3, entry 4). We thought that an amine in heterogeneous phase should not interfere with the performance of the catalyst, allowing us to perform a more efficient transformation. In order to achieve this goal, we designed a new phase-switching strategy[9] using a silica-grafted primary amine as a phase switch tag (Table 3.3, entries 5−16). This brought a noteworthy change in the outcome of the one-pot reaction, leading to the preparation of compound **3.4** in acceptable 60% yields

(Table 3.3, entry 7). Optimisation of the reaction parameters showed that mixing benzyl alcohol **1.18** and 1-heptanol **3.3** in a 3:1 ratio with $RuH_2CO(PPh_3)_3$ (4 mol %) and Xantphos (4 mol %) in the presence of silica-immobilised amine (0.9 mmol), at 120 °C under MW dielectric heating for 3 h without solvent, afforded a 75% yield of the desired cross-coupling product **3.4** (Table 3.3, entry 10). Interestingly, when catalyst loading was halved (2 mol %) the activity and selectivity of the catalyst system remained unchanged (Table 3.3, entry 11).

Notably, silica-immobilized amine can be recovered by simple filtration at the end of the reaction and reused several times. The reusability was studied by recycling the amine in five consecutive dehydrogenative cross-coupling experiments of benzyl alcohol **1.18** with 1-heptanol **3.3**, under the optimised reaction conditions. At the end of each reaction, the solid supported amine recovered was washed with CH_2Cl_2 (3x5 mL), dried under vacuum at 40 °C overnight, and then subjected to the next run. We observed that the silica-grafted amine can be recycled at least 5 consecutive times without significant loss of its efficiency (Table 3.4).



Scheme 3.5
*Optimised one-step procedure for the synthesis of **3.4***

Table 3.3 *Optimisation of the one-step protocol*[a]

Entry	Amine (mmol)	1.18/3.3 (mmol)	Solv.	T (°C)	Time (h)	Conv. (%)[b]	3.4/3.5[b]	Yield (%)[c]
1	$MeNH_2$ (2)	2:1	THF	130	3	< 10	-	-
2	$MeNH_2$ (2)	2:1	THF	130	6	15	-	-
3	$MeNH_2$ (0.5)	2:1	THF	130	3	100	76:24	40
4	$MeNH_2$ (0.25)	2:1	THF	130	6	100	66:44	28
5	Si-NH_2 (0.4)[d]	2:1	neat	130	3	> 90	75:25	35
6	Si-NH_2 (0.6)	2:1	neat	130	3	> 90	77:23	44
7	Si-NH_2 (0.9)	2:1	neat	130	3	> 90	83:17	60
8	Si-NH_2 (1.5)	2:1	neat	130	3	51	-	-
9	Si-NH_2 (0.9)	2:1	neat	130	3	100	90:10	70
10	Si-NH_2 (0.9)	3:1	neat	120	3	100	90:10	75
11	Si-NH_2 (0.9)	3:1	neat	120	3	100	90:10	75[e]
12	Si-NH_2 (0.9)	3:1	neat	110	3	88	88:12	59[e]
13	Si-NH_2 (0.9)	3:1	neat	120	2	72	85:15	-[e]
14	no amine	3:1	neat	120	3	< 5	-	-[e]
15	Si-NH_2 (0.9)	3:1	toluene	120	3	< 5	-	-[e]
16	Si-NH_2 (0.9)	3:1	THF	120	3	< 5	-	-[e]

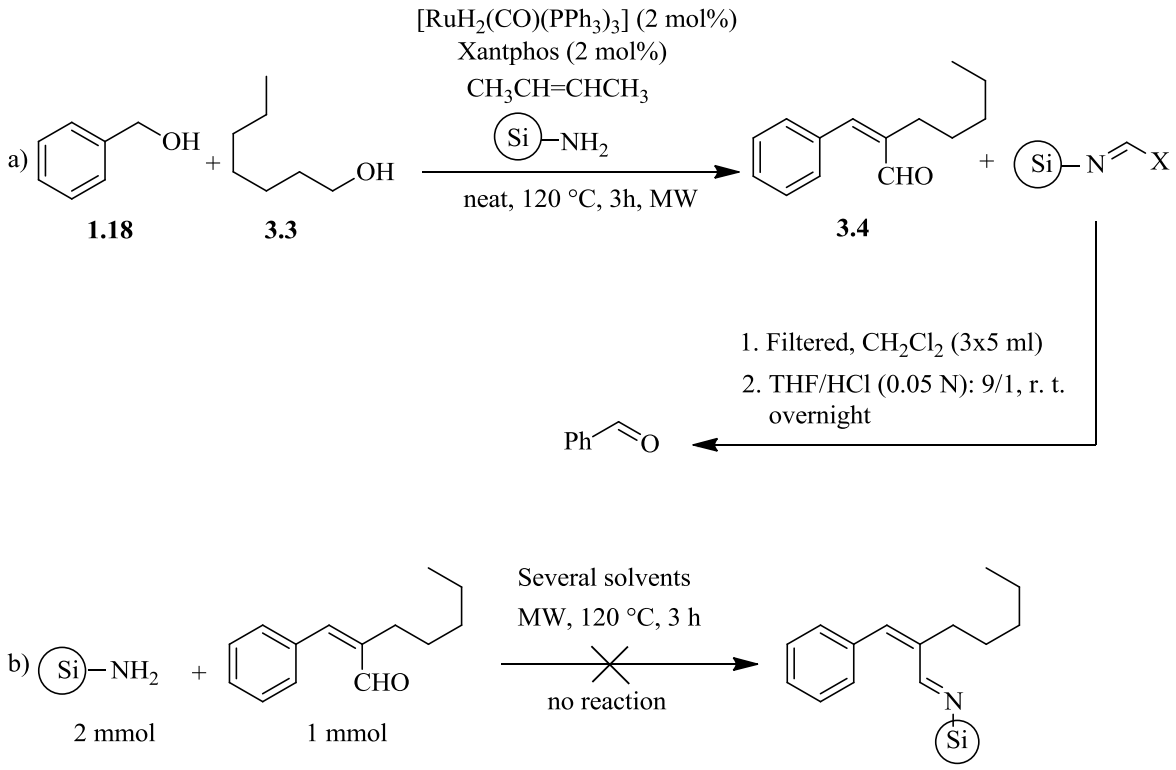
[a]Unless otherwise specified, reactions were performed under microwave dielectric heating at the stated temperature using $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%), crotononitrile (5 mmol). [b]Ratio determined by ^1H NMR spectroscopy. [c]Yields of isolated product after column chromatography. [d]Reaction performed by using amine-grafted silica gel with particle size 40-63 μm. [e]Reactions performed using 2 mol% of $RuH_2(CO)(PPh_3)_3$ and 2 mol% of Xantphos.

Table 3.4 *Catalyst recycle experiments*

Recycles	Conversion (%)[a]	Ratio 3.4/3.5[b]	Yield 3.4 (%)[c]
fresh	100	90:10	75
1	100	92:08	73
2	100	90:10	71
3	100	91:09	72
4	100	89:11	70
5	100	90:10	71

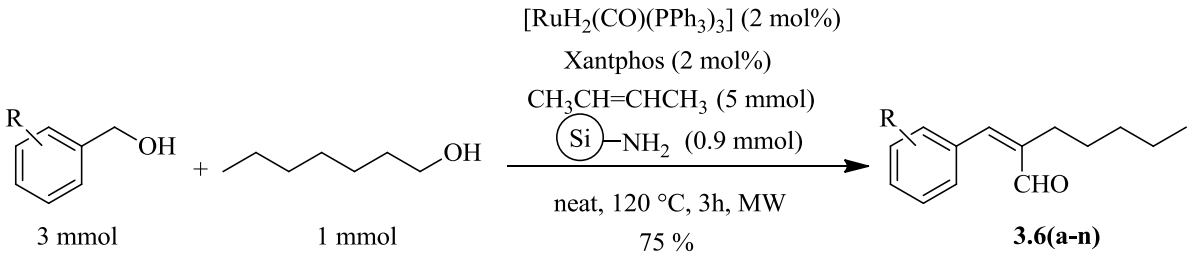
Reaction conditions: benzyl alcohol (3 mmol), 1-heptanol (1 mmol), crotononitrile (5 mmol), (Si)-NH_2 (0.9 mmol), $RuH_2CO(PPh_3)_3$/Xantphos (2 mol%), solvent-free, 120 °C, 3 h. [a]Conversion of 1-heptanol determined by ^{1}H NMR spectroscopy analysis. [b]Determined by ^{1}HNMR. [c]Yields of isolated product after column chromatography.

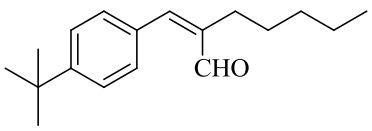
In order to determine the presence of any residual unsaturated aldehyde on the solid support at the end of the cross-coupling reaction, the resulting silica-grafted amine was first filtered off and washed several times with DCM (3x5 mL) and then treated with an acid aqueous solution THF/HCl (0.05 N): 9/1 (5 ml). The mixture has shaken overnight at room temperature releasing in solution only benzaldehyde (Scheme 3.6a). Even 24 h after, there were no detectable amounts of the compound **3.4** in the solution. In a separate experiment, the unsaturated aldehyde **3.4** (1 mmol) was treated with an excess of fresh silica-grafted amine (2 mmol) under the optimised reaction condition described for the cross-coupling reaction between benzyl alcohol **1.18** and 1-heptanol **3.3** (Scheme 3.6b). Even after a prolonged reaction time (overnight), the compound **3.4** was almost quantitatively recovered from the solution. Any attempt of end-attachment of the unsaturated aldehyde **3.4** to the silica failed even when solvent (THF, Toluene etc) was used.



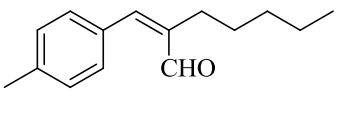
Scheme 3.6
*Analysis of the silica-grafted amine after dehydrogenative cross-coupling reaction between benzyl alcohol **1.18** and 1-heptanol **3.3***

To understand the substrate scope and limitations of this procedure better, different aromatic alcohols and 1-heptanol were reacted under the optimised reaction conditions (Scheme 3.7). In general, substituents at different positions on the phenyl ring did not have a significant effect on the efficiency and selectivity of this procedure (Scheme 3.7, products **3.6a-d**). Electron-withdrawing groups on the aromatic ring provided slightly better results than electron-donating substituents, probably due to the increased electrophilicity of the imine intermediate (Scheme 3.7, compare, for example, products **3.6f** and **3.6h**). The reaction proceeded successfully even with benzylic alcohols bearing halogen substituents on the aromatic ring, leading to good yields of halogenated cinnamaldehydes **3.6h-j** (Scheme 3.7). Contrary to other electron-withdrawing groups, *p*-Nitrobenzylic alcohol afforded the corresponding aldehyde **3.6k** in a slightly lower but still acceptable yield (Scheme 3.7). We were delighted to notice that base-sensitive residues such as carboxymethyl ester or phenol were well tolerated under these conditions (Scheme 3.7, products **3.6l** and **3.6m**).

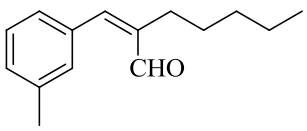




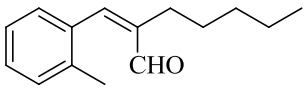
3.6a (57 %)



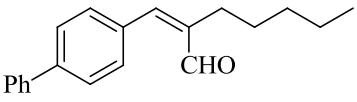
3.6b (61 %)



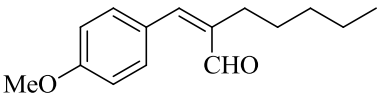
3.6c (62 %)



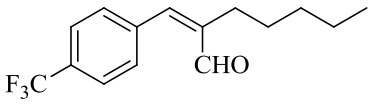
3.6d (64 %)



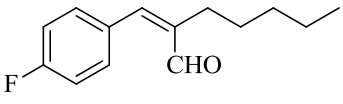
3.6e (55 %)



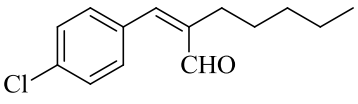
3.6f (48 %)



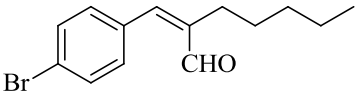
3.6g (56 %)



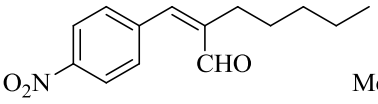
3.6h (73 %)



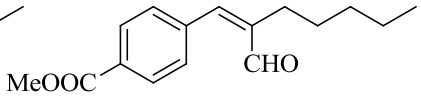
3.6i (66 %)



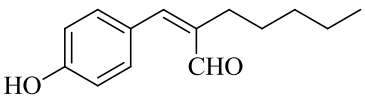
3.6j (62 %)



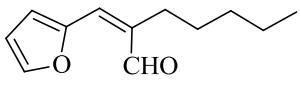
3.6k (50 %)



3.6l (59 %)



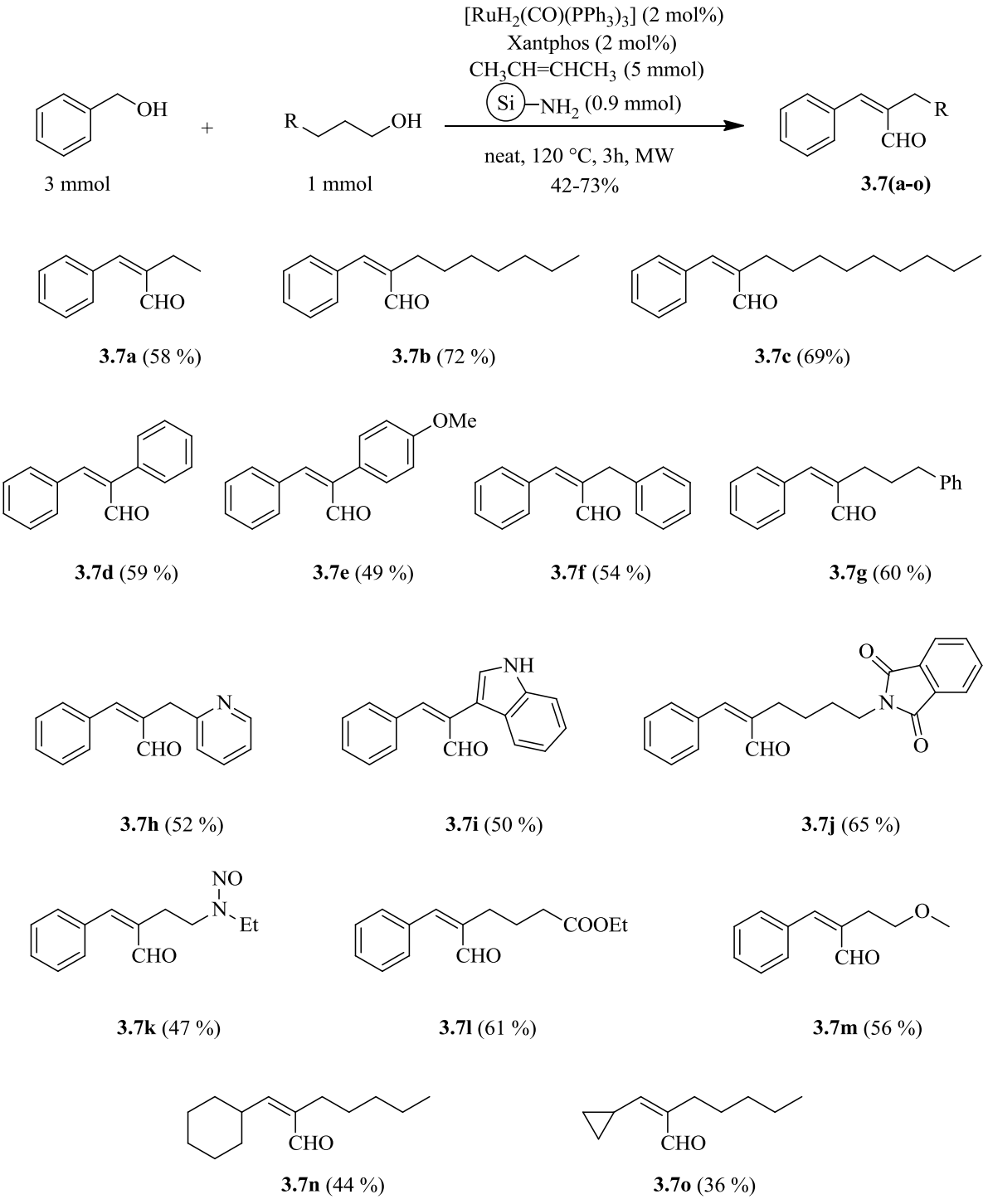
3.6m (57 %)



3.6n (42 %)

Scheme 3.7
The reaction of 1-heptanol with substituted benzylic alcohols

To assess the versatility of the method, the reaction between benzyl alcohol **1.18** and a broad range of aliphatic alcohols was also investigated (Scheme 3.8). The reaction proceeded smoothly to give the corresponding products **3.7a-o** in 47-72% yields. Interestingly, primary alcohols containing pyridyl and indolyl motifs reacted well with benzyl alcohol, resulting in an interesting combination of different heterocyclic rings on the α,β-unsaturated aldehyde skeleton (Scheme 3.8, products **3.7h** and **3.7i**). In addition, a variety of functional moieties offering versatile synthetic functionality for further transformations were successfully incorporated (Scheme 3.8, products **3.7j-m**). All the products, with the only exception of aldehyde **3.7k**, were isolated as E-isomers (>98%), showing an excellent stereoselectivity for the reaction. We were pleasantly surprised by the high rate of unknown compounds prepared (products **3.6a,b,d,e,h,i,l-n**, **3.7c**, **3.7g-o**, Schemes 3.7 and 3.8) using this method, suggesting that our approach could help in solving a synthetic problems still opened for α,β-unsaturated aldehyde synthesis.



Scheme 3.8
The reaction of benzyl alcohol with different primary alcohols

Even though in principle this reaction may be applicable to the coupling between two linear aliphatic alcohols, this is a more challenging transformation. In fact, when both intermediate aldehydes are enolisable, it is possible to obtain four different products deriving from

homocoupling and heterocoupling. Interestingly, we observed a discrete selectivity towards the cross-coupling product when 1-heptanol was reacted with cyclohexanemethanol and cyclopropane methanol (Scheme 3.8, products **3.7n** and **3.7o**). This is probably due to geometric constraints of substrates which make the enolisation more difficult. In addition to the ring strain present on a three-membered carbon cycle, the exocyclic double bond that forms during enolisation imposes steric strain on the cyclopropane ring, and to a lesser extent on a cyclohexyl ring.[10] This can be appreciated by comparing the bond lengths and bond angles of cyclopropane and methylenecyclopropane. The strain in methylenecyclopropane can be seen in the increase of the length of the C-CH_2 bonds and difference in bond angle (Figure 3.2).

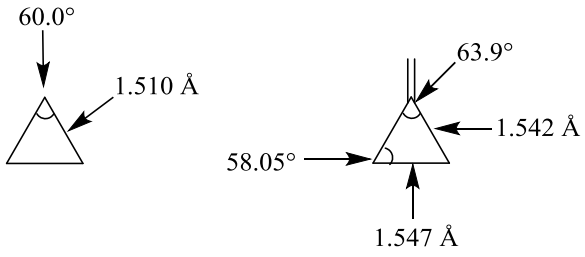


Figure 3.2
Bond lenght and angles in cycloproane ring

Therefore, enolisation of linear aliphatic aldehyde 1-heptanal demands less energy than enolisation of aldehydes derived from cyclohexanemethanol and cyclopropanemethanol. This is the reason of the observed, although low, selectivity. On the contrary, when two linear aliphatic aldehydes have the same propensity to enolise, obtaining selectivity is still an unresolved problem.

3.3 Conclusions

Selective cross aldol condensation of aldehydes is a challenging topic of intensive research. Major problems derive from the propensity of aldehydes to react with themselves giving self-condensation products. The development of efficient and selective methods to overcome this drawback is a high priority. Until now, progress has been limited to the discovery of new selective catalysts, i. e. metal or solid supported catalysts and organocatalysts. Considering the commercial importance of cinnamaldehydes and their applications in several fields, we focused

our attention on development of a sustainable method for the small-scale production of these high value products, with a high potential to scale-up to industrial quantities.

