

**New organometallic catalysts for process-friendly
redox neutral alkylations**

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Abstract

Borrowing hydrogen chemistry is a convenient method of carrying out alkylation reactions, by forming carbonyl compounds from alcohols *in situ*, creating more reactive intermediates. These aldehydes or ketones react and the resulting product is reduced by return of the hydrogen abstracted from the alcohol starting material. Previous work within the Marsden group led to the development of a new family of catalysts for *N*-alkylation borrowing hydrogen reactions, featuring a Cp* ligand functionalised with an amine tether.

The possibility for expanding the scope of these catalysts to polyfunctionalised compounds was investigated, including protected and unprotected diamines and diols, and the synthesis of pharmaceutically relevant compounds. Optimisation studies were carried out to reach the highest turnover number for our catalyst, reaching a maximum turnover number of 2250 for our model reaction of the alkylation of piperidine with benzyl alcohol.

After a brief investigation into the synthesis of new catalysts bearing modified tethers was unsuccessful, methodology was developed for the synthesis of our original catalyst under conditions more viable for scale-up.

Experiments were carried out to determine the catalyst's potential for carrying out *C*-alkylation reactions. In particular, carbonyl alkylations via an aldol pathway were successful, and were shown to be viable for a series of substituted acetophenones and benzyl alcohols, as well as various heteroaromatic compounds. A one-pot procedure for alkylation and subsequent reduction to the respective alcohol compound was developed and utilised to synthesise a series of compounds based on the taccabulin natural products, which were tested for anti-cancer activity.

Finally, the possibility of these reactions being carried out to a lower yield in the absence of catalyst was investigated. The scope of these uncatalyzed reactions was determined to include only aromatic ketones, while our catalyst was shown to be able to carry out alkylations onto alkyl ketones with either aromatic or alkyl alcohols.

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Abbreviations

α	<i>alpha</i>
δ	Chemical shift in ppm
λ	Wavelength
ω	<i>Omega</i>
Ac	Acetyl
ACS	American Chemical Society
aq	Aqueous
ap	Apparent
Ar	Aryl
Bn	Benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	Broad
Bu	Butyl
C	Celsius
cod	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadiene
CPME	Cyclopentyl methyl ether
Cy	Cyclohexane
d	Doublet
dba	Dibenzylideneacetone
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	<i>N,N</i> -Diisopropylethylamine

DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DMT	Dimercaptotriazine
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppf	Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
eq	Equivalent(s)
e.r.	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
h	Hour(s)
Hex	Hexane
HRMS	High-resolution mass spectrometry
GC	Gas chromatography
<i>i</i>	iso
IPA	Isopropyl alcohol
IR	Infrared
J	Coupling constant
m	multiplet
M	Molarity
Me	Methyl
min	Minute(s)
MOM	Methoxymethyl ether

mp	Melting point
MS	Mass spectrometry
NMP	<i>N</i> -Methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
<i>p</i>	Para
pent	Pentyl
Ph	Phenyl
ppm	Parts per million
PTSA	<i>p</i> -Toluenesulfonic acid
q	Quartet
RT	Room temperature
s	Singlet
SCRAM	η^5 -(pentamethylcyclopentadienyl)iridium(III) diiodide dimer
SM	Starting material
STAB	Sodium triacetoxyborohydride
<i>t</i>	Tertiary
t	Triplet
TBME	<i>tert</i> -butyl methyl ether
TFA	Trifluoroacetic acid
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TMS	Trimethylsilane
UV	Ultraviolet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

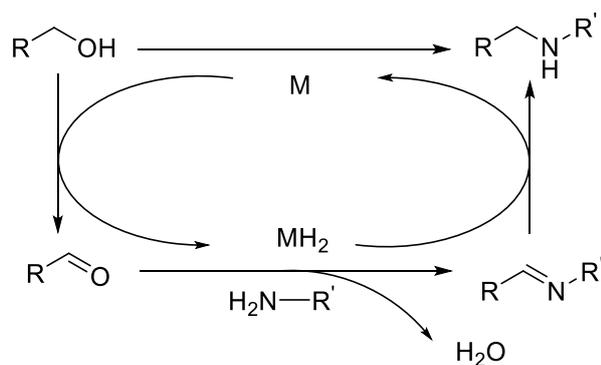
Chapter 1: Introduction

1.1 Borrowing Hydrogen

Transformations carried out using alcohols generally focus around reactions that take advantage of the nucleophilicity of the oxygen. However their high stability, ease of handling, low cost and low toxicity has led to their consideration as possible alkylating agents.¹ As the hydroxyl is not a good enough leaving group to be substituted in an S_N2 reaction, it must be either activated by conversion into an activated alcohol such as an alkyl halide, tosylate, triflate, etc. or by oxidation to form a carbonyl species which is then electrophilic enough to be attacked, which may then require the use of a reducing agent to obtain the desired product in the correct oxidation state, for example as in a reductive amination.