In the course of our studies, we developed a new and straightforward route to cinnamaldehyde derivatives through a Mannich-type reaction using alcohols instead of aldehydes as more environmentally friendly and stable starting materials. As an important feature, reactive aldehydes were generated *in situ* with high efficiency by hydrogen transfer, and they were present in the reaction mixture in low concentration at any given time of the reaction, thereby limiting side-reactions. Key to success was the use of a heterogeneous silica-supported amine that allowed us to perform the synthesis of a library of cinnamaldehydes in good yields and high selectivities in one-pot. We attributed the increased efficiency of the process to the heterogeneous nature of the amine that did not interfere with the activity of the catalyst, which instead was observed with amines in homogeneous phase. In addition, the bi-functional nature (acid-base) of silica-grafted amine could also give beneficial effects on both reactivity and selectivity. Other positive traits are the ease of recovery of the amine and its excellent reusability: the selectivity remained unchanged over catalyst recycling as well as the activity. This is an essential requirement when scaling the process up to synthetically useful quantities, and will favour the transfer from academic to industrial applications. In addition, using silica-grafted amine avoids the significant formation of liquid waste as well as the need of tedious post-reaction work-up procedures, that are the major drawbacks in traditional methods that require more than stoichiometric amounts of strong bases in homogeneous phase. Additional advantages derive from the possibility to perform reactions without solvent, which makes our protocol cleaner and greener.

3.4 References

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Chapter 4

Synthesis of Substituted Quinolines via *a Cross-Dehydrogenative Coupling of Alcohols and Aminoarenes*

4.1 Introduction

Quinoline is a heterocycle that consists of a benzene ring fused with a pyridine ring. It was first isolated from coal tar in 1834 by Runge,[1] and even now this remains the principal source of quinoline.[2] Quinoline itself has few applications, and is mainly used as a feedstock in the production of other specialty chemicals. Quinoline derivatives, however, are useful in a myriad of applications, ranging from chelating agents, dyes and pesticides to pharmaceutically active compounds.[3]

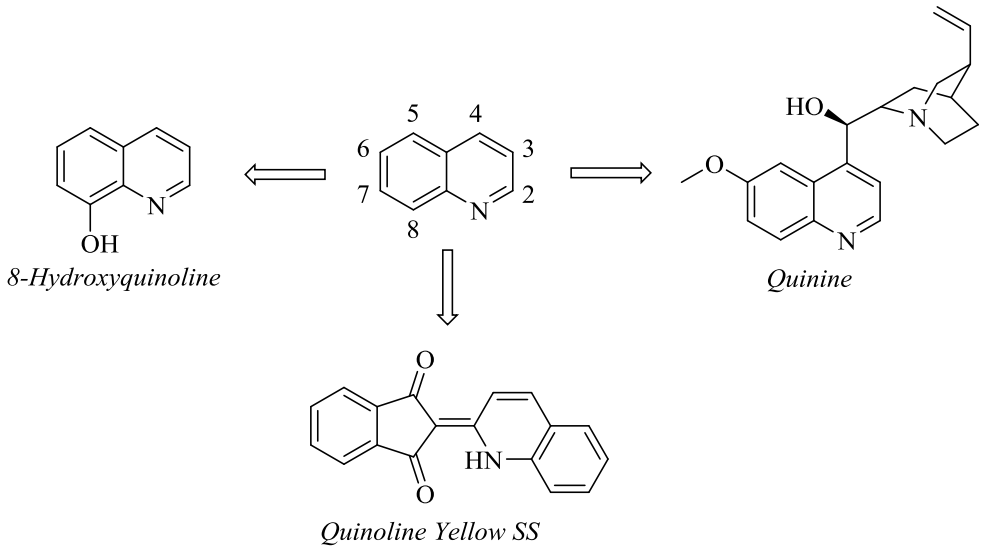


Figure 4.1.
Quinoline core and some of its derivatives: 8-hydroxyquinoline, a chelating agent, quinine, an anti-malaria drug and quinoline yellow, a colouring agent.

Quinoline derivatives are among the oldest substances isolated from natural resources and they are used in medicinal chemistry as anti-malarial, anti-bacterial, anti-inflammatory, anti-asthmatic and anti-hypertensive agents.[4] One of the most prominent examples is quinine, an antimalarial drug that is found naturally in plants as alkaloids.

In recent times, several members of quinoline family have displayed interesting electronic and photonic properties,[5] and for example tris(8-hydroxyquinolinato)aluminium (Figure 4.2), a coordination complex of aluminium and 8-hydroxychinoline, is used in organic light-emitting diodes (OLEDs). Other quinoline derivatives have found attractive applications as valuable synthons in the preparation of nano- and mesostructures.[6]

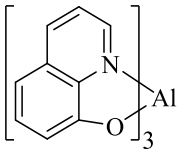


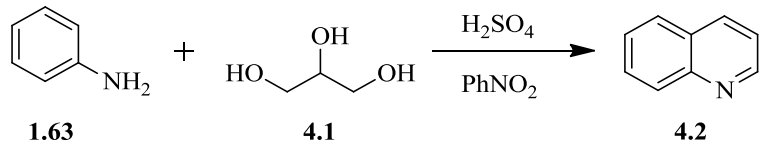
Figure 4.2
Tris(8-hydroxyquinolinato)aluminium

4.2 Quinoline Synthesis

The synthesis of quinolines has been continually reviewed during the last century. The first quinoline syntheses performed by Korner and König used allylanilines as starting materials but, unfortunately, this reaction was very low yielding. It was not until Skraup, Miller and von Döbner, and Friedländer that quinoline synthesis became practical. Indeed, in the late 19th century many new methods for quinoline synthesis emerged,[7] and some of the most common of these reactions are discussed below.

4.2.1 Skraup Reaction

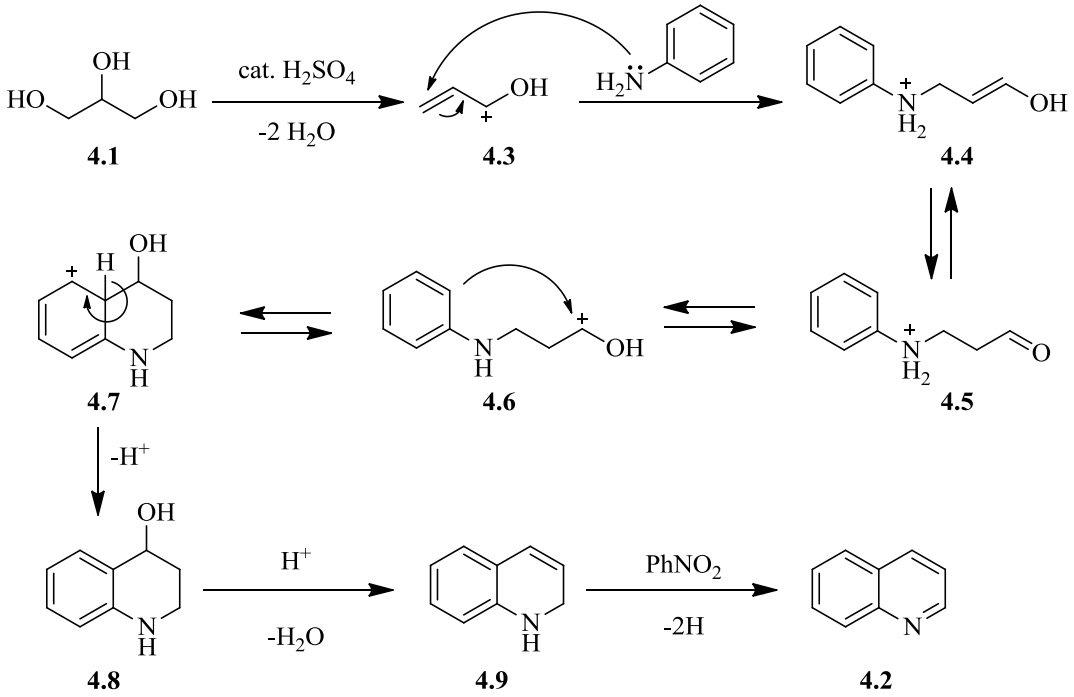
Skraup[7a] synthesis was named after a Czech chemist Zdenko Hans Skraup (1850-1910). In the early 1880s he synthesised quinoline by heating a mixture of nitroethane, aniline and glycerol with concentrated sulphuric acid. The first version of the Skraup synthesis yielded quinoline in very low yields,[8] but subsequently over the years the various modifications made to the reaction have rendered it a viable route to quinolines. When the reaction was performed for the first time, As_2O_3 was used as an oxidising agent and the reaction was known as violent reaction. In the modern version of Skraup synthesis nitrobenzene is used 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.[9] The direct use of acrolein is not recommended since it easily undergoes polymerisation under acid reaction conditions.



1.63 **4.1** **4.2**

Scheme 4.1
Skraup quinoline synthesis

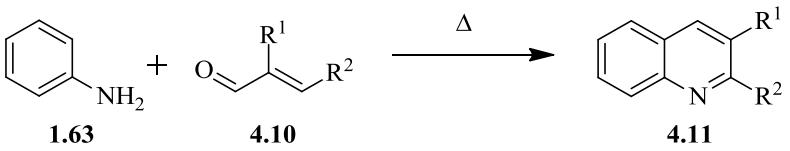
Even today, the reaction mechanism is unclear. It is believed that acrolein (obtained by dehydration of glycerol in presence of concentrated sulfuric acid) is an intermediate, which first undergoes 1,4-addition reaction followed by an intramolecular electrophilic aromatic substitution to give the corresponding dehydroquinoline **4.9** after dehydration. In the last step, nitrobenzene promotes the oxidation/aromatisation process affording final quinoline (Scheme 4.2).



Scheme 4.2
Reaction mechanism of Skraup reaction

4.2.2 Döbner-Miller Reaction

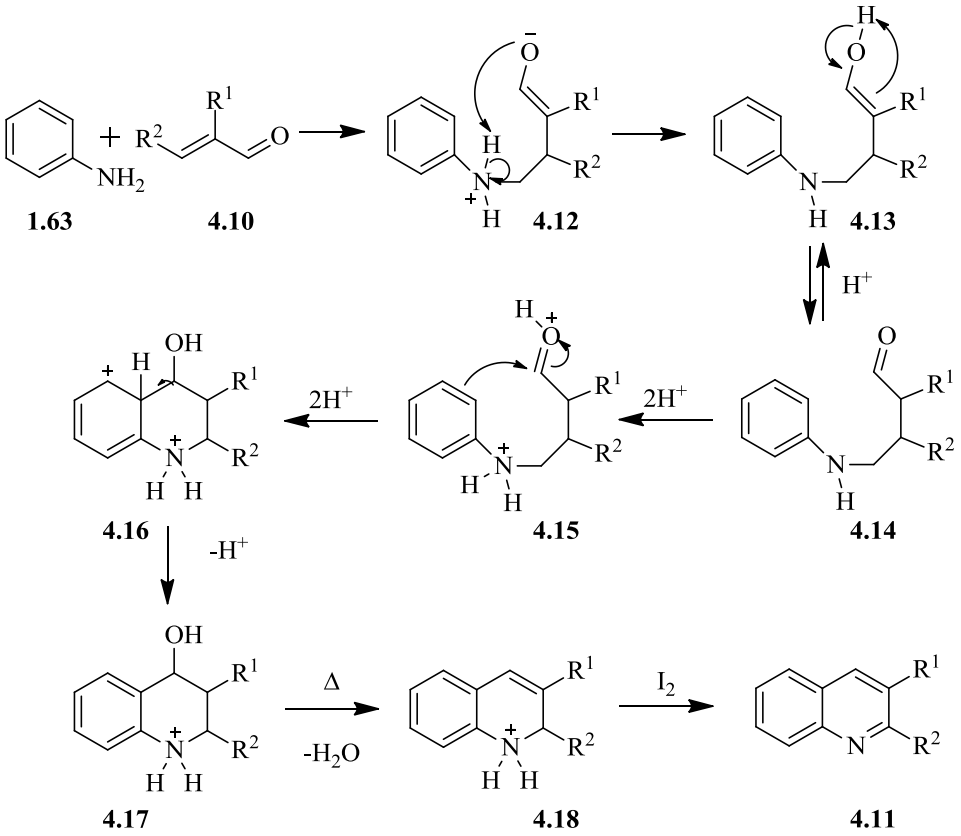
Oscar Döbner and Wilhelm Von Miller modified the original Skraup synthesis by replacing glycerol with an α,β-unsaturated aldehyde or ketone.[7b, 10] The method was further improved by Beyer, who used α,β-unsaturated carbonyl derivatives prepared *in situ* from two carbonyl compounds *via* an Aldol condensation.[11]



1.63 **4.10** **4.11**

Scheme 4.3
Döbner-Miller Reaction

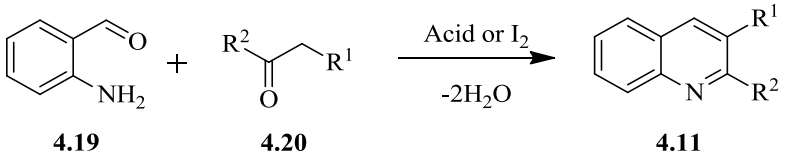
As for Skraup synthesis, the mechanism of Döbner-Miller reaction is still subject to debate. A plausible mechanism involves an initial attack of an aniline to the polarised C=C double bond of an unsaturated aldehyde, to generate the enolate **4.12**, that through 1,5-proton transfer gives the corresponding 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 through subsequent dehydration and oxidation (Scheme 4.4).



Scheme 4.4
A possible mechanism for the Döbner-Miller reaction with iodine as oxidant.

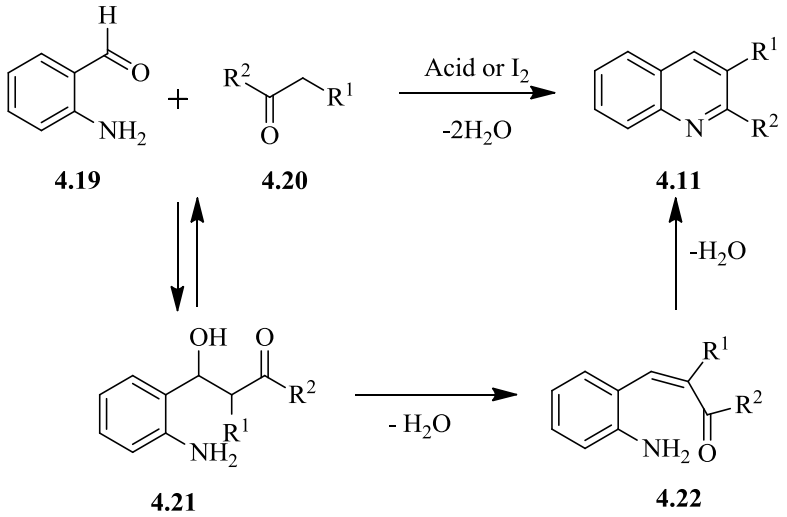
4.2.3 Friedländer Quinoline Synthesis

In the Friedländer synthesis a 2,3-disubstituted quinoline is formed *via* a reaction of 2-aminobenzaldehyde with ketones.[7c, 12] This method was developed by Friedrich Friedländer in the 1880s, and has subsequently been revisited various times.[13] The reaction can be catalysed by protic acids,[14] and Lewis acids.[15]



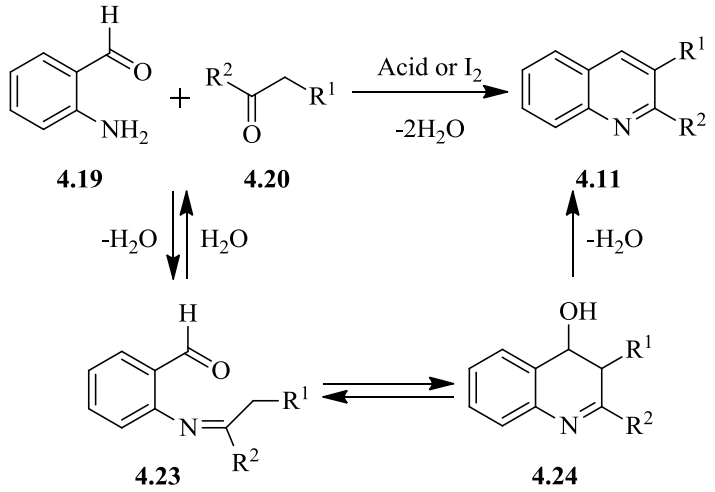
Scheme 4.5
Friedländer quinoline synthesis

Two viable reaction mechanisms exist for this reaction.[16] In the first mechanism 2-amino substituted carbonyl compound **4.19** and carbonyl compound **4.20** react in a rate-limiting step to aldol adduct **4.21**. This intermediate loses water in an elimination reaction to unsaturated carbonyl compound **4.22** and then loses water again in imine formation to quinoline **4.11**.



Scheme 4.6
A possible mechanism for Friedländer synthesis

In the second mechanism the first step is Schiff base formation to give imine **4.23**, followed by formation of **4.24**. Finally, elimination of H_2O gives quinoline **4.11**.[11]

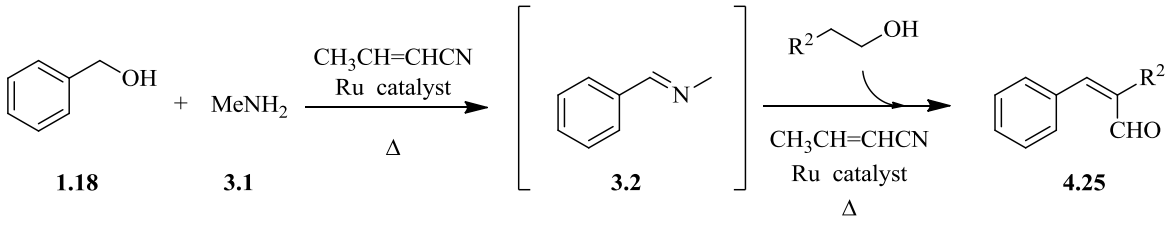


Scheme 4.7
A possible mechanism for Friedländer synthesis

4.3 Results and Discussion

Versatile applications of quinoline derivatives have resulted in an increased interest in developing new methodologies for the preparation of quinoline-based structures.[17] Despite the growing number of elegant syntheses of substituted quinolines that have been developed up to date, the use of harsh reaction conditions and some limits in the nature of reagents still make the development of more effective approaches an important topic in organic chemistry.[18] An acid-catalysed reaction between imines and enolisable aldehydes, a more recent evolution of the original Skraup synthesis, represents an interesting and versatile approach for preparation of functionalised quinolines.[17j, 19] Although this procedure provides a straightforward and practical access to quinolines, the starting materials can be very expensive or difficult to prepare, leaving considerable room for improvement.

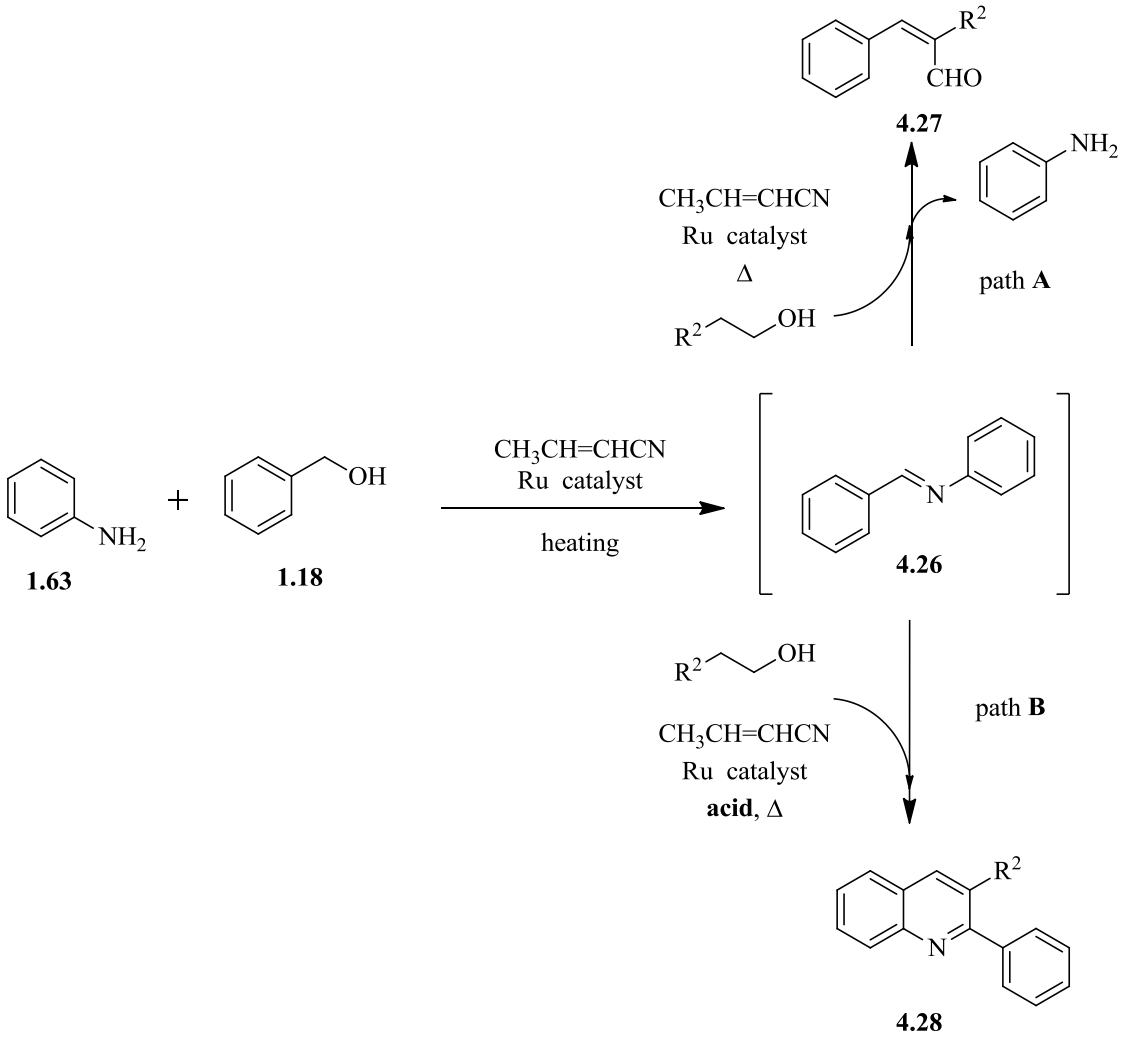
Chapter 3 describes a cross-dehydrogenative coupling (CDC) of two different primary alcohols in the presence of methylamine to obtain α-β-unsaturated aldehydes using a Ru-based catalyst.[20] In this reaction methylamine and benzyl alcohol react to form the corresponding imine **3.2**. The subsequent 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
Our strategy for the synthesis of α-β-unsaturated aldehydes

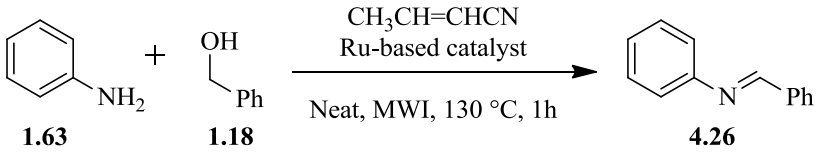
When using arylamines instead of methylamine in the imine formation step, this protocol might also be extendable to the preparation of substituted quinolines, thus improving the efficacy of the Skraup synthesis by using *hydrogen-transfer* methodology.[17l, 21] In the first step benzyl alcohol reacts with aniline leading to the imine intermediate **4.26** (Scheme 4.9). When **4.26** is submitted to a Mannich-type reaction with an aliphatic alcohol under acidic conditions, an acid-mediated cyclocondensation can take place instead of an elimination reaction, leading to quinoline **4.28** (Scheme 4.9, compare path A and path B). In this way it would be possible to

perform the reaction with simple and stable alcohols instead of aldehydes as starting materials.



Scheme 4.9
A strategy for the synthesis of quinolines from alcohols

The first task was the optimisation of the synthesis of arylimines using a hydrogen-transfer (HT) protocol. Aniline **1.63** and benzyl alcohol **1.18** were used as model substrates for establishing the optimal reaction conditions for Schiff base **4.26** formation (Scheme 4.10).



1.63 **1.18** **4.26**

Scheme 4.10
Optimisation of Schiff-base formation

We evaluated the performance of several Ru-based catalysts that are known to be particularly active in hydrogen transfer reactions. All of the ruthenium complexes studied gave reasonable yields of quinoline (Table 4.1, entries 1-5), and the best results were obtained with $RuH_2CO(PPh_3)_3$ (Table 4.1, entry 5). Different catalyst quantities were evaluated, and catalyst loading could be lowered to 4 mol% without decrease in the yield. 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, which led to a noticeable improvement on the catalyst efficiency (Table 4.1, entries 5 and 6). Using a slight excess of benzylalcohol further improved the Schiff base formation (Table 4.1, entries 7-10).

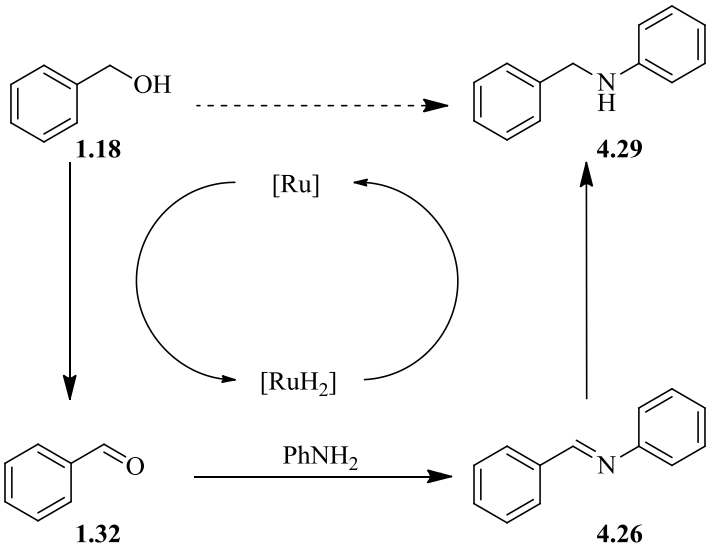
Table 4.1 *Catalyst screening for the Schiff-base formation of* ***4.1*** *with* ***4.30***

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 MWI. [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 was studied both with traditional heating and under MW conditions, and reactions proceeded smoothly in both cases. With MWI the reaction was complete in 1 h, whereas with traditional heating the imine formation required 24 h (Table 4.1, compare entries 9 and 12). Treatment of **1.63** (1 mmol) with 1.2 equivalents of **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 microwave dielectric heating at 130 °C for 1 h resulted in a quantitative conversion of **1.63** and **1.18** into imine **4.26** as determined by ^{1}HNMR analysis (Table 4.1, entry 9). Halving the reaction time or lowering the temperature caused the imine conversion to drop significantly

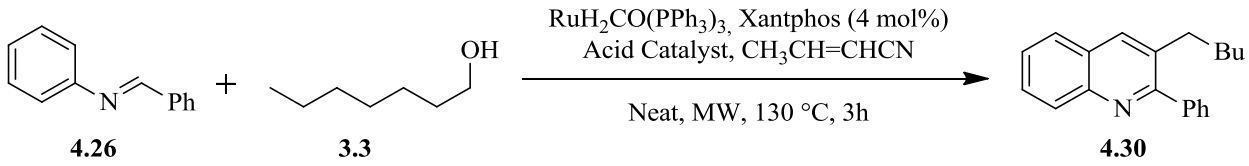
even after prolonged reaction times (Table 4.1, compare entries 15-17). When the reaction is performed without crotononitrile, benzyl alcohol is still oxidised quantitatively. Even so, the product imine was present in low quantities, as in the absence of a hydrogen acceptor the imine is reduced to give amine **4.29** through a borrowing hydrogen pathway, as shown in 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).



Scheme 4.11
*Reduction of imine **4.34** that occurs in the absence of crotononitrile*

Unfortunately all attempts in preparing Schiff bases 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.

Having now an efficient procedure for preparing imines in hand, we extended the application of our catalytic system to the reaction between imine **4.26** and heptanol **3.3** for the synthesis of quinolines. We were pleased to find that 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) afforded the corresponding quinoline **4.30** in good yields (Scheme 4.12).



4.26 **3.3** **4.30**

Scheme 4.12
Quinoline formation

Various acids were tested for the cyclocondensation step to form the quinoline. When HCl was used heptanol was not oxidised quantitatively, resulting in low yield of quinoline (Table 4.2, entries 1-2). One plausible reason can be that HCl inhibits the ruthenium catalyst used in the oxidation. We therefore decided to turn our attention to a heterogeneous acid (Table 4.2, entries 3-5), as this can be easily recycled. Unfortunately, again 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, CF_3COOH (TFA) was the most active in promoting the cyclisation reaction (Table 4.2, compare entries 1-7 with entry 9). We observed no product formation in the absence of an acid catalyst (Table 4.2, entry 11). Further optimisation studies showed that 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 any lower amounts of TFA resulted in diminished yields (Table 4.2, entry 10).

Table 4.2 *Optimisation of the cyclisation step*

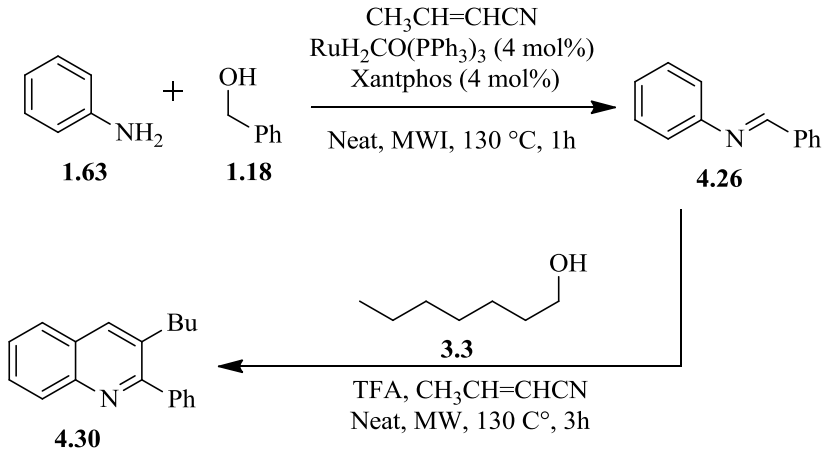
Entry	Acid Catalyst	**4.34** (mmol)	**4.35** (mmol)	Yield (%)[a]
1	HCl (0.5 mmol)[b]	3.0	1.0	10
2	HCl (0.5 mmol)[c]	3.0	1.0	12
3	SiO_2-OSO_3H (100 mg)	3.0	1.0	20
4	SiO_2-OSO_3H (250 mg)	3.0	1.0	20
5	SiO_2-OSO_3H (500 mg)	3.0	1.0	20
6	TsOH[d]	3.0	1.0	51
7	MsOH[e]	3.0	1.0	53
8	TFA (0.5 mmol)[f]	3.0	1.0	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)	1.5	1.0	51
16	TFA (0.3 mmol)	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. [e] Reaction preformed at 120 °C (MWI) for 3 h. [e] Reaction preformed at 130 °C (MWI) for 1 h.

Varying the molar alcohol **3.3** to imine **4.26** ratio under the optimised conditions afforded quinoline **4.30** in different yields (Table 4.2 entries 12-14). The best results were achieved with a 1.5:1 molar ratio (Table 4.2, entry 13). A decrease of the reaction temperature below 130 °C resulted in a significantly lower yields (Table 4.2, entries 15 and 16).

Once both steps were optimised separately, we attempted a direct one-pot conversion of benzyl alcohol **1.18**, aniline **1.63**, and 1-heptanol **3.3** into quinoline **4.30**. Unfortunately, performing both transformations in a one-pot fashion resulted in a complex reaction mixture where the main products were *N*-alkylated anilines. Therefore, we decided to carry out the synthesis of quinoline **4.30** *via* a telescopic reaction. This in the present case consists of a one-

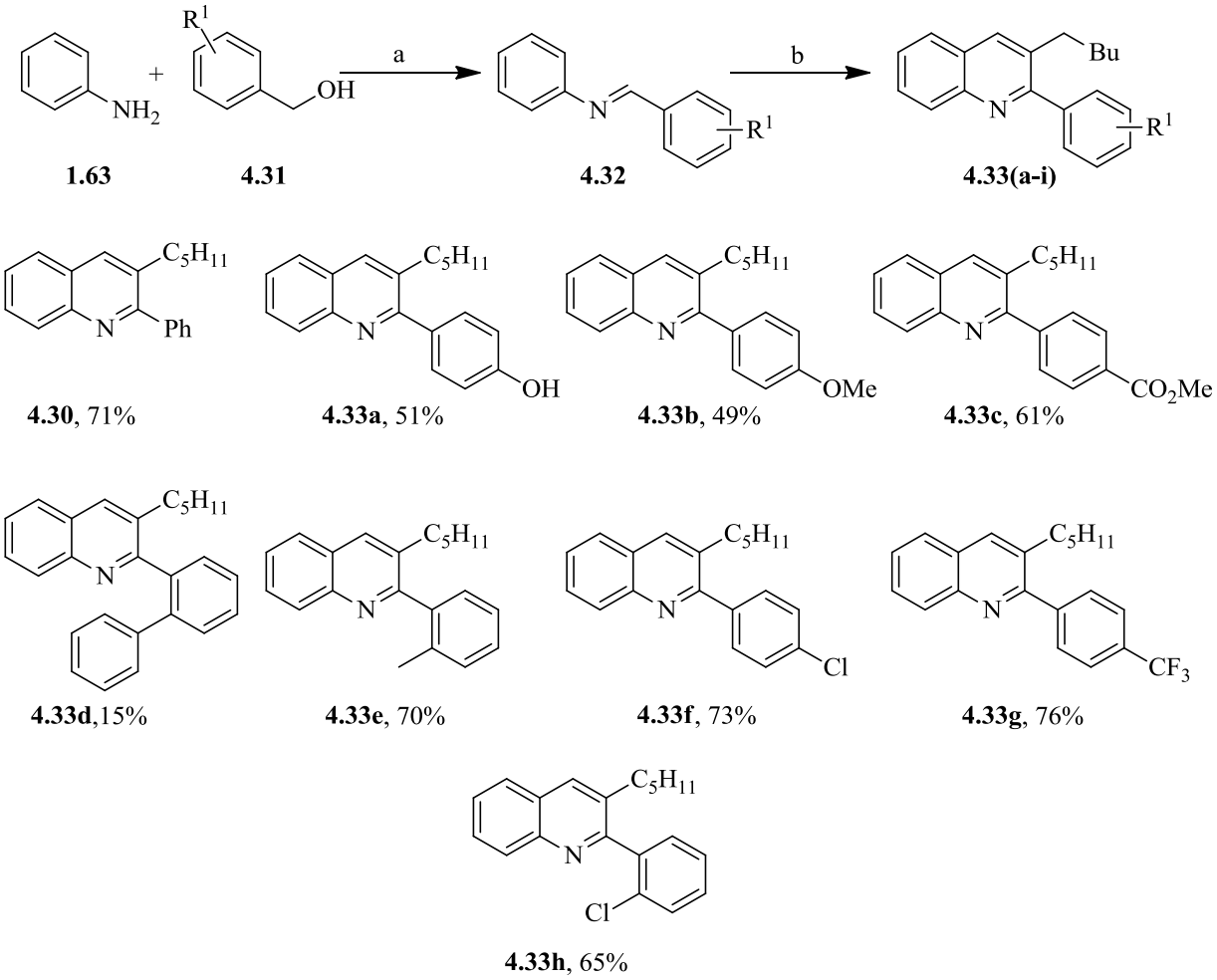
pot two-steps approach, that involves first the addition of benzyl alcohol, and then, in the second step, 1-heptanol into the reaction mixture (Scheme 4.13). The Ru-based catalyst was added in the first step, and it promotes the hydrogen transfer reactions in both steps of the process, while TFA was only added in the second step for promoting 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 via *a telescopic reaction*

In a typical optimised experiment, 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 MWI at 130 °C for 1 h. To the crude reaction mixture, 1-heptanol (1 mmol) was subsequently added, along with crotononitrile (2.2 mmol) and a catalytic amount of TFA (0.3 mmol). The resulting reaction mixture was heated (MWI) at 130 °C for further 3 h, affording the expected quinoline **4.30** in 71 % isolated yield.

We then used these optimised conditions to explore the scope and limitations of this procedure, combining a broad range of anilines with benzyl and aliphatic alcohols. First, we performed the reaction with substituted benzylic alcohols.



Scheme 4.14

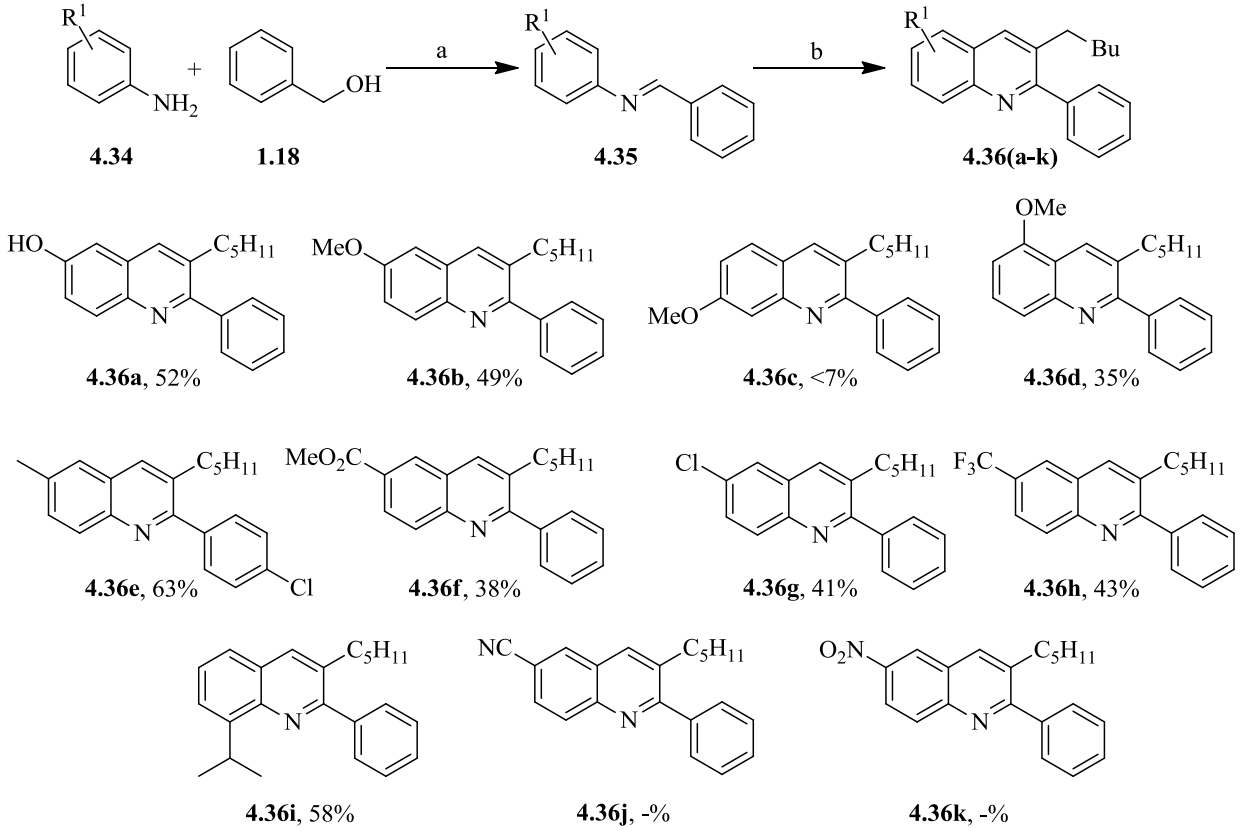
Synthesis of quinolines from substituted benzylic alcohols

a) $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%) , crotononitrile , Neat, MWI at 130 °C for 1 h.

b) TFA, crotononitrile,nNeat, MW, 130 C°, 3h

Alcohols bearing electron withdrawing groups on the aromatic system showed better activity than those bearing electron donating substituents, indicating that the reaction is sensitive to electronic effects (Scheme 4.14, compare quinolines **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. We also evaluated the effect of steric hindrance in this reaction, as shown by **4.33d** and **4.33e**. With a bulky substituent at the *ortho*-position of the aromatic ring, the yields of quinolines fell drastically (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**).