Both of these methods have significant drawbacks, activation of the alcohol species, or its oxidation and subsequent reduction of the product, usually generates stoichiometric quantities of waste materials and both methods introduce additional steps into a synthetic route. Additionally, alkyl halides and some aldehydes are known or suspected genotoxins, so reduction of their handling is generally desirable, and particular attention must be paid to their removal during purification in the synthesis of compounds destined for human consumption, such as pharmaceuticals. This means that the use of these methods is discouraged in late stages of such syntheses, limiting the options available to the chemist.²

An alternative to these methods is borrowing hydrogen methodology, sometimes called hydrogen auto-transfer.³ In these reactions, an alcohol is catalytically oxidised to form the corresponding carbonyl species, which then reacts before the product is reduced by return of the hydrogen taken during the oxidation step. This leads to the formation of the product that hypothetically would have been formed if the original alcohol were reactive enough to act as an alkylating agent. As an example, this methodology can be used in the *N*-alkylation of amines (**Scheme 1**), where the intermediate reacts with amine to form an imine, before being reduced to the corresponding more substituted amine.



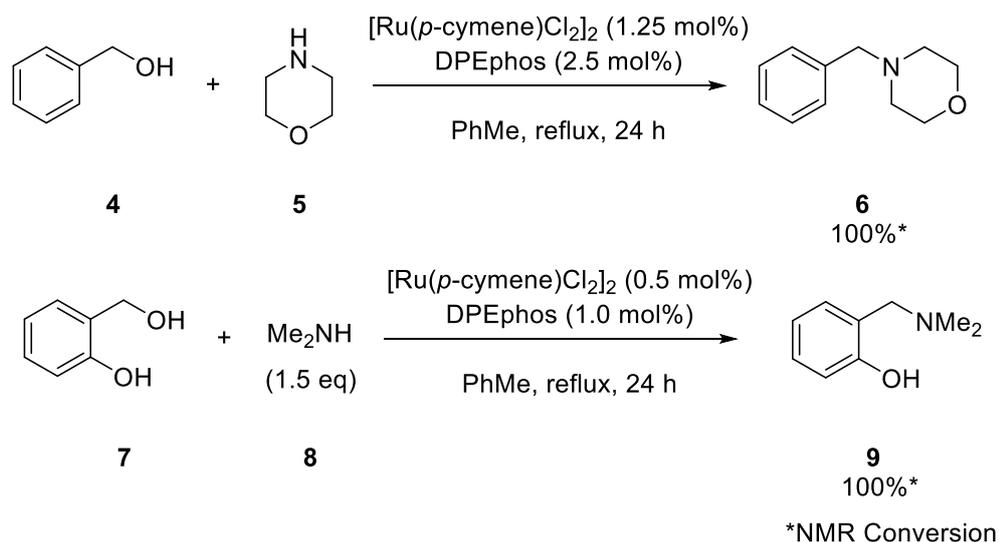
Scheme 1

This process avoids several of the disadvantages of the methods previously discussed: the aldehyde is generated *in situ* and is short-lived, reducing safety concerns, and efficiency has been increased by replacing two reactions with one. Additionally, the reaction also has a highly favourable atom economy, as the only by-product is water.

Borrowing hydrogen chemistry was first reported in 1981 by Grigg *et al.* and Watanabe *et al.*, in both cases using a ruthenium catalyst and a large excess of alcohol in order to *N*-alkylate an amine.^{4,5} In recent years, borrowing hydrogen methodology has received attention due to its potential to create greener industrial processes. This was highlighted by the ACS Green Chemistry Institute's Pharmaceutical Roundtable, which classed the activation of alcohols for nucleophilic substitution as one of the most important areas in their category of "currently used reactions that require improvement".⁶ This field has been thoroughly reviewed in the literature already, so this introduction will be selective in its attention, rather than attempting to be comprehensive.^{7,8,9} We will explore the progress in, and current state of, the application of borrowing hydrogen techniques towards both *N*-alkylation and *C*-alkylation transformations focusing on homogeneous catalysis, before examining mechanistic studies of these reactions and finishing with a review of previous work done in this area within the Marsden group.