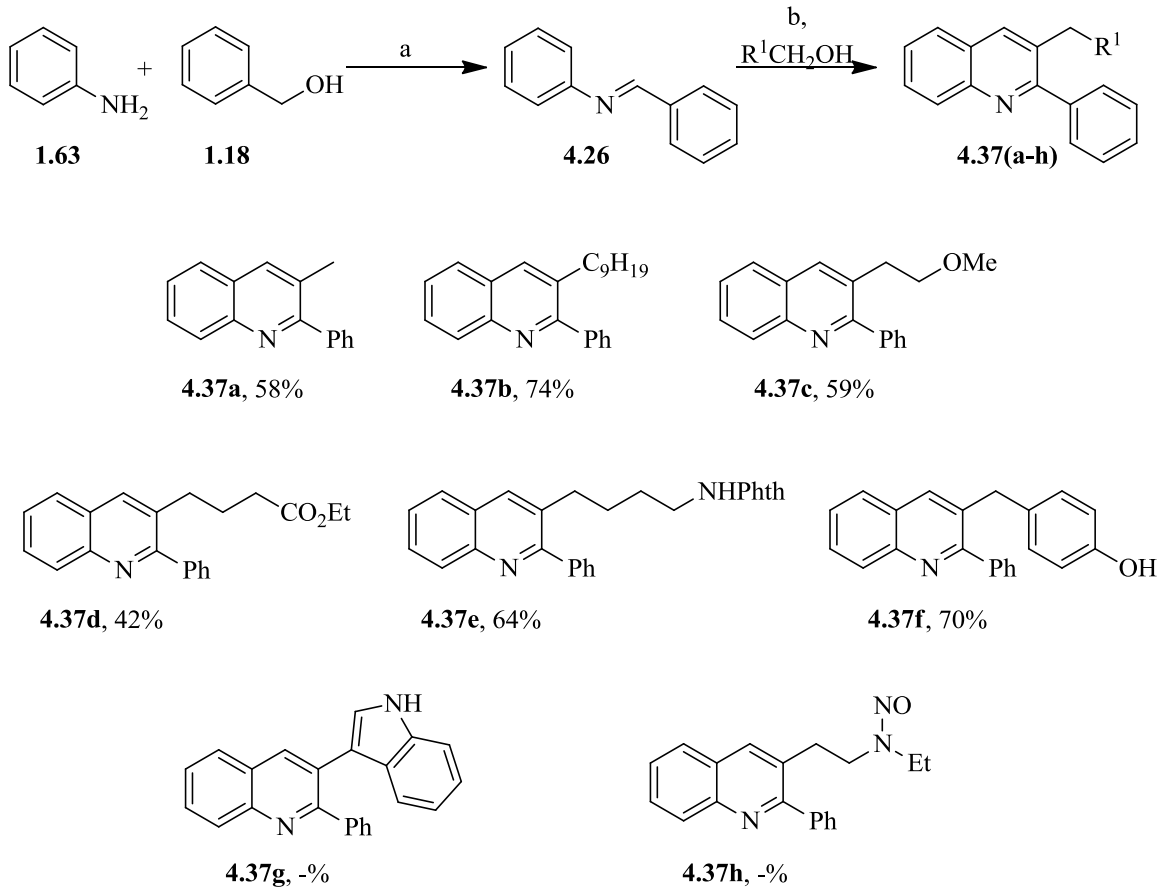
The protocol was then extended to a variety of arylamines (Scheme 4.15). A range of substituents were chosen to assess the feasibility of the reaction, and both electron withdrawing ant electron donating substituents were included. The study was completed with substituents in position *meta* to determine the regioselectivity of the reaction, and with 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°, 3h

Aniline derivatives with different functionalities worked satisfactorily although anilines containing electron withdrawing groups on the aromatic ring were found to be less reactive, giving slightly lower yields (Scheme 4,14, compare for example products **4.36b** and **4.36h**). 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, we synthesised quinolines with different aliphatic alcohols 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.

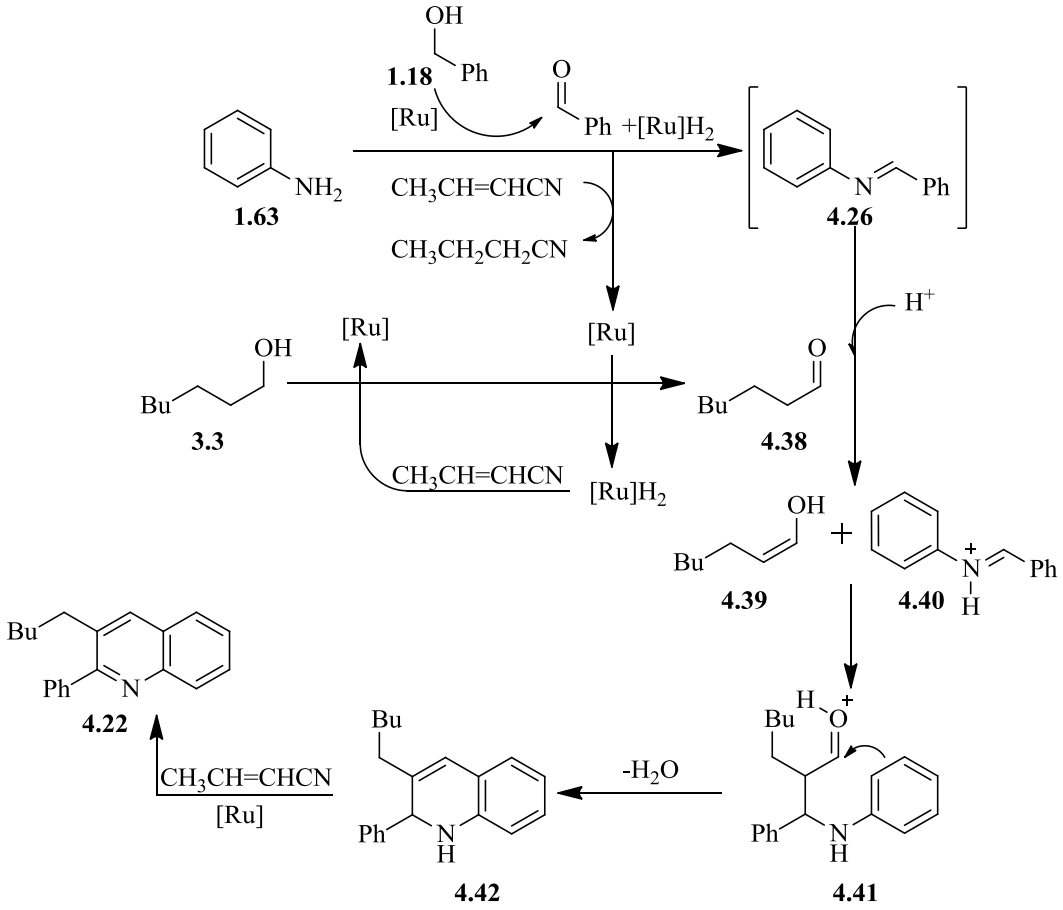


Scheme 4.16
Synthesis of quinolines with functionalised aliphatic alcohols
a) $RuH_2CO(PPh_3)_3$ (4 mol%), Xantphos (4 mol%), crotononitrile , Neat, MWI at 130 °C for 1 h.
b) TFA, crotonitrile, Neat, MWI, 130 C°, 3h

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** did we not observe any product formation (Scheme 4.16).

We proposed a reaction mechanism that 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 the imine intermediate **4.26** works as a 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, we did indeed obtain quinoline **4.22**, albeit with a lower yield (51%). We hypothesise 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.

4.4 Conclusions

We 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, which are 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 and, in addition, application of microwave irradiation heating considerably reduced reaction times. The possibility to carry out the reaction neat and without stoichiometric amounts of oxidants makes this reaction more environmentally benign and no cumbersome purification techniques are necessary. Many of the compounds synthesised using this procedure were previously unknown (78%), suggesting that our methodology may provide a direct route to quinoline structures inaccessible by a conventional approach.

4.5 References

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Chapter 5

Experimental

5.1 Materials and Methods

5.1.1 General Experimental Method

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. Flash column chromatography was performed with Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using *p*-anisaldehyde (otherwise $KMnO_4$) solution with subsequent heating. The eluents were technical grade and distilled prior to use. ^{1}H NMR spectra were recorded at 25 °C. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian VXR 300 (300 MHz) or a Bruker Avance III (400 MHz) NMR spectrometer at 25 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentuplet, sex = sextuplet, sept = septuplet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (*J*) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm). Deuterated NMR solvents were obtained from Aldrich. High resolution mass spectra (HRMS) were obtained by using electron impact (EI) or electrospray (ESI). Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thikness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 (m 3 min), to 300 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thikness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 (m 3 min), to 300 °C at the rate of 10 °C/min. The gas was used as a carrier gas. Temperatures of injection port and FID were kept constant

at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data.

5.1.2 Microwave Irradiation Experiments

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. The microwave heating was carried out at 130 °C using "*dynamic power*" mode with maximum power of 250 W for 3 hrs and operating at a frequency of 2.45GHz. The reaction mixtures were stirred with a magnetic stir bar during the irradiation. During the course of reactions, 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.

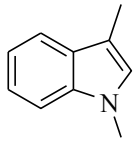
5.2 Ru Catalysed Cross-Dehydrogenative Coupling of Alcohols with Arylhydrazines: a New Entry to Indole Synthesis

5.2.1 General Procedure for the Preparation of Indole Derivatives

A typical reaction of *N*-Methyl-*N*-Phenylhydrazine with 1-propanol is described here to exemplify the general reaction procedure. Under argon stream, a mixture of 1-propanol (60 mg, 75 µl, 1 mmol), $Ru_3(CO)_{12}$ (13 mg, 0.02 mmol, 2 mol%), BIPHEP (16 mg, 0.03 mmol, 3 mol%), crotononitrile (67 mg, 82 µl, 1 mmol), *N*-Methyl-*N*-Phenylhydrazine (122 mg, 1 mmol) in *tert*-amyl alcohol (2.5 mL) was placed in a 10-mL microwave reaction vessel. To this red-rust solution anhydrous $ZnCl_2$ (136 mg, 1 mmol) was slowly added. Then the system was flushed with argon and the resulting reaction mixture was irradiated for 3 h at 130 °C in a microwave oven. Completion of reaction was monitored by thin layer chromatography. The solvent was removed under vacuum and the product was purified by flash chromatography.

5.2.2 Characterisation Data for Compounds (2.42-2.48a-v)

1,3-Dimethyl-1*H*-indole (2.42)



Colourless oil (93% isolated yield).

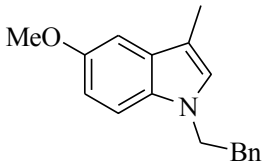
R_f= 0.63 (hexane/AcOEt: 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.58 (ddd, J^1 = 7.9 Hz, J^2= 1.2 Hz, J^3 = 0.8 Hz, 1H, ArH), 7.29-7.20 (m, 2H, ArH), 7.10 (ddd, J^1 = 7.9 Hz, J^2 = 6.5 Hz, J^3 = 1.2 Hz; 1H, ArH), 6.83 (s, 1H, CH), 3.74 (s, 3H, CH_3), 2.33 (d, J = 1.0 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):136.9 (s, Cq), 128.6 (s, Cq), 126.5 (s, CH), 121.4 (s, CH), 118.9 (s, CH), 118.4 (s, CH), 110.1 (s, Cq), 108.9 (s, CH), 32.4 (s, CH_3), 9.5 (s, CH_3).

These assignments matched with those previously published.[1]

5-Methoxy-3-methyl-1-phenethyl-1*H*-indole (2.45a)



Light yellow oil (89 % isolated yield).

R_f= 0.3 (4:1 hexane/AcOEt: 96/4).

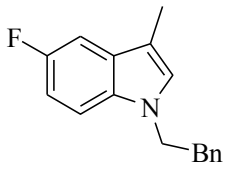
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.19 (m, 3H), 7.14 (d, J = Hz, 8.9 Hz, 1H), 7.07 (dd, J^1 = 7.3 Hz, J^2 = 1.7 Hz, 2H), 6.99 (d, J = 2.5 Hz, 1H), 6.85 (dd, J^1 =8.8 Hz, J^2= 2.5 Hz, 1H), 6.69 (d, J = 0.6 Hz, 1H), 4.19 (t, J = 7.5 Hz, 2 H), 3.85 (s, 3H), 3.01 (t, J =7.5 Hz, 2H), 2.25 (d, J = 0.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm**)**: 153.6, 138.7, 131.4, 129.0, 128.6, 128.4, 126.4, 126.0, 111.5, 109.8, 109.6, 100.9, 55.9, 47.9, 36.9, 9.5.

HRMS Calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1476.

These assignments matched with those previously published.[2]

5-Fluoro-3-methyl-1-phenethyl-1*H*-indole (2.45b)



Pale yellow oil (82% isolated yield).

R_f =0.29 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.27-3.11 (m, 5H), 7.07 (d, *J* =7.2 Hz, 2H), 6.91 (t, *J* = 8.8 Hz, 1H), 6.75 (s, 1H), 4.22 (t, *J* = 7.4 Hz, 2H), 3.03 (t, *J* = 7.4 Hz, 2H), 2.23 (s, 3H).

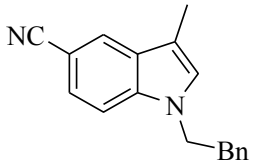
^{13}CNMR (75 MHz, $CDCl_3$) δ (ppm): 158.6 and 156.3 (d, J_{C-F}= 174 Hz, 1C), 138.5,132.7, 129.0 and 128.9 (d, J_{C-F}= 7 Hz, 1C), 128.7 and 128.6 (d, J_{C-F}= 8 Hz, 1C), 127.0, 126.6, 110.1 and 110.0 (d, J_{C-F}= 3 Hz, 1C), 109.7 and 109.4 (d, J_{C-F}= 20 Hz, 1C), 109.6 and 109.5 (d, J_{C-F}= 7 Hz, 1C), 103.9, 103.7, 48.0, 36.9, 9.5.

^{19}FNMR (376.5 MHz, $CDCl_3$, CF_3COOH used as internal standard) δ (ppm): -125.98 (td, J^1 = 9.4 Hz, J^2= 4.1 Hz, 1F);

^{19}F NMR (376.5 MHz, $CDCl_3$, decoupled) δ (ppm): -125.98 (s, 1F).

HRMS Calcd for $C_{17}H_{16}FN$: 253.1267. Found: 253.1259.

3-Methyl-1-phenethyl-1*H*-indole-5-carbonitrile (2.45c)



Colourless oil (83% isolated yield)

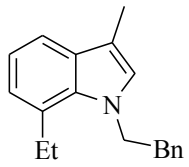
R_f = 0.40 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 3H), 7.24-7.17 (m, 2H), 7.13-7.08 (m, 2H), 6.74 (s, 1H), 4.27 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR (75 MHz, CDCl3) δ (ppm): 138.7, 136.0, 128.8, 128.7, 128.6, 126.6, 125.4, 121.4, 119.0, 118.5, 110.2, 109.1, 47.9, 37.0, 9.5.

HRMS Calcd for $C_{18}H_{16}N_2$: 260.1313. Found: 260.1321

7-ethyl-3-methyl-1-phenethyl-1*H*-indole (2.45d)



Colourless oil (78% isolated yield).

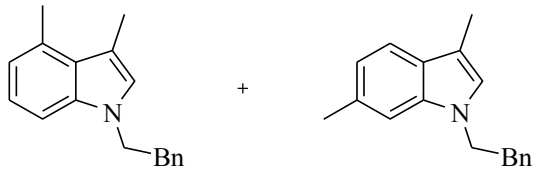
R_f = 0.41 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (dd, J^1 = 7.7 Hz, J^2 = 1.5 Hz, 1H), 7.33-7.25 (m, 3H), 7.13 (dd, J^1 = 7.3 Hz, J2 = 1.6 Hz, 2H), 7.03 (dd, J^1 = 13.3 Hz, J^2 = 7.3 Hz, 2H), 6.72 (s, 1H), 4.41 (t, J = 8.4 Hz, 2H), 3.10-2.98 (m, 4H), 2.28 (s, 3H), 1.36 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.5, 133.9, 130.4, 128.7, 128.6, 127.3, 127.2, 126.6, 122.6, 119.1, 117.1, 110.8, 50.2, 38.9, 25.8, 16.0, 9.5.

HRMS Calcd for $C_{19}H_{21}N$: 263.1674. Found: 263.1662.

3,6-Dimethyl-1-phenethyl-1*H*-indole + 3,4-Dimethyl-1-phenethyl-1*H*-indole (2.45e)



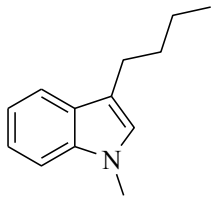
Colourless oil (80% isolated yield).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, J = 8 Hz, 0.5H), 7.30-7.21 (m, 3H), 7.14-7.12 (m, 2H), 7.07-7.03 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 0.5H), 6.80 (d, *J* = 7.2 Hz, 0.3H), 6.67 (d, *J* = 8, 0.7 H), 4.22 (t, J^1 = 7.6 Hz, 2H), 3.06 (t, J^1 = 7.6 Hz, 2H), 2.71 (s, CH_3Ar, 1.3H), 2.48 (s, CH_3Ar, 1.7H), 2.47 (d, *J* = 0.8 Hz, C=C-CH_3,1.3H), 2.27 (d, *J* = 0.8 Hz, C=C-CH_3, 1.7H).

^{13}C NMR (75 MHz, CDCl3) δ (ppm): 138.8, 136.5, 131.6, 131.1, 128.8, 128.6, 127.2, 126.8, 126.6, 125.7, 124.8, 121.5, 120.4, 120.1, 118.7, 111.1, 110.1, 109.1, 107.1, 47.84, 47.77, 36.94, 36.81, 22.0, 20.1, 12.9, 9.6.

3-Butyl-1-methyl-1*H*-indole (2.48a)



Pale yellow oil (78% isolated yield).

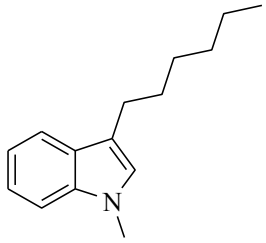
R_f = 0.58 (hexane/AcOEt: 98/2).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.63 (ddt, J^1 = 7.9 Hz, J^2 = 1.2 Hz, J^3 = 0.7 Hz, 1H), 7.36–7.20 (m, 2H), 7.12 (dddd, J^1 = 8.0 Hz, J^2 = 6.8 Hz, J^3 = 1.3 Hz, J^4 = 0.5 Hz, 1H), 6.84 (s, 1H), 3.76 (s, 3H), 2.77 (t, J = 7.8 Hz, 2H), 1.80–1.63 (m, 2H), 1.50–1.32 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.0, 128.0, 125.9, 121.3, 119.0, 118.3, 115.6, 109.0, 32.6, 32.4, 24.7, 22.7, 14.0.

These assignments matched with those previously published.[3]

3-Hexyl-1-methyl-1*H*-indole (2.48b)



Colourless oil (71% isolated yield).

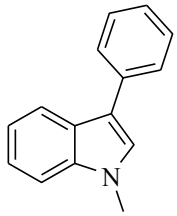
R_f = 0.64 (hexane/AcOEt: 98/2).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64–7.59 (m, 1H), 7.35–7.18 (m, 2H), 7.11 (ddt, J^1 = 7.8 Hz, J^2 = 6.9 Hz, J^3 = 1.1 Hz, 1H), 6.84 (s, 1H), 3.75 (s, 3H), 2.73 (t, J = 7.5 Hz, 2H), 1.72 (pent, J = 6.7 Hz, 2H), 1.51–1.25 (m, 6H), 0.91 0.89 (t, J = 6.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.0, 128.0, 125.9, 121.4, 119.1, 118.4, 115.7, 109.1, 32.5, 31.8, 30.5, 29.42, 25.1, 22.7, 14.2.

These assignments matched with those previously published.[4]

1-Methyl-3-phenyl-1*H*-indole (2.48c)



Light yellow oil (76% isolated yield).

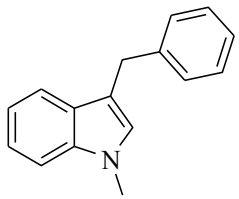
R_f = 0.33 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.30-7.24 (m, 3H), 7.21-7.17 (m, 1H), 3.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.5, 135.6, 128.7, 127.1, 126.5, 126.0, 125.6, 121.9, 119.8, 119.7, 116.4, 109.5, 32.83.

These assignments matched with those previously published.[5]

3-Benzyl-1-methyl-1H-indole (2.48d)



Pale yellow oil (86% yield).

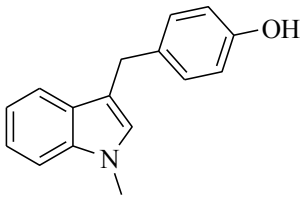
R_f = 0.42 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (dt, J^1 = 7.9 Hz, J^2 = 0.9 Hz, 1H), 7.35-7.14 (m, 7H), 7.08 (ddd, J^1 = 8.0, 6.9 Hz, J^2 =1.2 Hz, 1H), 6.76 (s, 1H), 4.12 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.8, 137.5, 129.0, 128.6, 128.2, 127.4, 126.1, 121.9, 119.5, 119.1, 114.5, 109.4, 37.8, 31.8.

These assignments matched with those previously published.[6]

4-((1-Methyl-1*H*-indol-3-yl)methyl)phenol (2.48e)



Reddish oil (83% yield).

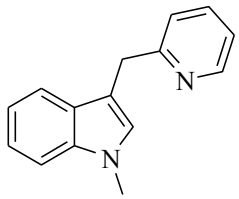
R_f = 0.15 (hexane/AcOEt: 9/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (dt, J^1= 7.9 Hz, J^2 = 0.9 Hz, 1H), 7.36-7.22 (m, 2H), 7.21-7.05 (m, 3H), 6.76-6.73 (ps, 3H), 4.92 (bs, 1H, OH), 4.06 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.6, 137.2, 133.7, 129.7, 127.7, 127.0, 121.5, 119.2, 118.6, 115.1, 114.7, 109.0, 32.5, 30.6.

HRMS Calcd for $C_{16}H_{15}NO$: 237.1154. Found: 237.1141.

1-Methyl-3-(pyridin-2-ylmethyl)-1*H*-indole (2.48f)



Colourless oil (67% yield).

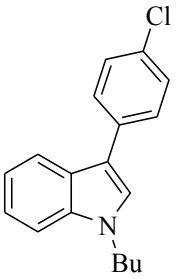
R_f = 0.26 (hexane/AcOEt: 7/3).

^{1}H NMR (400 MHz, $CDCl^3$) δ (ppm): 8.57 (ps, 1H), 8.44 (d, *J* = 3.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.34-7.16 (m, 3H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.77 (s, 1H), 4.10 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.9, 147.3, 137.2, 136.9,136.3, 127.5, 127.2, 123.4, 121.8, 119.0, 114.9, 113.0, 109.3, 32.7, 28.8.

HRMS Calcd for $C_{15}H_{14}N_2$: 222.1157. Found: 222.1145.

1-Butyl-3-(4-chlorophenyl)-1*H*-indole (2.48g)



Colourless oil (80% yield).

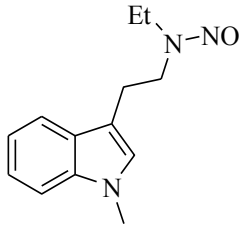
R_f = 0.41 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.45-7.42 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 4.16 (t, *J* = 7.1 Hz, 2H), 1.89 (quintet, *J* = 7.4 Hz, 2H), 1.42 (q, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$) δ (ppm): 136.8, 134.2, 131.1, 128.8, 128.3, 126.0, 125.6, 121.9, 120.0, 119.7, 115.4, 109.8, 46.1, 32.2, 20.2, 13.7.

HRMS Calcd for $C_{18}H_{18}ClN$: 283.1128. Found: 283.1133.

***N*-ethyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)nitrous amide (2.48h)**



Colourless oil (86% isolated yield).

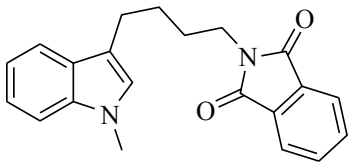
R_f = 0.47 (hexane/AcOEt: 7/3).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.60 (ddt, J^1 = 19.4 Hz, J^2 =7.9 Hz, J^3 =1.0 Hz, 1H), 7.30 (ddt, J^1 = 8.2 Hz, J^2 =4.6 Hz, J^3 =0.9 Hz, 1H), 7.23 (dddd, J^1 = 8.2 Hz, J^2 = 6.8 Hz, J^3 =3.1 Hz, J^4 =1.3 Hz, 1H), 7.13 (ddt, J^1 = 7.9 Hz, J^2 = 6.9 Hz, J^3 = 0.9 Hz, 1H), 6.88 (s, 0.5H), 6.84 (s, 0.5 H), 4.37 (t, *J* = 7.6 Hz, 1H), 4.00 (q, *J* = 7.3 Hz, 1H), 3.73 (s, 1.5H, NMe), 3.72 (s, 1.5H, NMe); 3.82 (t, *J* = 7.6 Hz, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 3.22 (td, J^1 = 7.6 Hz, J^2 = 0.8 Hz, 1H), 2.95 (td, J^1 = 7.6 Hz, J^2 =0.7 Hz, 1H), 1.32 (t, *J* = 7.3 Hz, 1.5H), 1.07 (t, *J* = 7.2 Hz, 1.5H).

^{13}C NMR (75 MHz, DMSO-d_6, 50 °C) δ (ppm): 137.2, 128.1, 127.8, 121.7, 119.0, 118.8, 110.7, 110.1, 52.3, 44.5, 32.7, 24.7, 11.4.

HRMS Calcd for $C_{13}H_{17}N_3O$: 231.1372. Found: 231.1381.

2-(4-(1-Methyl-1*H*-indol-3-yl)butyl)isoindoline-1,3-dione (2.48i)



Pale yellow oil (75% isolated yield).

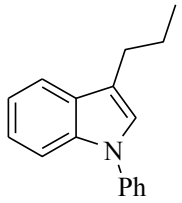
R_f = 0.15 (hexane/AcOEt: 9/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (dd, J^1 = 5.4 Hz, J^2 = 3.1 Hz, 2H), 7.66 (td, J^1 = 5.2 Hz, J^2 = 2.1 Hz, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.27-7.10 (m, 2H), 7.10-7.00 (m, 1H), 6.81 (s, 1H), 3.70 (m, 5H), 2.78 (t, J = 6.9 Hz, 2H), 1.84-1.60 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.5, 137.0, 133.9, 132.2, 127.9, 126.2, 123.2, 121.4, 119.0, 118.6, 114.7, 109.1, 37.9, 32.6, 28.5, 27.6, 24.6.

HRMS Calcd for $C_{21}H_{20}N_2O_2$: 332.1525. Found: 332.1518.

1-Phenyl-3-propyl-1*H*-indole (2.48l)



Pale yellow oil (73% isolated yield).

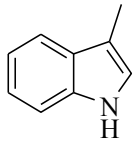
R_f = 0.59 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (ddd, J^1 = 7.5 Hz, J^2 = 1.5 Hz, J^3 = 0.8 Hz, 1H), 7.57 (ddd, J^1 = 8.3 Hz, J^2 = 1.3 Hz, J^3 = 0.8 Hz, 1H), 7.51 (s, 2H), 7.50 (s, 2H), 7.36-7.28 (m, 1H), 7.26-7.16 (m, 2H), 7.14-7.13 (m, 1H), 2.79 (dd, J^1 = 8.1 Hz, J^2 = 7.0 Hz, 2H), 1.82-1.72 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl^3$) δ (ppm): 140.0, 136.0, 129.5, 125.9, 125.0, 124.0, 122.2, 119.7, 119.3, 118.0, 110.4, 109.2, 27.2, 23.2, 14.2.

These assignments matched with those previously published.[7]

3-Methyl-1*H*-indole (2.48m)



White crystalline solid mp 95-97 °C (lit.[8] 96 °C) (43% yield).

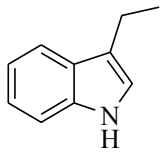
R_f = 0.47 (hexane/AcOEt: 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 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).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.5, 129.7, 122.0, 121.7, 119.3, 119.0, 111.9, 111.1, 9.8.

These assignments matched with those previously published.[9]

3-Ethyl-1*H*-indole (2.48n)



Clear oil (Lit.[10] mp = 43–45 °C) (40% isolated yield).

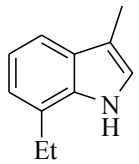
R_f = 0.49 (hexane/AcOEt: 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 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).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.5, 132.2, 127.5, 121.9, 120.4, 119.1, 118.9, 110.0, 18.3, 14.4.

These assignments matched with those previously published.[11]

7-Ethyl-3-methyl-1*H*-indole (2.48o)



Colourless oil (41% isolated yield).

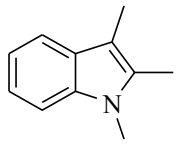
R_f = 0.58 (hexane/AcOEt: 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83 (bs, NH, 1H), 7.49 (d, J = 6.0 Hz, 1H), 7.11 (dt, J^1 = 14.4 Hz, J^2 = 7.2 Hz, 2H), 6.97 (dd, J^1 = 2.2 Hz, J^2 = 1.1 Hz, 1H), 2.87 (q, J = 7.5 Hz, 2H), 2.37 (d, J = 3 Hz, 3H), 1.39 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 135.4, 128.3, 126.5, 121.4, 120.7, 119.7, 116.8, 112.4, 24.2, 14.0, 9.9.

These assignments matched with those previously published.[12]

1,2,3-Trimethyl-1*H*-indole (2.48p)



Pale yellow oil (59% isolated yield).

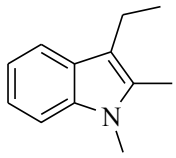
R_f = 0.6 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (d, J = 7.5 Hz, 1H), 7.27 (dd, J^1 = 7.9 Hz, J^2 = 1.0 Hz, 1H), 7.23- 7.15 (m, 1H), 7.11 (ddd, J^1 = 7.6 Hz, J^2 = 6.9 Hz, J^3 =1.3 Hz, 1H), 3.67 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.7, 132.8, 128.6, 120.7, 118.8, 118.1, 108.5, 106.4, 29.7, 10.3, 9.0.

These assignments matched with those previously published.[13]

3-Ethyl-1,2-dimethyl-1*H*-indole (2.48q)



Colourless oil (61% isolated yield).

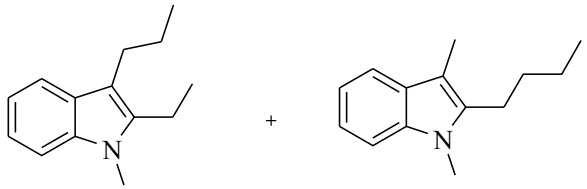
R_f = 0.50 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 (dd, J^1 = 7.8 Hz, J^2 = 0.7 Hz, 1H), 7.32-7.28 (m, 1H), 7.20 (ddd, J^1 = 8.0 Hz, J^2 = 7.0 Hz, J^3 = 1.1 Hz, 1H), 7.12 (ddd, J = 7.8, 6.9, 1.0 Hz, 1H), 3.69 (s, 3H), 2.79 (q, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.5, 132.0, 127.4, 120.3, 118.5, 118.0, 113.2, 108.5, 29.4, 17.7, 15.8, 10.0.

These assignments matched with those previously published.[14]

2-Ethyl-1-methyl-3-propyl-1*H*-indole + 2-butyl-1,3-dimethyl-1*H*-indole (2.48r)



Colorless oil (65% isolated yield).

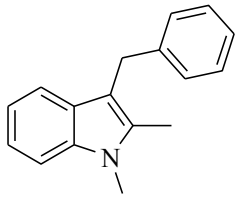
R_f = 0.6 (hexane/AcOEt: 96/4).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (dddd, J = 13.6, 7.8, 1.2, 0.7 Hz, 1H, we have set this integral as reference value), 7.24-7.22 (m, 1H), 7.14 (tdd, J = 7.6, 2.0, 1.2 Hz, 1H), 7.09-7.03 (m, 1H), 3.67 (s, 1H, NMe), 3.66 (s, 2H, NMe), 2.75 (pq, 7.2 Hz, 3H), 2.68 (t, J = 7.6 Hz, 1H), 2.25 (s, C=C-Me, 2H), 1.65 (pq, J = 7.4 Hz, 1H), 1.59-1.51 (m, 3H), 1.40 (pq, J = 7.4 Hz, 2H), 1.20 (t, J = 7.6 Hz, 1H), 0.97 (pq, J = 4.5 Hz, 2H), 0.92 (pt, J = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.4, 137.1, 136.7, 136.6, 128.4, 127.9, 120.5, 120.4, 118.5, 118.4, 118.0, 111.0, 108.5, 108.4, 106.3, 32.1, 29.6, 29.5, 26.6, 24.6, 24.2, 22.5, 17.7, 14.8, 14.3, 14.0, 8.8.

These data are in accordance with those published in the literature.[15]

3-Benzyl-1,2-dimethyl-1*H*-indole (2.48s)



Greenish oil (62% isolated yield).

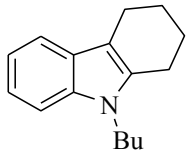
R_f = 0.35 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 7.8 Hz, 1H), 7.25-7.06 (m, 7H), 7.05- 6.97 (m, 1H), 4.08 (s, 2H), 3.62 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 142.0, 136.7, 133.6, 128.3, 128.2, 120.0, 125.7, 120.6, 118.9, 118.4, 109.8, 108.6, 30.5, 29.6, 10.5.

These data are in accordance with those published in the literature.[16]

9-Butyl-2,3,4,9-tetrahydro-1*H*-carbazole (2.48t)



Amber oil (80% isolated yield).

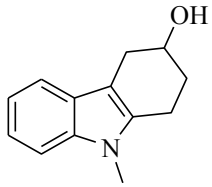
R_f = 0.41 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 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).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.0, 135.2, 127.2, 120.5, 120.2, 118.2, 117.6, 109.1, 42.6, 32.5, 23.3, 22.2, 21.0, 20.3.

These assignments matched with those previously published.[17]

9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol (2.48u)



Dark oil (52% isolated yield).

R_f = 0.26 (hexane/AcOEt: 7/3).

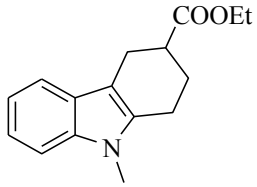
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, J = 7.65 Hz, 1H), 7.29-7.22 (m, 1H), 7.16 (td, J^1 = 7.2 Hz, J^2 = 0.8 Hz, 1H), 7.04 (td, J^1 = 7.2 Hz, J^2 = 0.8 Hz, 1H), 4.27 (m, 1H), 3.62 (s, 3H), 3.11 (dd, J^1 = 15.24 Hz, J^2 = 4.71, 1H), 2.94-2.64 (m, 3H), 2.20-1.98 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.3, 134.2, 127.0, 120.8, 118.8, 117.6, 108.6, 105.9, 67.5, 30.9, 30.6, 29.1, 19.5.

HRMS Calcd for $C_{13}H_{15}NO$: 201.1154. Found: 201.1163.

These assignments matched with those previously published.[18]

Ethyl 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (2.48v)



Brown oil (62% isolated yield).

R_f = 0.15 (hexane/AcOEt: 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (d, J = 7.47 Hz, 1H), 7.26-7.24 (m, 1H), 7.16 (dt, J^1 = 7.98 Hz, J^2 = 1.4 Hz, 1H), 7.07 (dt, J^1 = 7.98 Hz, J^2 = 1.4 Hz, 1H), 4.2 (dq, J^1 = 7.15 Hz, J^2 = 1.59, 2H), 3.62 (s, 3H), 3.09 (dd, J^1 = 15.24 Hz, J^2 = 5.4 Hz, 1H), 2.95-2.83 (m, 2H), 2.80-2.77 (m, 2H), 2.45-2.30 (m, 1H), 2.10-1.9 (m, 1H), 1.3 (t, J = 7.15 Hz ,3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.6, 137.0, 134.7, 126.8, 120.8, 118.8, 117.8, 108.5,107.5, 60.5, 40.3, 29.1, 25.8, 24.0, 21.4, 14.3.

These assignments matched with those previously published.[19]

5.3 Pd/C-Catalysed Dehydrogenative Generation of Imines from Amines. Application to Indole Synthesis Via Cross-Dehydrogenative Coupling of Amines with Arylhydrazines

5.3.1 General procedure for the preparation of arylhydrazone derivatives.

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 **2.51** as pale yellow oil (213 mg, 98 %).

5.3.2 General procedure for the preparation of indole derivatives.

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 heated, under vigorous stirring at 130 ˚C for 3 hours.

5.3.3 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.

5.3.4 Palladium leaching test

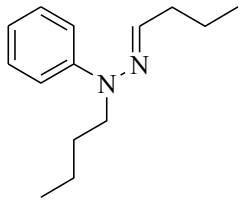
ICP-MS Analyses: prior to ICP-MS analyses, samples were subjected to a complete mineralization/dissolution process. The filtrate obtained after hot filtration of the reaction mixture was evaporated under reduced pressure. A mixture of concentrated H_2SO_4 (3 mL) and fuming HNO_3 (2 mL) was added to the 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.

5.3.5 Characterisation data for compounds (2.51-2.71)

1-Butyl-2-butylidene-1-phenylhydrazine (2.51)



Pale yellow oil (98 % isolated yield).

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

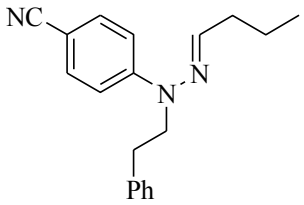
IR (film) cm^{-1}: 2958, 2930, 2871, 1595, 1498, 1390, 1333, 1278, 1223, 1166, 1117.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

4-(2-Butylidene-1-phenethylhydrazinyl)benzonitrile (2.56a)



Crystalline white solid (94 % isolated yield); m.p 69-70 °C.

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

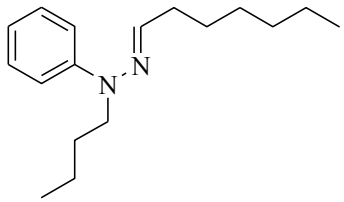
IR (film) cm^{-1}: 3026, 2959, 2870, 2215, 1601, 1509, 1397, 1337, 1133, 830.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.34-7.30 (m, 2H), 7.26 (dd, J = 6.0 Hz, 1.2 Hz, 1H), 7.22-7.19 (m, 4H), 7.04 (t, J = 5.2 Hz, 1H), 3.98 (t, J = 7.8 Hz, 2H), 2.85 (d, J = 7.9 Hz, 2H), 2.35 (dt, J = 7.3, 3.7 Hz, 2H), 1.62-1.56 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 149.9, 139.0, 138.2, 133.4, 128.9, 128.7, 126.9, 120.2, 113.2, 101.0, 45.7, 35.1, 31.2, 20.5, 13.8.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.22; H, 7.30; N, 14.48.

1-Butyl-2-heptylidene-1-phenylhydrazine (2.56b)



Light yellow oil (97 % isolated yield).

R_f = 0.68 (hexane/AcOEt: 98/2).

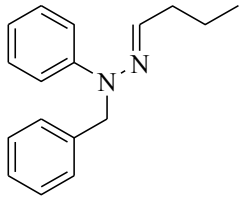
IR (film) cm^{-1}: 2957, 2927, 2856, 1595, 1480, 1467, 1390, 1332, 1278, 1224, 1166, 1117, 1034, 747.

^{1}H NMR (400 MHz; CDCl$_3$): δ 7.28-7.23 (m, 2H), 7.21-7.18 (m, 2H), 6.88-6.81 (m, 2H), 3.71 (t, J = 7.8 Hz, 2H), 2.35 (td, J^1 = 7.5 Hz, J^2 = 5.3 Hz, 2H), 1.56 (dt, J = 9.0, 4.8 Hz, 4H), 1.35 (td, J = 17.4, 10.5 Hz, 8H), 0.97 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz; CDCl$_3$): δ147.7, 135.5, 129.0, 114.2, 119.3, 45.2, 33.2, 31.8, 29.0, 27.6, 27.0, 22.6, 20.4, 14.1, 14.0.