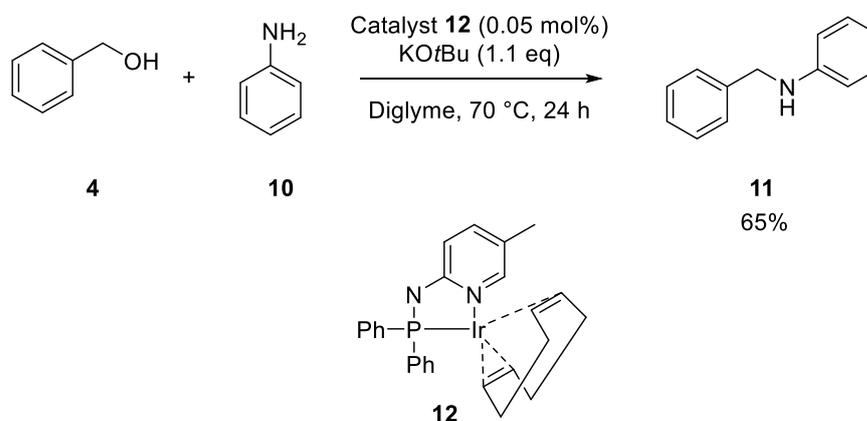
1.2 *N*-Alkylation Reactions

Other early work, in this case by Murahashi *et al.* demonstrated the use of borrowing hydrogen methodology to carry out alkylations with aliphatic alcohols, albeit requiring



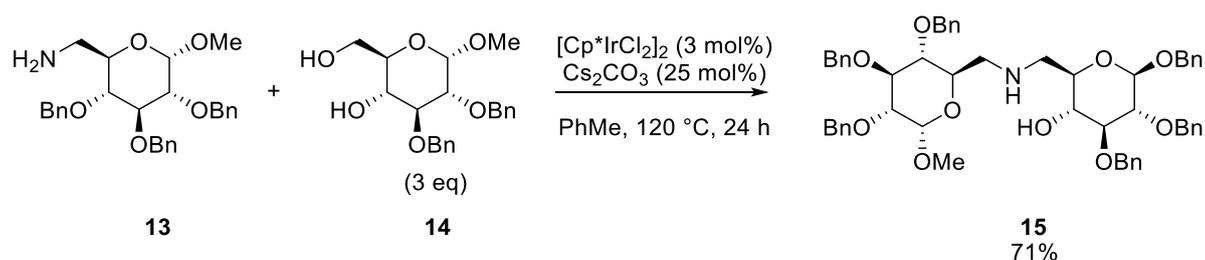
Scheme 3

Taking this line of improvement further, work by Kempe and Michlik demonstrated the alkylation of aniline with benzyl alcohol at temperatures of only 70 °C and using 0.05 mol% catalyst loading (**Scheme 4**)¹². For this they used a catalyst with a *P,N*-ligand **12**, the best performing of a family of ligands of their own design, with variation on the phosphorus substituents and at the *para* position of the aminopyridine. The low temperature and catalyst loading here would be highly beneficial in a large-scale setting where efficiency is of the essence, however the superstoichiometric quantity of KO^tBu required, and subsequent waste, are disadvantages compared with other methods.