Anal. Calcd for C$_{17}$H$_{28}$N$_2$: C, 78.40; H, 10.84; N, 10.76. Found: C, 78.48; H, 10.80; N, 10.72.

1-Benzyl-2-butylidene-1-phenylhydrazine (2.56c)



Light yellow oil (96 % isolated yield);

R_f = 0.49 (4% AcOEt:hexane);

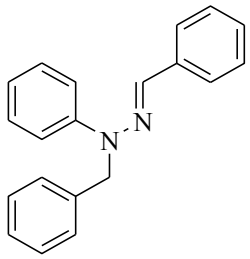
IR (film) cm^{-1}: 3062, 2959, 2930, 2870, 1595, 1497, 1454, 1393, 1331, 1239, 1147, 946, 749.

^{1}H NMR (400 MHz; CDCl$_3$): δ 7.33-7.24 (m, 7H), 7.17 (d, J = 7.1 Hz, 2H), 6.88-6.84 (m, 1H), 6.70 (t, J = 5.3 Hz, 1H), 4.99 (s, 2H), 2.25 (td, J = 7.4, 5.3 Hz, 2H), 1.49 (q, J = 7.4 Hz, 2H), 0.89 (d, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz; CDCl$_3$): δ 174.1, 147.2, 134.4, 129.0, 119.5, 114.2, 51.53, 39.5, 33.9, 32.7, 26.9, 24.5, 9.9.

These assignments matched with those previously published.[22]

1-Benzyl-2-benzylidene-1-phenylhydrazine (2.56d)



Crystalline colourless solid (94 % isolated yield), m.p. 111-112 °C (Lit.[23] 112 °C).

R_f = 0.61 (AcOEt/hexane: 1/9).

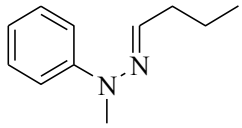
IR (film) cm^{-1}: 3060, 3026, 1948, 1590, 1564, 1496, 1452, 1394, 1351, 1333, 1311, 1242, 1222, 1148, 1073, 1044, 1026, 992, 955, 918, 901, 877, 778.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.38 (t, *J* = 9.7 Hz, 3H), 7.31-7.27 (m, 6H), 7.21 (dt, *J* = 6.8, 3.3 Hz, 4H), 6.93 (t, *J* = 7.2 Hz, 1H), 5.12 (s, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 148.0, 136.7, 135.8, 132.6, 129.3, 129.1, 128.6, 128.0, 127.4, 126.3, 126.2, 120.9, 114.9, 50.5.

These assignments matched with those previously published.[24]

2-Butylidene-1-methyl-1-phenylhydrazine (2.56e)



Light yellow oil (98 % isolated yield).

R_f = 0.47 (hexane/AcOEt: 96/4).

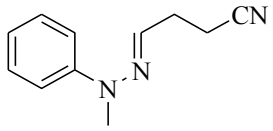
IR (film) cm^{-1}: 3025, 2959, 2931, 2872, 2245, 1596, 1501, 1456, 1380, 1316, 1196, 1179, 1147, 1106, 1051, 1029, 994, 954, 633.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.28-7.21 (m, 4H), 6.87-6.81 (m, 2H), 3.21 (s, 3H), 2.34 (td, J^1 = 7.4, J^2 = 5.4 Hz, 2H), 1.59 (q, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 148.4, 136.0, 129.0, 119.7, 114.8, 35.1, 33.1, 21.0, 13.9.

These assignments matched with those previously published.[25]

4-(2-Methyl-2-phenylhydrazono)butanenitrile (2.56f)



Colourless oil (78% isolated yield).

R_f = 0.27 (hexane/AcOEt: 9/1).

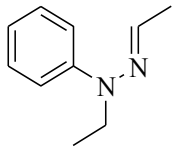
IR (film) cm^{-1}: 2959, 2929, 2872, 2247, 1595, 1498, 1391,1333, 1278, 1226, 1171, 1123, 1036, 993, 912, 749.

^{1}H NMR (400 MHz; CDCl$_3$): δ 7.31-7.22 (m, 4H), 6.92-6.89 (m, 1H), 6.82 (t, *J* = 3.4 Hz, 1H), 3.25 (s, 3H), 2.71 (qd, J^1 = 6.0 Hz, J^2 = 4.6 Hz, 4H).

^{13}C NMR (100 MHz; CDCl$_3$): δ 147.9, 136.2, 129.0, 120.5, 119.7, 115.0, 33.2, 28.7, 14.9.

Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.47; H, 7.06; N, 22.47.

1-Ethyl-2-ethylidene-1-phenylhydrazine (2.56g)



A light yellow oil (95 % isolated yield).

R_f = 0.42 (4% AcOEt/hexane).

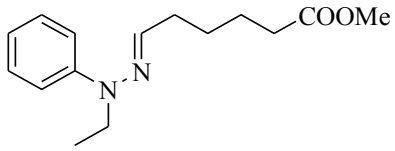
IR (film) cm^{-1}: 3059, 3024, 2975, 2934, 2911, 1594, 1578, 1498, 1447, 1397, 1376, 1361, 13291260, 1177, 1132, 1108, 1073, 1033, 1014, 800, 748.

^{1}H NMR (400 MHz; CDCl$_3$): δ 7.28-7.19 (m, 4H), 6.91 (q, *J* = 5.2 Hz, 1H), 6.86-6.82 (m, 1H), 3.81 (t, *J* = 7.1 Hz, 2H), 2.03 (d, *J* = 5.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz; CDCl$_3$): δ 147.2, 131.0, 129.1, 119.5, 114.3, 39.8, 19.1, 10.1.

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.04; H, 8.65; N, 17.31.

Methyl-6-(2-ethyl-2-phenylhydrazono)hexanoate (2.56h)



Pale yellow oil (75% isolated yield).

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

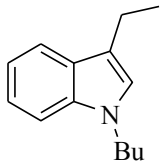
IR (neat) cm^{-1}: 2948, 1736, 1595, 1498, 1435, 1391, 1332, 1260, 1176, 1115, 1074, 1033, 994, 749.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.21-7.18 (m, 2H), 6.90-6.82 (m, 2H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 2.41-2.35 (m, 4H), 1.76-1.69 (m, 2H), 1.65-1.60 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 174.1, 147.2, 134.4, 129.1, 119.5, 114.2, 51.5, 39.5, 33.9, 32.8, 27.0, 24.5, 9.9.

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.61; H, 8.49; N, 10.71

1-Butyl-3-ethyl-1*H*-indole (2.57)



A light yellow oil (97% isolated yield).

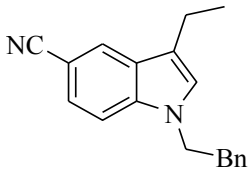
IR (film) cm^{-1}: 3024, 2962, 1611, 1485, 1465, 1362, 1184, 735.

^{1}H NMR (400 MHz, $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

These assignments matched with those previously published.[24]

3-Ethyl-1-phenethyl-1*H*-indole-5-carbonitrile (2.60a)



Colourless oil (86% isolated yield).

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

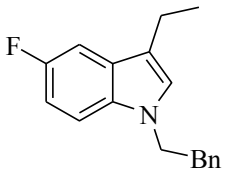
IR (film) cm^{-1}: 2963, 2924, 2853, 2216 (CN), 1613, 1482, 1454, 1375.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60b)



Colourless oil (90 % isolated yield).

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

IR (film) cm^{-1}: 3062, 3027, 2962, 2929, 2873, 1578, 1486, 1454, 1194.

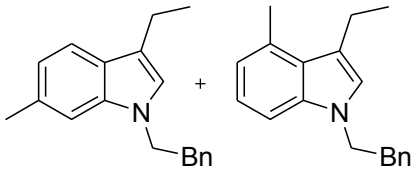
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.28-7.20 (m, 4H), 7.15 (dd, J^1 = 8.9 Hz, J^2 = 4.3 Hz, 1H), 7.06 (dd, J^1 = 7.9 Hz, 1.5 Hz, 2H), 6.91 (td, J^1 = 9.1 Hz, J^2 = 2.5 Hz, 1H), 6.74 (s, 1H), 4.25 (t, J = 7.4 Hz, 2H), 3.05 (t, J = 7.4 Hz, 2H), 2.68 (qd, J^1 = 7.5, J^2 = 0.9 Hz, 2H), 1.25 (d, J = 7.5 Hz,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

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

^{19}F NMR (376 MHz; $CDCl_3$): δ -126.0 (s).

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 (2.60c)



Pale yellow oil (92 % isolated yield).

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

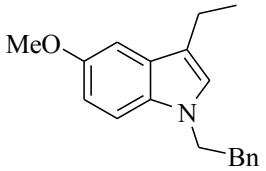
IR (film) cm^{-1}: 3026, 2961, 1603, 1553, 1495, 1468, 1361, 1180.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60d)



Light yellow oil (93 % yield).

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

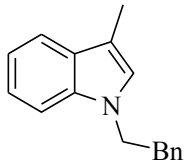
IR (film) cm^{-1}: 3062, 3027, 2960, 2246, 1619, 1603, 1578, 1487, 1453, 1360, 1222.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60e)



Amber oil (94% isolated yield).

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

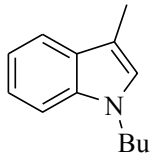
IR (film) cm^{-1}: 3028, 2959, 1601, 1550, 1498, 1464, 1359, 1182.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 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).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 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 (2.60f)



Colourless oil (95 % isolated yield).

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

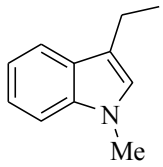
IR (film) cm^{-1}: 3053, 2957, 2929, 1467, 1362.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

These assignments matched with those previously published.[26]

3-Ethyl-1-methyl-1*H*-indole (2.60g)



Clear oil (96% isolated yield).

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

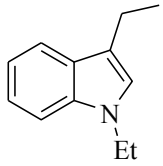
IR (film) cm^{-1}: 3053, 2962, 2929, 1472, 1376.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 137.1, 127.8, 125.4, 121.4, 119.0, 118.4, 117.3, 109.1, 32.5, 18.3, 14.7.

These assignments matched with those previously published.[27]

1,3-Diethyl-1*H*-indole (2.60h)



Clear oil (97 % isolated yield).

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

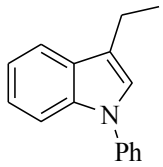
IR (film) cm^{-1}: 3052, 2964, 2930, 1613, 1469, 1370, 1225, 736.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 136.1, 127.9, 123.6, 121.3, 119.2, 118.4, 117.4, 109.2, 40.7, 18.4, 15.5, 14.7.

These assignments matched with those previously published.[28]

3-Ethyl-1-phenyl-1*H*-indole (2.60i)



Light yellow oil (57 % isolated yield).

R_f = 0.53 (hexane).

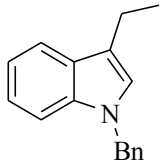
IR (neat) cm^{-1}: 3051, 2963, 2929, 2852, 1597, 1500, 1456, 1378, 1225.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

These assignments matched with those previously published.[29]

1-Benzyl-3-ethyl-1*H*-indole (2.60l)



Pale yellow oil (85% isolated yield).

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

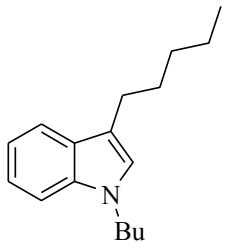
IR (film) cm^{-1}: 3059, 3028, 2960, 2930, 2875, 1610, 1495, 1480, 1465, 1450, 1355, 1175, 806, 735.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

These assignments matched with those previously published.[30]

1-Butyl-3-pentyl-1*H*-indole (2.60m)



Light yellow oil (90 % isolated yield).

R_f = 0.7 (hexane/AcOEt: 98/2).

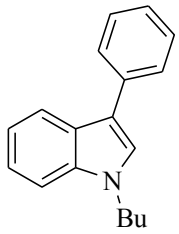
IR (neat) cm^{-1}: 2956, 2927, 2871, 1467, 1370;

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

1-Benzyl-3-phenyl-1*H*-indole (2.60n)



Colourless crystals, mp 62-63 °C [lit.[31] 61–63°C] (80% isolated yield).

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

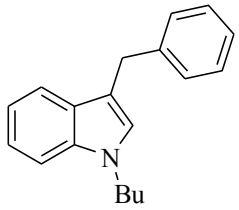
IR (film) cm^{-1}: 3108, 1613, 1483, 1461, 1365, 1344, 1270, 1194.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

These assignments matched with those previously published.[32]

3-Benzyl-1-butyl-1*H*-indole (2.60o)



Pale yellow oil (83 % isolated yield).

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

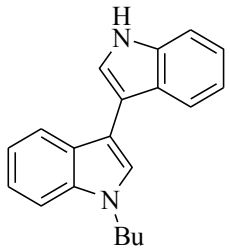
IR (neat) cm^{-1}: 3057, 3025, 2957, 2929, 2871, 1595, 1494, 1481, 1467.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (101 MHz; $CDCl_3$): δ 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 (2.60p)



Pale yellow oil (48 % isolated yield).

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

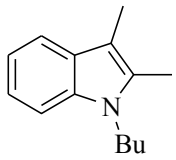
IR (neat) cm^{-1}: 3410 (NH), 2956, 2926, 1457, 1337, 1236.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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.

1-Butyl-2,3-dimethyl-1*H*-indole (2.60q)



Colourless oil (86 % isolated yield).

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

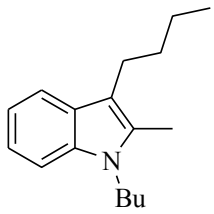
IR (film) cm^{-1}: 3051, 2957, 2929, 2871, 1614, 1469.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (101 MHz; $CDCl_3$): δ 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.

Analytical data matched with those previously published.[33]

1,3-Dibutyl-2-methyl-1*H*-indole (2.60r)



Colourless oil (84 % isolated yield).

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

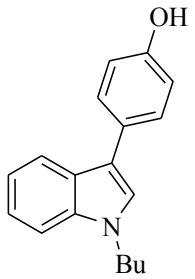
IR (neat) cm^{-1}: 3050, 2956, 2928, 2633, 2871, 1566, 1468, 1362.

^{1}H NMR (400 MHz, $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60s)



Colourless oil (82% isolated yield).

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

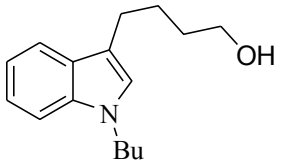
IR (film) cm^{-1}: 3418, 2957, 2084, 1642, 1550, 1504, 1466, 1372, 1334, 1230, 1159, 836.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60t)



Pale yellow oil (85 % isolated yield).

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

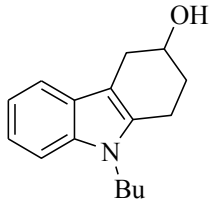
IR (film) cm^{-1}: 3357 (-OH), 3051, 2931, 2871, 1468, 1368, 1333.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (101 MHz; $CDCl_3$): δ 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 (2.60u)



Amber oil (75 % isolated yield).
R_f = 0.14 (hexane/AcOEt: 8/2).

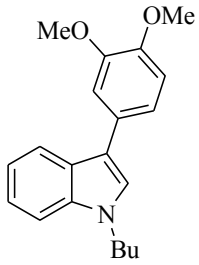
IR (neat) cm^{-1}: 3357, 2925, 1614, 1467, 1429, 1370, 1180.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 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).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 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 (2.60v)



Colourless oil (86 % isolated yield).

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

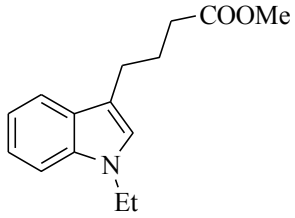
IR (neat) cm^{-1}: 2957, 2923, 2631, 1585, 1548, 1508, 1466, 1249, 1136.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 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 (2.60z)



Yellow oil (65% isolated yield).

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

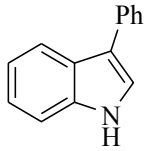
IR (film) cm^{-1}: 3053, 2983, 2927, 2853, 1732, 1461, 1437, 1421, 1374, 1265, 1013, 737.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 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-Phenyl-1*H*-indole [34] (2.71)



White powder, m.p. 86-87 °C; [Lit.[35] mp 86-88 °C]; (73 % isolated yield).

R_f = 0.5 (hexane/AcOEt: 8/2).

IR (film) cm^{-1}: 3410, 3391, 3052, 3030, 2927, 1594, 1539, 1485, 1457, 1418, 1338, 1260, 1239, 1185, 1118, 1012, 955, 910.

^{1}H NMR (400 MHz; $CDCl_3$): δ 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ 136.7, 135.6, 128.8, 127.5, 126.0, 125.8, 122.5, 121.8, 120.4, 119.9, 118.4, 111.4.

These assignments matched with those previously published.[36]

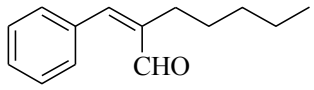
5.4 Synthesis of Cinnamaldehyde Derivatives through a One-Pot Dehydrogenative Cross-Coupling of Primary Alcohols

5.4.1 General Procedure for the Preparation of α,β-Unsaturated Aldehydes

The model reaction of benzyl alcohol with 1-heptanol is described here to exemplify the general reaction procedure. $RuH_2(CO)(PPh_3)_3$ (0.055 g, 0.06 mmol) and Xantphos (0.035 g, 0.06 mmol) were added to an oven dried 10-mL microwave reaction vessel, followed by crotononitrile (0.33 g, 0.40 ml, 5.0 mmol), benzyl alcohol (0.32 g, 0.31 ml, 3.0 mmol), 1-heptanol (0.12 g, 0.14 ml, 1.0 mmol) and grafted amine (0.520 g, 0.9 mmol). The tube was then sealed under nitrogen or argon and the reaction mixture was irradiated at 120 °C for 3 hrs in a microwave oven. After completion of the reaction, the silica-grafted amine was filtered out and washed with CH_2Cl_2 (3×5 mL). The collected filtrate was condensed under reduced pressure to get the crude product, which was analysed by ^1H NMR spectroscopy integrating the aldehyde CHO peaks. The crude mixture was purified by chromatography on a silica gel column using hexane/ethyl acetate: 9/1 as eluent to give α,β-unsaturated aldehyde **3.4** (0.152 g, 75 %). All products prepared by the above procedure were characterized spectroscopically as shown below.

5.4.2 Characterisation data for compounds (3.4-3.7o)

(E)-2-benzylideneheptanal (3.4)



Colourless oil (75 % isolated yied),

R_f = 0.43 (hexane/AcOEt: 9/1).

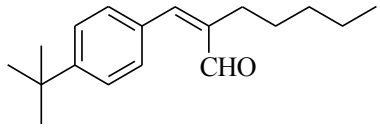
IR (film) cm^{-1}: 2955, 2928, 2858, 2711, 1682, 1624, 1455, 1088.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.54 (s, 1H), 7.50-7.38 (m, ArH, 5H), 7.20 (s, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.54-1.46 (m, 2H), 1.38-1.31 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.6, 149.7, 143.3, 134.9, 129.6, 129.5, 128.7, 32.0, 27.9, 24.7, 22.3, 13.9.

These assignments matched with those previously published.[37]

(E)-2-(4-(Tert-butyl)benzylidene)heptanal (3.6a)



Colourless oil (57 % isolated yield).

R_f = 0.54 (hexane/AcOEt: 9/1).

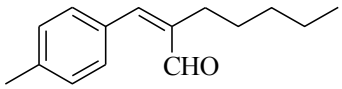
IR (film) cm^{-1}: 2963, 2928, 2858, 1681, 1619, 1453, 1081.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.53 (s, 1H), 7.47 (s, 4H), 7.17 (s, 1H), 2.54 (t, *J* = 8.0 Hz, 2H), 1.53-1.47 (m, 2H), 1.35 (bs, 13H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.8, 153.2, 149.8, 142.7, 132.2, 129.8, 125.8, 34.9, 32.2, 31.2, 28.0, 24.8, 22.5, 14.1.

HRMS: m/z calcd for $C_{18}H_{27}O$: 259.2062 $[M+H]^+$. Found: 259.2065**.**

(E)-2-(4-Methylbenzylidene)heptanal (3.6b)



Colourless oil (61 % isolated yield).