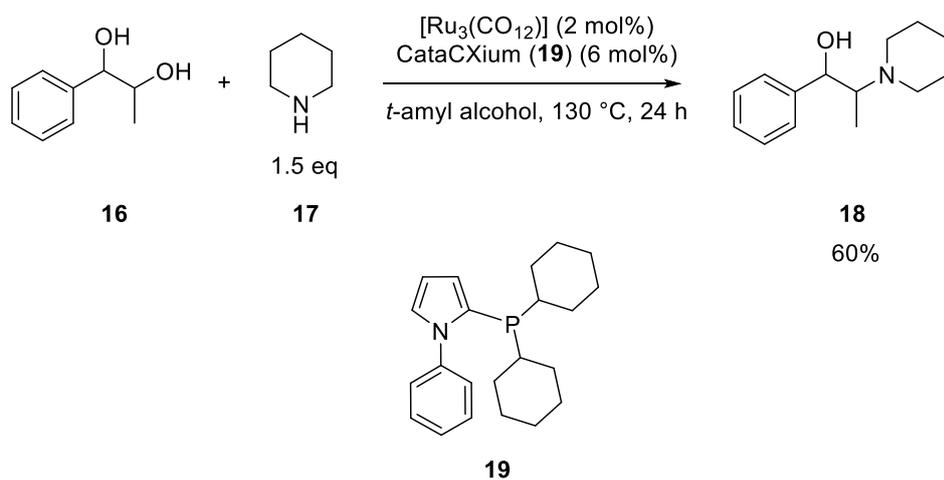
Scheme 4

Moving towards reactions which show a greater functional group tolerance, Martín-Matute *et al.* used the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer as a catalyst to carry out alkylations both onto carbohydrate amines and using carbohydrate alcohols.¹³ In most cases the non-reacting hydroxyl groups on the carbohydrates were protected as OBn groups (as is common in carbohydrate chemistry), and their reactions showed good tolerance for the ether groups, however a highlight of this work was the regioselective amination at a carbohydrate alcohol's primary alcohol in the presence of an unprotected secondary alcohol (**Scheme 5**), taking advantage of the lower reactivity of the secondary position.



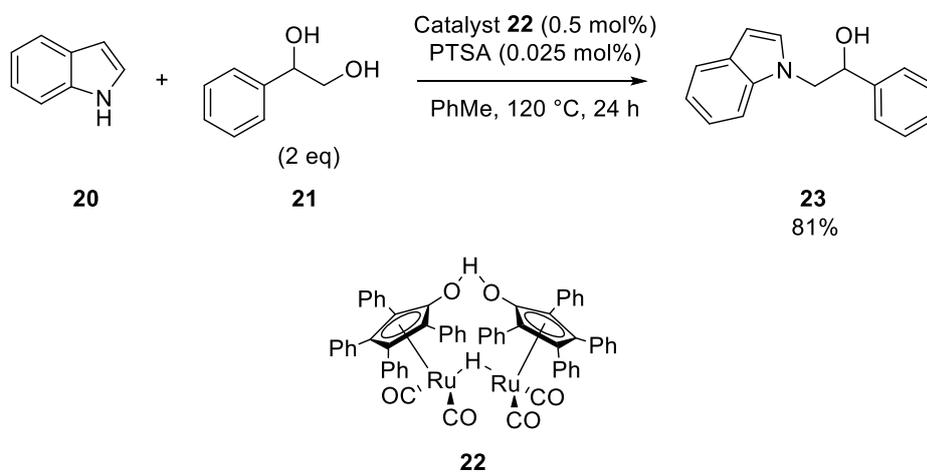
Scheme 5

A more comprehensive demonstration of regioselectivity was given in work by Beller *et al.*, which focused on the mono-alkylation of vicinal diols.¹⁴ They were able to demonstrate excellent yields and selectivities for alkylation with the primary alcohol of 1-phenyl-1,2-ethanediol with piperidine, using $[\text{Ru}_3(\text{CO})_{12}]$, although they did require the relatively expensive *N*-phenyl-2-(dicyclohexyl-phosphanyl)pyrrole (CataCXium PCy, **19**) as a ligand, and the reactions were carried out with little solvent. This selectivity was maintained across a range of amines and also when symmetrical diols were used. Some selectivity was also obtained when 1-phenyl-1,2-propanediol was used (**Scheme 6**), though this dropped significantly because the less sterically hindered alcohol no longer had the additional factor of being oxidised to an aldehyde, rather than the less reactive ketone.



Scheme 6

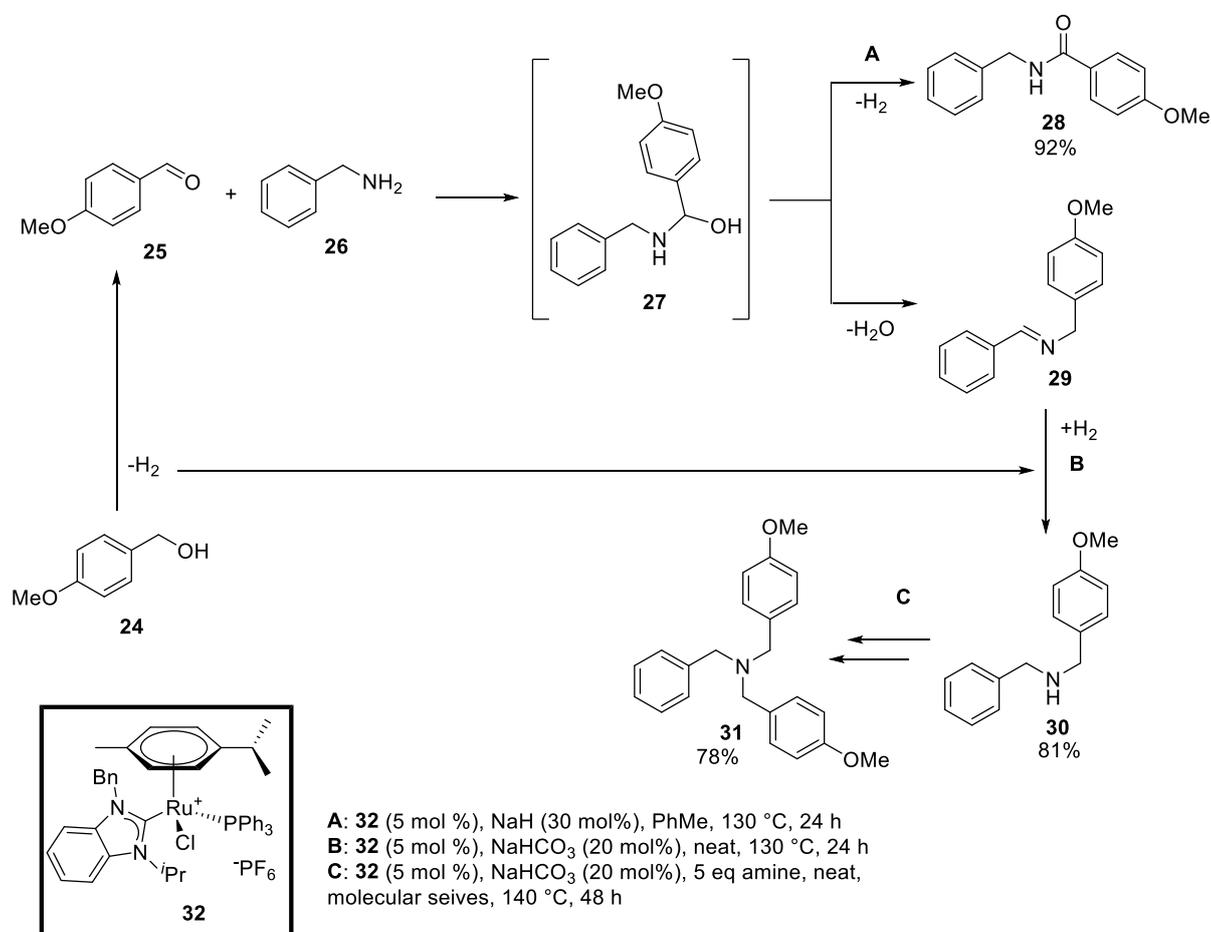
Later work by Beller *et al.* achieved the first *N*-alkylation of indole using borrowing hydrogen methodology.¹⁵ Indole is interesting not just because of its role in various biologically relevant compounds, but also because its nitrogen is particularly electron poor, and so a difficult target for alkylation. They achieved alkylation with 9 different alcohols onto 6 different indoles, in the presence of halides, ethers and, building on their work above, a diol (**Scheme 7**).



Scheme 7

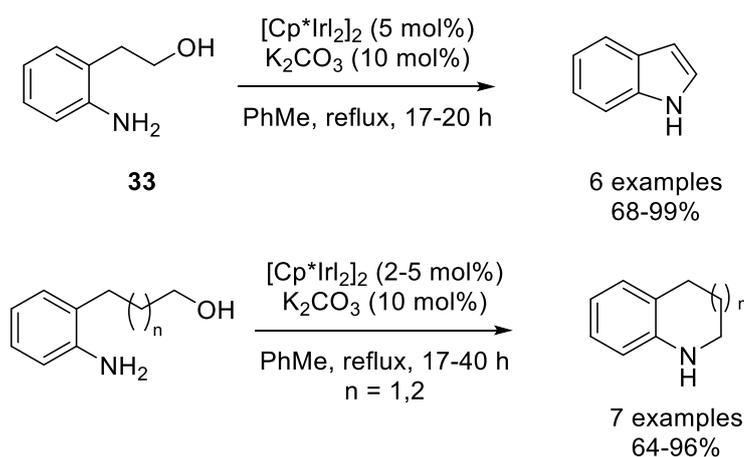
To achieve this, they used the Shvo catalyst **22**,¹⁶ a versatile homogenous catalyst known to be capable of carrying out various redox reactions, and *p*-toluenesulfonic acid.