R_f = 0.55 (hexane/AcOEt: 9/1).

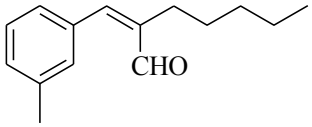
IR (film) cm^{-1}: 2963, 2927, 2864, 2715, 1681, 1619, 1458, 1083.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.52 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.16 (s, 1H), 2.53 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H), 1.53-1.46 (m, 2H), 1.39-1.32 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.8, 150.0, 142.6, 140.0, 132.2, 129.8, 129.6, 32.1, 27.9, 24.8, 22.4, 21.5, 14.0.

HRMS (ESI): *m/z* calcd for $C_{15}H_{21}O$: 217.1592 $[M+H]^+$. Found: 217.1589.

(*E*)-2-(3-methylbenzylidene)heptanal (3.6c)



Light yellow oil (62 % isolated yield).

R_f = 0.55 (hexane/AcOEt: 9/1).

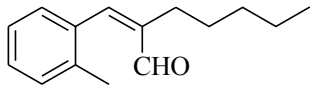
IR (film) cm^{-1}: 2927, 1681, 1624, 1172, 1086, 784.

^{1}H-NMR (400 MHz; $CDCl_3$): δ = 9.53 (s, 1H), 7.34-7.31 (m, 3H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.18 (s, 1H), 2.54-2.50 (m, 2H), 2.40 (s, 3H), 1.54-1.46 (m, 2H), 1.40-1.32 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.8, 150.0, 143.3, 138.4, 135.0, 130.5, 130.3, 128.7, 126.7, 32.1, 28.0, 24.8, 22.4, 21.5, 14.0.

These assignments matched with those previously published.[38]

(E)-2-(2-methylbenzylidene)heptanal (3.6d)



Pale yellow oil (64 % isolated yield).

R_f = 0.56 (hexane/AcOEt: 9/1).

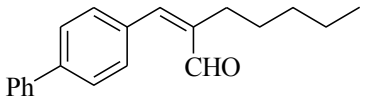
IR (film) cm^{-1}: 2928, 2858, 2710, 1686, 1624, 1458, 1372, 1292, 1087.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.61 (s, 1H), 7.39 (s, 1H), 7.30-7.24 (m, 4H), 2.37 (t, *J* = 7.9 Hz, 2H), 2.33 (s, 3H), 1.46-1.39 (m, 2H), 1.26-1.24 (m, 4H), 0.84 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.6, 148.8, 144.2, 136.7, 134.2, 130.4, 129.1, 128.2, 125.9, 31.9, 28.2, 24.8, 22.3, 20.0, 14.0.

HRMS: m/z calcd for $C_{15}H_{21}O$: 217.1592 $[M+H]^+$. Found: 217.1597.

(*E*)-2-([1,1'-Biphenyl]-4-ylmethylene)heptanal (3.6e)



Light yellow oil (55 % isolated yield).

R_f = 0.42 (hexane/AcOEt: 9/1).

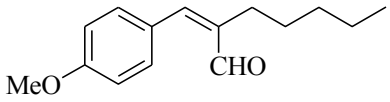
IR (film) cm^{-1}: 2946, 2857, 1679, 1615, 1487, 1286, 1085.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.57 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41-7.39 (m, 1H), 7.23 (s, 1H), 2.58 (t, *J* = 8.0 Hz, 2H), 1.54-1.52 (m, 2H), 1.42-1.35 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.7, 149.3, 143.3, 142.3, 140.1, 134.0, 130.3, 129.0, 127.9, 127.4, 127.1, 32.2, 28.0, 24.9, 22.5, 14.1.

HRMS: *m/z* calcd for $C_{20}H_{23}O$: 279.1749 $[M+H]^+$. Found: 279.1745.

(*E*)-2-(4-Methoxybenzylidene)heptanal (3.6f)



Amber oil (48 % isolated yield);

R_f = 0.28 (hexane/AcOEt: 9/1).

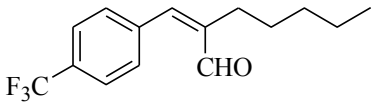
IR (film) cm^{-1}: 2972, 2870, 1682, 1615, 1170, 1087, 1031.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.49 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.12 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 2.54 (t, *J* = 7.9 Hz, 2H), 1.53-1.46 (m, 2H), 1.40-1.33 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.7, 160.8, 149.7, 141.3, 131.8, 127.7, 114.3, 55.4, 32.2, 27.8, 24.7, 22.5, 14.1.

These assignments matched with those previously published.[39]

(*E*)-2-(4-(Trifluoromethyl)benzylidene)heptanal (3.6g)



Pale yellow oil (56 % isolated yield);

R_f = 0.31 (hexane/AcOEt: 9/1).

IR (film) cm^{-1}: 2958, 2931, 1687, 1324, 1167, 1128, 1068.

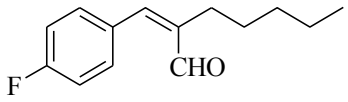
^{1}H NMR(400 MHz; $CDCl_3$): δ = 9.59 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.24 (s, 1H), 2.50 (t, *J* = 8 Hz, 2H), 1.51-1.47 (m, 2H), 1.36-1.32 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 195.2, 147.4, 145.2, 138.4, [131.5, 131.2, 130.9, 130.6] (q, *J* = 32.7 Hz, C-CF_3, 1C), 129.6, [125.79, 125.75, 125.72, 125.68] (q, *J* = 3.7 Hz, CF_3CC(Ar)C, 1C), [127.9, 125.2, 122.5, 119.8] (q, *J* = 270 Hz, CF_3, 1C), 32.0, 28.1, 24.8, 22.4, 14.0.

^{19}F NMR (376 MHz; $CDCl_3$, decupled): δ = -62.9.

These assignments matched with those previously published.[38]

(*E*)-2-(4-Fluorobenzylidene)heptanal (3.6h)



Light yellow oil (73 % isolated yield);

R_f = 0.42 (hexane/AcOEt: 9/1).

IR (film) cm^{-1}: 2930, 2860, 1683, 1624, 1600, 1508, 1465, 1399, 1294, 1236, 1159, 1086, 829.

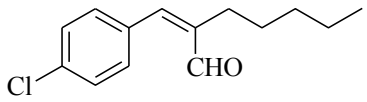
^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.53 (s, 1H), 7.49 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.16-7.12 (m, 3H), 2.51 (t, *J* = 8.0 Hz, 2H), 1.52-1.44 (m, 2H), 1.39-1.31 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.5, [164.5, 162.0] (d, $J_{C\text{-}F}$ = 250.0 Hz, C(Ar)-F, 1C), 148.4, 143.1, [131.7, 131.6] (d, $J_{C\text{-}F}$ = 8.3 Hz, CH(Ar), 1C), [131.22, 131.19] (d, $J_{C\text{-}F}$ = 3.6 Hz, C(Ar)C=C, 1C), [116.1, 115.9] (d, $J_{C\text{-}F}$ = 21.6 Hz, F-C(Ar)CH(Ar), 1C), 32.1, 27.9, 24.7, 22.4, 14.0.

^{19}F NMR (376 MHz; $CDCl_3$, decupled): δ = -110.3.

HRMS: *m/z* calcd for $C_{14}H_{18}FO$: 221.1342 $[M+H]^+$. Found: 221.1345.

(*E*)-2-(4-Chlorobenzylidene)heptanal (3.6i)



Brown oil (66 % isolated yield).

R_f = 0.37 (hexane/AcOEt: 9/1).

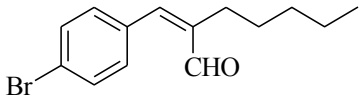
IR (film) cm^{-1}: 2957, 2931, 2862, 1703, 1592, 1490, 1092, 1014, 821.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.54 (s, 1H), 7.42 (s, 4H), 7.15 (s, 1H), 2.50 (t, *J* = 8.0 Hz, 2H), 1.51-1.44 (m, 2H), 1.37-1.33 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 195.4, 148.1, 143.8, 135.5, 133.4, 130.8, 129.1, 32.1, 27.9, 24.7, 22.4, 14.0.

HRMS: *m/z* calcd for $C_{14}H_{18}ClO$: 237.1046 $[M+H]^+$. Found: 237.1040.

(*E*)-2-(4-Chlorobenzylidene)heptanal (3.6j)



Light yellow oil (62 % isolated yield);

R_f = 0.37 (hexane/AcOEt: 9/1).

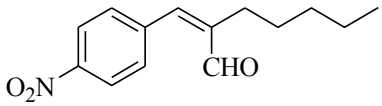
IR (film) cm^{-1}: 2968, 2934, 2858, 1681, 1619, 1585, 1478, 1395, 1112, 1078.

^{1}H-NMR (400 MHz; $CDCl_3$): δ = 9.54 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 2.49 (t, *J* = 8.0 Hz, 2H), 1.51-1.43 (m, 2H), 1.36-1.32 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ = 195.4, 148.1, 143.9, 133.9, 132.1, 131.0, 123.9, 32.1, 27.9, 24.8, 22.4, 14.0.

These assignments matched with those previously published.[38]

(*E*)-2-(4-Nitrobenzylidene)heptanal (3.6k)



Brown oil (50 % isolated yield);

R_f = 0.18 (hexane/AcOEt: 9/1).

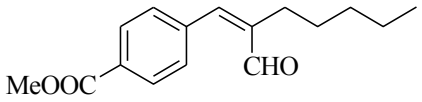
IR (film) cm^{-1}: 2930, 2859, 1685, 1596, 1520, 1346, 1085, 896.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.61 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.27 (s, 1H), 2.50 (t, *J* = 8.0 Hz, 2H), 1.53-1.45 (m, 2H), 1.36-1.30 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 194.8, 147.8, 146.2, 146.0, 141.3, 130.0, 124.0, 32.0, 28.1, 24.9, 22.3, 14.0.

These assignments matched with those previously published.[39]

(*E*)-Methyl 4-(2-formylhept-1-en-1-yl)benzoate (3.6l)



Light yellow oil (69 % isolated yield).

R_f = 0.23 (hexane/AcOEt: 9/1).

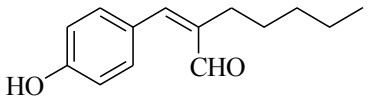
IR (film) cm^{-1}: 2955, 2931, 2863, 1724, 1686, 1507, 1435, 1279, 1109, 972.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.58 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.24 (s, 1H), 3.95 (s, 3H), 2.51 (t, *J* = 8 Hz, 2H), 1.50-1.45 (m, 2H), 1.36-1.29 (m, 4H), 0.89 (t,*J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.3, 166.4, 148.0, 145.0, 139.3, 130.6, 129.9, 129.4, 52.3, 32.0, 28.1, 24.8, 22.4, 14.0.

HRMS: *m/z* calcd for $C_{16}H_{21}O_3$: 261.1491 $[M+H]^+$. Found: 216.1497.

(*E*)-2-(4-Hydroxybenzylidene)heptanal (3.6m)



Crystalline white solid (57 % isolated yield), m.p. 118-120 °C;

R_f = 0.5 (hexane/AcOEt: 7/3).

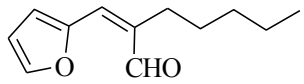
IR (film) cm^{-1}: 3241, 2921, 1654, 1600, 1574, 1509, 1285, 1230, 1176, 1084.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.49 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.12 (s, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.68 (bs, Ar-OH, 1H), 2.54 (t, *J* = 8.0 Hz, 2H), 1.51-1.46 (m, 2H), 1.42-1.29 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 196.1, 157.2, 150.2, 141.2, 132.0, 127.7, 115.9, 32.1, 27.8, 24.7, 22.5, 14.0.

HRMS: *m/z* calcd for $C_{14}H_{18}O_2Na$: 241.1204 $[M+Na]^+$. Found: 241.1209.

(*E*)-2-(Furan-2-ylmethylene)heptanal (3.6n)



Light yellow oil (42 % isolated yield).

R_f = 0.40 (hexane/AcOEt: 9/1).

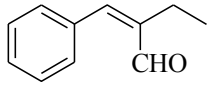
IR (film) cm^{-1}: 2968, 2929, 2866, 2717, 1678, 1625, 1472, 1384, 1366, 1279, 1088, 1026, 886.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.47 (s, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 6.94 (s, 1H), 6.75 (d, *J* = 3.5 Hz, 1H), 6.56 (dd, *J* = 3.2, 1.8 Hz, 1H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.47-1.43 (m, 2H), 1.36-1.33 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 194.4, 151.4, 145.3, 140.1, 135.1, 116.4, 112.6, 32.1, 28.0, 24.8, 22.5, 14.0

HRMS: *m/z* calcd for $C_{12}H_{17}O_2$:193.1229 $[M+H]^+$. Found: 193.1226.

(*E*)-2-Benzylidenebutanal (3.7a)



Light yellow oil (58 % isolated yield).

R_f = 0.42 (hexane/AcOEt: 9/1).

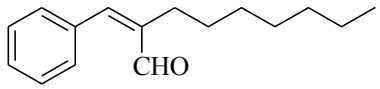
IR (film) cm^{-1}: 2943, 2929, 1677, 1602, 1510, 1258, 1176, 1031.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.55 (s, 1H), 7.52-7.40 (m, 5H), 7.21 (s, 1H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.6, 149.6, 144.5, 134.9, 129.65, 129.58, 128.8, 18.1, 12.9.

These assignments matched with those previously published.[40]

(*E*)-2-Benzylidenenonanal (3.7b)



Light yellow oil (72 % isolated yield).

R_f = 0.48 (hexane/AcOEt:9/1).

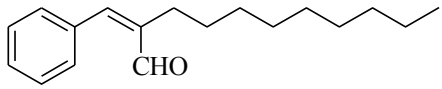
IR (film) cm^{-1}: 2951, 2925, 2854, 1687, 1602, 1506, 1465, 1095, 870.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.58 (s, 1H), 7.55-7.42 (m, 5H), 7.23 (s, 1H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.53-1.50 (m, 2H), 1.35-1.30 (m, 8H), 0.91 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.7, 149.8, 143.4, 135.0, 129.7, 129.5, 128.8, 31.8, 29.9, 29.0, 28.3, 24.8, 22.7, 14.1.

These assignments matched with those previously published.[41]

(*E*)-2-Benzylideneundecanal (3.7c)



Light yellow oil (69 % isolated yield).

R_f = 0.56 (hexane/AcOEt: 9/1).

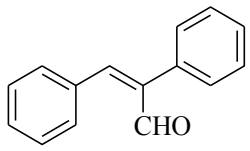
IR (film) cm^{-1}: 2924, 2854, 1683, 1624, 1464, 1082, 755.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.56 (s, 1H), 7.46 (ddd, *J* = 22.6, 15.1, 7.3 Hz, 5H), 7.22 (s, 1H), 2.54 (t, *J* = 7.9 Hz, 2H), 1.54-1.46 (m, 2H), 1.40-1.36 (m, 2H), 1.34-1.22 (m, *J* = 15.6 Hz, 10H), 0.89 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.7, 149.8, 143.4, 135.0, 129.7, 129.5, 128.8, 31.9, 29.9, 29.5, 29.4, 29.3, 28.3, 24.8, 22.7, 14.1.

HRMS: *m/z* calcd for $C_{18}H_{27}O$: 259.2062 $[M+H]^+$. Found: 259.2066.

(*E*)-2,3-diphenylacrylaldehyde (3.7d)



Crystalline white solid (59 % isolated yield), m.p. 64-66 °C.

R_f = 0.26 (hexane/AcOEt: 9/1).

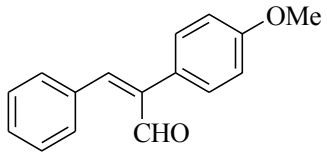
IR (film) cm^{-1}: 3048, 2847, 2738, 1666, 1625, 1597, 1499, 1447, 1094, 1070.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.78 (s, 1H), 7.40 (dt, *J* = 6.4, 3.5 Hz, 4H), 7.28 (dd, *J* = 5.5, 2.6 Hz, 1H), 7.23 (s, 1H), 7.21-7.19 (m, 5H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 193.9, 150.2, 141.8, 134.1, 133.4, 130.8, 130.3, 129.4, 128.9, 128.5, 128.3.

These assignments matched with those previously published.[42]

(*E*)-2-(4-Methoxyphenyl)-3-phenylacrylaldehyde (3.7e)



Yellow solid (49 % isolated yield), m.p. 90-92 °C (lit.,[7] mp 91–91.5 °C).

R_f = 0.16 (hexane/AcOEt: 9/1).

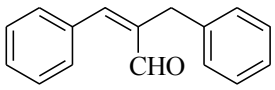
IR (film) cm^{-1}: 2932, 2851, 1691, 1513, 1246, 1082.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.75 (s, 1H), 7.34 (s, 1H), 7.28-7.24 (m, 5H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 194.3, 159.6, 149.9, 141.4, 134.3, 130.7, 130.6, 130.1, 128.5, 125.2, 114.4, 55.3.

These assignments matched with those previously published.[43]

(*E*)-2-Benzyl-3-phenylacrylaldehyde (3.7f)



Light yellow oil (54 % isolated yield).

R_f = 0.3 (hexane/AcOEt: 9/1).

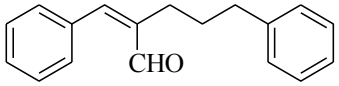
IR (film) cm^{-1}: 3027, 1680, 1624, 1494, 1451, 1144, 1085.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.68 (s, 1H), 7.49-7.45 (m, 3H), 7.37 (t, *J* = 3.1 Hz, 3H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 3H), 3.94 (s, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 195.2, 151.6, 140.5, 138.4, 134.6, 130.0, 129.8, 128.9, 128.7, 128.0, 126.3, 30.5.

These assignments matched with those previously published.[44]

(*E*)-2-benzylidene-5-phenylpentanal (3.7g)



Light yellow oil (60 % isolated yield).

R_f = 0.4 (hexane/AcOEt: 9/1).

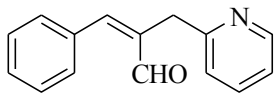
IR (film) cm^{-1}: 3111, 3055, 2833, 1680, 1612, 1498, 1449, 1195, 1125, 1083, 750.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.54 (s, 1H), 7.35-7.32 (m, 5H), 7.31-7.26 (m, 2H), 7.20-7.18 (m, 4H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.58-2.54 (m, 2H), 1.86-1.79 (m, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.7, 150.0, 142.8, 141.8, 134.7, 129.7, 129.6, 128.80, 128.6, 128.4, 125.9, 36.0, 29.7, 24.2.

HRMS: *m/z* calcd for $C_{18}H_{19}O$: 251.1436 $[M+H]^+$. Found: 251.1431.

(*E*)-3-Phenyl-2-(pyridin-2-ylmethyl)acrylaldehyde (3.7h)



Light yellow oil (52 % isolated yield).

R_f = 0.13 (hexane/AcOEt: 9/1).

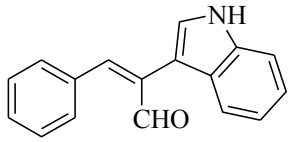
IR (film) cm^{-1}: 3069, 3037, 2958, 2905, 1679, 1625, 1424, 1274, 1089, 712.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.69 (s, 1H), 8.45-8.43 (m, 2H), 7.55 (s, 1H), 7.45-7.40 (m, 6H), 7.18 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.93 (s, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 194.8, 152.0,149.7, 147.8, 139.6, 135.5, 134.20, 134.00, 130.2, 129.6, 129.0, 123.5, 27.9.

HRMS: *m/z* calcd for $C_{15}H_{14}NO$: 224.1075 $[M+H]^+$. Found: 224.1069.

(*E*)-2-(1*H*-Indol-3-yl)-3-phenylacrylaldehyde (3.7i)



Brown oil (50 % isolated yield).

R_f = 0.28 (hexane/AcOEt: 8/2).

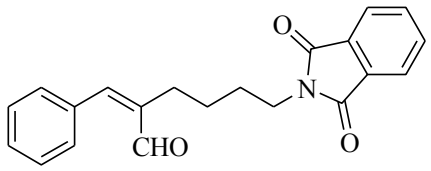
IR (film) cm^{-1}: 3378, 3055, 2833, 1672, 1639, 1528, 1014, 853, 744.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.85 (s, 1H), 8.49 (bs, 1H), 7.48 (s, 1H), 7.38-7.34 (m, 4H), 7.26-7.22 (m, 1H), 7.19-7.14 (m, 3H), 6.92 (s, 1H), 6.91 (s, 1H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 194.8, 149.5, 136.2, 135.0, 134.3, 130.5, 129.9, 128.4, 125.6, 125.2, 122.2, 120.8, 119.9, 111.3, 107.6.

HRMS: *m/z* calcd for $C_{17}H_{14}NO$: 248.1075 $[M+H]^+$. Found: 248.1081.

(*E*)-2-Benzylidene-6-(1,3-dioxoisoindolin-2-yl)hexanal (3.7j)



Yellow crystalline solid (65 % isolated yield), m.p. 88-90 °C.

R_f = 0.2 (hexane/AcOEt: 8/2)

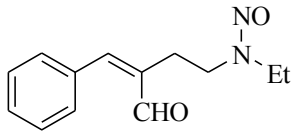
IR (film) cm^{-1}: 3060, 2938, 2864, 2715, 1770, 1712, 1680, 1622, 1397, 1098, 1036.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.53 (s, 1H), 7.82 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.42-7.36 (m, 5H), 7.23 (s, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.9 Hz, 2H), 1.75 (pent, *J* = 7.5 Hz, 2H), 1.54 (pent, *J* = 7.5 Hz, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.5, 168.4, 150.2, 142.5, 134.8, 133.9, 132.1, 129.7, 129.6, 128.9, 123.2, 37.8, 28.7, 25.5, 24.3.

HRMS: *m/z* calcd for $C_{21}H_{20}NO3$: 334.1443 $[M+H]^+$. Found: 334.1438.

(*E*)-*N*-ethyl-*N*-(3-formyl-4-phenylbut-3-en-1-yl)nitrous amide (**33**) and **(*Z*)-*N*-ethyl-*N*-(3-formyl-4-phenylbut-3-en-1-yl)nitrous amide (3.7k)**



Recovered as an inseparable mixture of E/Z isomers (65/35).

Amber oil (47 % isolated yield).

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

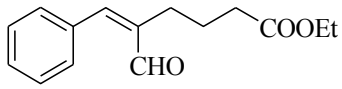
IR (film) cm^{-1}: 2981, 1680, 1625, 1454, 1353, 1232, 1129, 1070, 1022, 754.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.59 (s, 0.35 H), 9.56 (s, 0.65 H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.48-7.45 (m, 3H), 7.36 (s, 1H), 4.23-4.17 (m, 2H), 3.69-3.65 (m, 1H), 3.57-3.52 (m, 1H), 3.03-2.99 (m, 1H), 2.76-2.72 (m, 1H), 1.45 (t, *J* = 7.3 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.3, 195.0, 152.54, 152.53, 138.1, 137.8, 134.1, 133.9, 130.4, 130.2, 130.1, 129.3, 129.2, 129.1, 49.5, 47.7, 41.8, 38.8, 24.6, 22.0, 14.0, 11.2.

HRMS: *m/z* calcd for $C_{13}H_{17}N_2O_2$: 233.1290 $[M+H]^+$. Found: 233.1297.

(*E*)-Ethyl 5-formyl-6-phenylhex-5-enoate (3.7l)



Colourless oil (61 % isolated yield).

R_f = 0.24 (hexane/AcOEt: 9/1).

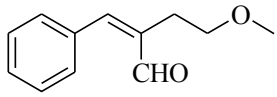
IR (film) cm^{-1}: 2979, 1731, 1680, 1624, 1374, 1182, 1131, 757.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.56 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.48-7.39 (m, 3H), 7.26 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.84 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 195.5, 173.2, 150.6, 142.1, 134.7, 129.8, 128.9, 128.4, 60.4, 34.2, 24.2, 23.4, 14.3.

HRMS: *m/z* calcd for $C_{15}H_{19}O_3$: 247.1334 $[M+H]^+$. Found: 247.1327.

(*E*)-2-Benzylidene-4-methoxybutanal (3.7m)



Amber oil (56 % isolated yield).

R_f = 0.25 (hexane/AcOEt: 9/1).

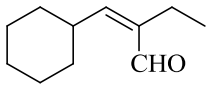
IR (film) cm^{-1}: 2626, 1681, 1626, 1112, 1084, 756.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.58 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.43 (dt, *J* = 11.8, 6.2 Hz, 3H), 7.36 (s, 1H), 3.56 (t, *J* = 7.0 Hz, 2H), 3.34 (s, 3H), 2.85 (t, *J* = 7.0 Hz, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 195.5, 151.8, 139.3, 134.6, 129.8, 129.7, 128.8, 70.4, 58.7, 25.6.

HRMS: *m/z* calcd for $C_{12}H_{15}O_2$: 191.1072 $[M+H]^+$. Found: 191.1069.

(E)-2-(Cyclohexylmethylene)butanal (3.7n)



Light yellow oil (44 % isolated yield).

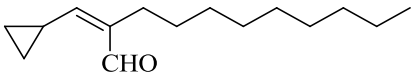
R_f = 0.5 (hexane/AcOEt: 9/1); IR (film) cm-1: 2957, 2928, 2853, 1689, 1643, 1602, 1441, 1124, 1049.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.33 (s, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 2.57-2.49 (m, 1H), 2.26 (q, *J* = 7.5 Hz, 2H), 1.81-1.76 (m, 2H), 1.70-1.67 (m, 3H), 1.37-1.31 (m, 2H), 1.26-1.18 (m, 3H), 0.98 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 195.6, 159.6, 143.3, 37.9, 32.2, 25.8, 25.4, 17.5, 14.0.

HRMS: *m/z* calcd for $C_{11}H_{19}O$: 167.1436 $[M+H]^+$. Found: 167.1445.

(*E*)-2-(cyclopropylmethylene)undecanal (3.7o)



Colourless oil (38 % isolated yield).

R_f = 0.4 (hexane/AcOEt: 9/1).

IR (film) cm^{-1}: 2924, 2854, 1681, 1635, 1456, 1096, 1052.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1H), 5.74 (d, *J* = 10.6 Hz, 1H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.83 (dtd, *J* = 15.9, 8.1, 4.2 Hz, 1H), 1.40 (q, *J* = 7.0 Hz, 2H), 1.36-1.18 (m, *J* = 10.4 Hz, 12H), 1.10 (td, *J* = 7.1, 4.5 Hz, 2H), 0.88 (t, *J* = 6.6 Hz, 3H), 0.72 (p, *J* = 4.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 160.3, 142.1, 31.9, 29.6, 29.6, 29.5, 29.3, 28.9, 24.1, 22.7, 14.1, 12.3, 9.5.

HRMS: *m/z* calcd for $C_{15}H_{27}O$: 223.2062 $[M+H]^+$. Found: 223.2060.

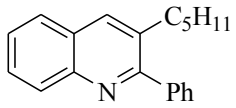
5.5 Synthesis of substituted quinolines via a cross-dehydrogenative coupling of alcohols and aminoarenes

5.5.1 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 ^1H 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.

5.5.2 Characterisation data for compounds (4.30-4.37f)

3-Pentyl-2-phenylquinoline (4.30)



White solid (71% isolated yield), m.p. 42-44 °C (lit.,[45] 43-44 °C).

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

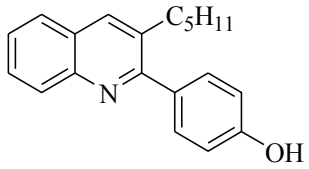
IR (film) cm^{-1}: 3059, 2955, 2927, 2858, 1636, 1487, 1418, 1007.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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.

These assignments matched with those previously published.[45]

4-(3-Pentylquinolin-2-yl)phenol (4.33a)



Yellow oil (51% isolated yield).

R_f = 0.3 (hexane/AcOEt: 7/3);

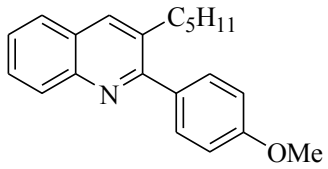
IR (film) cm^{-1}: 2959, 2924, 2855, 2367, 1646, 1275.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{20}H_{21}NO$: 292.1701 $[M+H]^+$. Found: 292.1705.

2-(4-methoxyphenyl)-3-pentylquinoline (4.33b)



White solid (49% isolated yield), m.p. 43-45 °C (lit.,[45] 44-45°C),

R_f = 0.6 (hexane/AcOEt: 7/3),

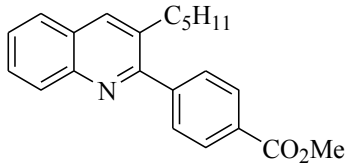
IR (film) cm^{-1}: 3058, 3000, 2955, 2929, 2858, 1608, 1515, 1420, 1247, 1174,

^{1}H NMR (400 MHz; $CDCl_3$): δ= 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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.

These assignments matched with those previously published.[45]

Methyl 4-(3-pentylquinolin-2-yl)benzoate (4.33c)



Dark yellow oil (61% isolated yield).

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

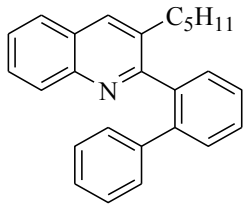
IR (film) cm^{-1}: 3060, 2953, 2928, 2858, 1724, 1612, 1435, 1277, 1112, 1016;

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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);

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{22}H_{24}NO_2$: 334.1807 $[M+H]^+$. Found: 334.1810.

2-(Biphenyl-2-yl)-3-pentylquinoline (4.33d)



Colourless oil (15% isolated yield).

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

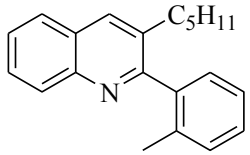
IR (film) cm^{-1}: 3059, 2954, 2926, 2856, 2359, 1621, 1598, 1488.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{26}H_{26}N$: 352.2065 [M+H]+. Found: 352.2063.

3-Pentyl-2-o-tolylquinoline (4.33e)



Colourless oil (70% isolated yield)

R_f = 0.44 (hexane/AcOEt: 9/1);

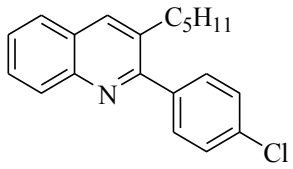
IR (film) cm^{-1}: 2955, 2926, 2857, 1636, 1487, 1417, 1262.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{21}H_{24}N$: 290.1909 $[M+H]^+$. Found: 290.1911.

2-(4-chlorophenyl)-3-pentylquinoline (4.33f)



Brown oil (73% isolated yield).

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

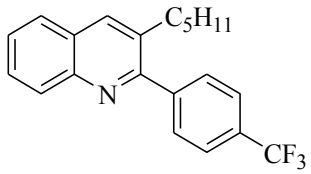
IR (film) cm^{-1}: 2955, 2927, 2858, 1647, 1488, 1419, 1091.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{20}H_{21}ClN$: 310.1363 $[M+H]^+$. Found: 310.1360.

3-Pentyl-2-(4-(trifluoromethyl)phenyl)quinolone (4.33g)



White solid (76% isolated yield), m.p. 65-67 °C.

R_f = 0.53 (hexane/AcOEt: 9/1).

IR (film) cm^{-1}: 2959, 2923, 2859, 1646, 1328, 1164, 1125, 1107, 1068.

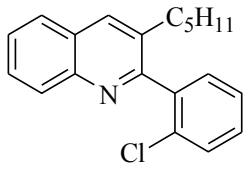
^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.11 (d, *J* = 8 Hz, 1 H), 8.10 (s, 1 H), 7.82 (d, *J* = 8 Hz, 1 H), 7.76 (d, *J* = 8 Hz, 2 H), 7.70-7.66 (m, 3 H), 7.55 (t, *J* = 7 Hz, 1 H), 2.75 (t, *J* = 8 Hz, 2 H), 1.54 (quint. *J* = 7 Hz, 2 H), 1.24-1.23 (m, 4 H), 0.82 (t, *J* = 6 Hz, 3 H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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;

^{19}F NMR (376 MHz; $CDCl_3$, decoupled): δ = -62.55;

HRMS: m/z calcd for $C_{21}H_{21}F_3N$: 344.1626 $[M+H]^+$.Found: 344.1624.

2-(2-Chlorophenyl)-3-pentylquinoline (4.33h)



Colourless oil (65% isolated yield).

R_f = 0.6 (DCM).

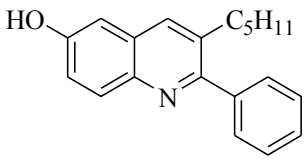
IR (film) cm^{-1}: 3059, 2954, 2927, 2858, 2359, 2332, 1489, 1435, 1418, 1067.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{20}H_{21}ClN$: 310.1363 $[M+H]^+$. Found: 310.1367.

3-Pentyl-2-phenylquinolin-6-ol (4.36)



White solid (52% isolated yield), m.p. 191-193 °C (lit.[1] 190-193 °C).

R_f = 0.2 (hexane/AcOEt: 7/3).

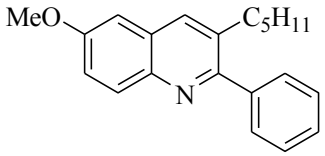
IR (film) cm^{-1}: 3418 (br), 3060, 2956, 2928, 2858, 2250, 1621, 1492, 1458, 1394, 1345, 1228.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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.

These assignments matched with those previously published.[45]

6-Methoxy-3-pentyl-2-phenylquinoline (4.36b)



White solid (49% isolated yield) m.p. 30-32 °C (lit.,[1] 31-32 °C).

R_f = 0.22 (hexane/AcOEt: 9/1).

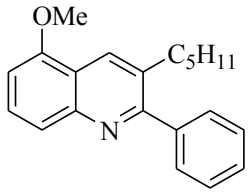
IR (film) cm^{-1}: 3060, 2955, 2928, 2858, 1625, 1490, 1227, 1029.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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;

These assignments matched with those previously published.[45]

5-Methoxy-3-pentyl-2-phenylquinoline (4.36d)



Colourless oil (33% isolated yield).

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

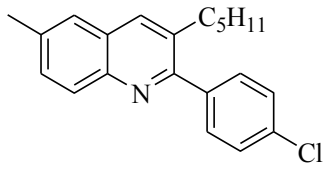
IR (film) cm^{-1}: 2955, 2926, 2856, 1625, 1489, 1222.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{21}H_{24}NO$: 306.1858 $[M+H]^+$. Found: 306.1861.

2-(4-Chlorophenyl)-6-methyl-3-pentylquinoline (4.36e)



Clear oil (63% isolated yield).

R_f = 0.49 (DCM).

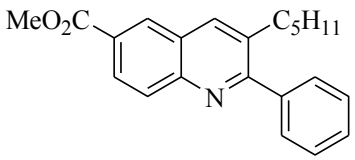
IR (film) cm^{-1}: 2955, 2927, 2858, 1598, 1488, 1092, 1011.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ =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: m/z calcd for $C_{21}H_{23}ClN$: 324.1519 $[M+H]^+$. Found: 324.1516.

Methyl 3-pentyl-2-phenylquinoline-6-carboxylate (4.36f)



White solid (38% isolated yield), m.p. 123-126 °C.

R_f = 0.31 (DCM).

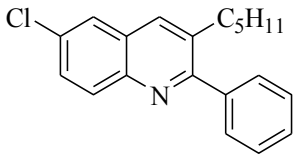
IR (film) cm^{-1}: 2952, 2926, 2857, 2361, 2331, 1712, 1621, 1446, 1256, 1197.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ =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: m/z calcd for $C_{22}H_{24}NO_2$: 334.1807 $[M+H]^+$. Found: 334.1808.

6-Chloro-3-pentyl-2-phenylquinoline (4.36c)



Colourless oil (41% isolated yield).

R_f = 0.63 (DCM).

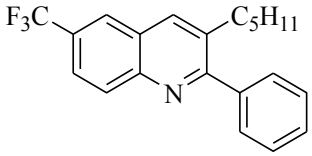
IR (film) cm^{-1}: 3059, 2955, 2927, 2858, 2355, 2337, 1593, 1551, 1475, 1339, 1268.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{20}H_{21}ClN$: 310.1363 $[M+H]^+$. Found: 310.1361.

3-Pentyl-2-phenyl-6-(trifluoromethyl)quinoline (4.36h)



White solid (43% isolated yield), m.p. 81-84 °C.

R_f = 0.48 (hexane/AcOEt: 9/1).

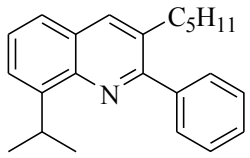
IR (film) cm^{-1}: 2953, 2933, 1635, 1453, 1287, 1121.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{21}H_{21}F_3N$: 344.1626 $[M+H]^+$. Found: 344.1624.

8-Isopropyl-3-pentyl-2-phenylquinoline (4.36i)



Colourless oil (58% isolated yield).

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

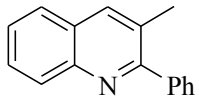
IR (film) cm^{-1}: 2957, 2926, 2860, 1646, 1476, 1465, 1276

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{23}H_{28}N$: 318.2222 $[M+H]^+$. Found: 318.2223.

3-Methyl-2-phenylquinoline (4.37a)



Colorless oil (58% isolated yield).

R_f = 0.47 (hexane/AcOEt: 8/2);

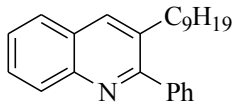
IR (film) cm^{-1}: 3059, 2925, 1636, 1599, 1488, 1411, 1271.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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.

These assignments matched with those previously published.[46]

3-Nonyl-2-phenylquinoline (4.37b)



Colourless oil (74% isolated yield).

R_f = 0.47 (hexane/AcOEt: 9/1);

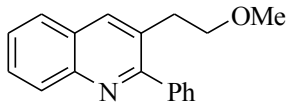
IR (film) cm^{-1}: 3059, 2925, 2853, 1646, 1487, 1418, 1268.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{24}H_{30}N$: 332.2378 $[M+H]^+$. Found: 332.2376.

3-(2-Methoxyethyl)-2-phenylquinoline (4.37c)



Dark brown oil (59% isolated yield).

R_f = 0.32 (hexane/AcOEt: 8/2).

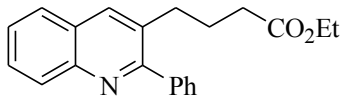
IR (film) cm^{-1}: 3059, 2925, 2359, 2320, 1647, 1635, 1488, 1111.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR(100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{18}H_{18}NO$: 264.1388 $[M+H]^+$. Found: 264.1391.

Ethyl 4-(2-phenylquinolin-3-yl)butanoate (4.37d)



Brown oil (42% isolated yield).

R_f =0.29 (hexane/AcOEt: 8/2).

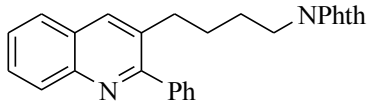
IR (film) cm^{-1}: 3058, 2979, 2935, 2870, 2360, 1731, 1487, 1419, 1017.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{21}H_{22}NO_2$: 320.1651 $[M+H]^+$. Found: 320.1655.

2-(4-(2-Phenylquinolin-3-yl)butyl)isoindoline-1,3-dione (4.37e)



White solid (64% isolated yield), m.p. 146-153 °C.

R_f = 0.32 (hexane/AcOEt: 7/3).

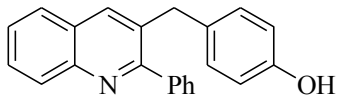
IR (film) cm^{-1}: 2940, 2863, 2321, 1770, 1710, 1646, 1396, 1036.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 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).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 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: m/z calcd for $C_{27}H_{23}N_2O_2$: 407.1760 $[M+H]^+$.Found: 407.1762.

4-((2-Phenylquinolin-3-yl)methyl)phenol (4.37f)



White solid (70% isolated yield), m.p. 255-260 °C.

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

IR (film) cm^{-1}: 3449 (br), 3059, 3024, 2924, 2855, 1613, 1514, 1454, 1265.

^{1}H NMR (400 MHz; DMSO-*d*$_6$): δ = 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).

^{13}C NMR (100 MHz; DMSO-*d*$_6$): δ =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: m/z calcd for $C_{22}H_{18}NO$: 312.1388 $[M+H]^+$. Found: 312.1386.

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