A unique example of the versatility of borrowing hydrogen methodology comes from Xie and Huynh, who demonstrated for the first time the ability to use their reaction conditions to obtain secondary or tertiary amines or the corresponding amides by changing their choice of base and solvent.¹⁷ They propose that the direction of the reaction is determined by the fate of a hemiaminal intermediate formed after addition of the amine to the carbonyl compound (**Scheme 8**). If the hemiaminal is oxidised before it can eliminate water, the amide product (**28**) is formed, otherwise it proceeds via the usual borrowing hydrogen pathway to form the secondary amine (**30**) and may go on to form the tertiary amine (**31**). The authors note that there is no additional hydrogen acceptor required for the second oxidation to form the amide, but do not suggest a mechanism for regeneration of the active catalyst; an obvious possibility is the liberation of hydrogen gas.



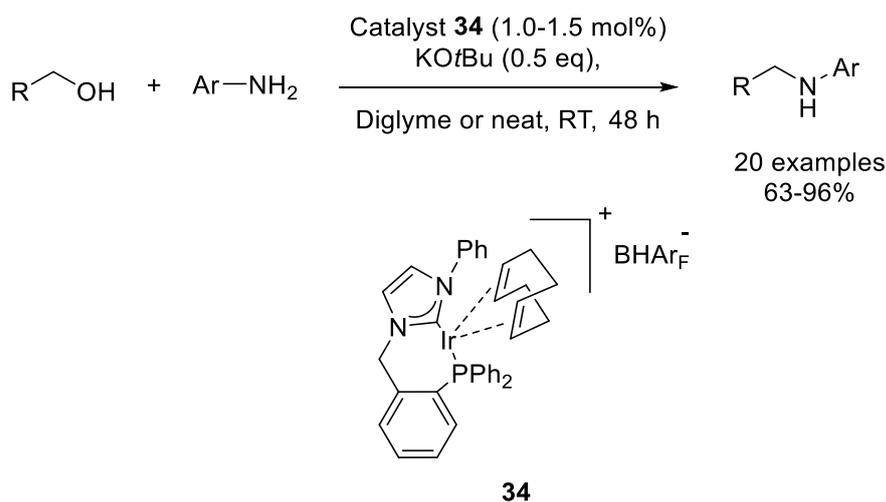
Scheme 8

Various pieces of work have also taken advantage of borrowing hydrogen techniques in order to construct heterocyclic compounds. Work by Fujita *et al.* in 2002 explored the intramolecular cyclisation of amino alcohols to yield indoles, a range of 1,2,3,4-tetrahydroquinolines and 2,3,4,5-tetrahydro-1-benzazepine.¹⁸ In the case of the indoles, hydrogen is not returned to the final compound, making the process hydrogen transfer rather than hydrogen borrowing. Using the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer as their catalyst, they were able to cyclise compounds with their hydroxyl group on various lengths of carbon chains in order to obtain their desired products (**Scheme 9**).



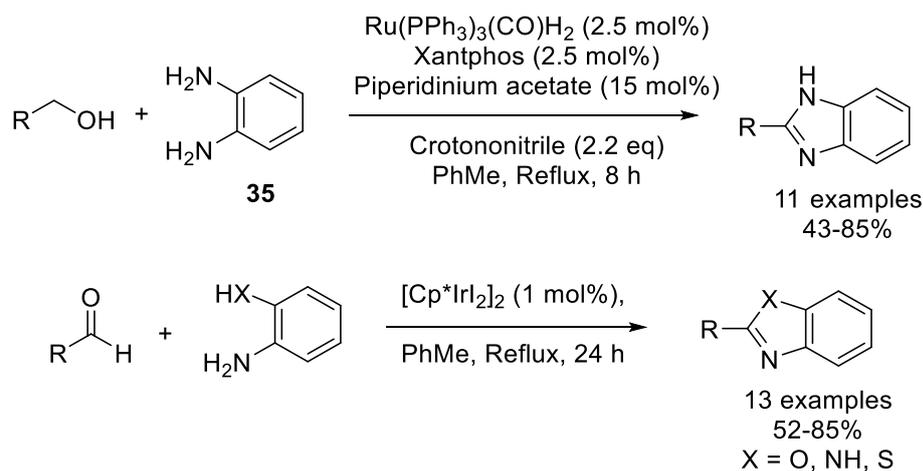
Scheme 9

Enyong and Moasser reported impressively mild conditions in their synthesis of pyrrolidines and piperidines among other secondary amines.¹⁹ Synthesising their products from primary amines and the respective n -alkyl diol, they used temperatures of 55 °C and obtained all of their products in quantitative yield using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ along with an amino amide ligand. This work was taken to its logical conclusion by Andersson and Li, who achieved the alkylation of anilines by borrowing hydrogen methodology at room temperature (**Scheme 10**).²⁰ Although the substrate scope is limited to just anilines, the first instance of this chemistry under ambient conditions is nonetheless worthy of attention.



Scheme 10

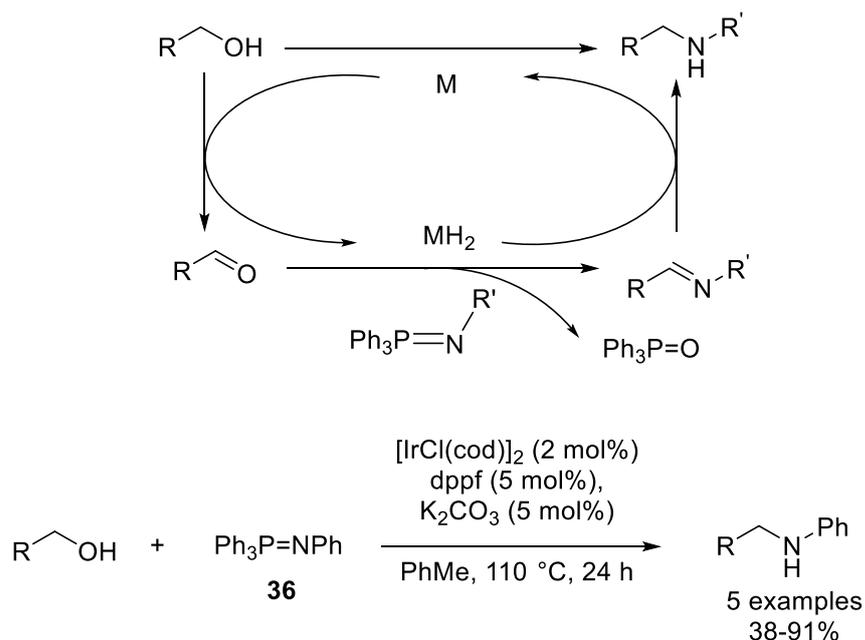
Borrowing hydrogen techniques have also been used to synthesise heterocycles bearing more than one heteroatom. Madsen and Nordstrøm synthesised examples of the important pharmacophore piperazine from vicinal diols and diamines in good to excellent yields using only 0.5 mol% $[\text{Cp}^*\text{IrCl}_2]_2$ and 5 mol% NaHCO_3 in both water and toluene, demonstrating a tolerance for polar solvents not generally seen in the borrowing hydrogen literature.²¹ Another example comes from Marsden and Williams, who synthesised benzimidazoles, benzoxazoles and benzothiazoles (**Scheme 11**).²² In the case of benzimidazoles this was achieved starting from an alcohol compound, which formed an imine after oxidation by $\text{Ru}(\text{PPh}_3)_3(\text{CO})\text{H}_2$, as in standard borrowing hydrogen reactions, which was in equilibrium with the corresponding dihydrobenzazole, before a further oxidation in the presence of crotononitrile as a hydrogen acceptor furnished the desired product. Aside from the superstoichiometric crotononitrile, this reaction also used Xanthpos and piperidinium acetate in order to achieve its highest conversions. In contrast, benzoxazoles and benzothiazoles could be synthesised from aldehydes in a reaction catalysed by $[\text{Cp}^*\text{IrI}_2]_2$ (SCRAM) without need of a sacrificial hydrogen acceptor or any other additives; the authors suggested that in this case the aromitisation was mediated by loss of H_2 from an intermediate (di)hydridoiridium complex.



Scheme 11

Although they make up a minority in the literature, it is worth also discussing borrowing hydrogen reactions which carry out *N*-alkylation transformations by means other than reacting an alcohol with an amine. One example is to proceed via an aza-Wittig pathway, as demonstrated by Williams and Cami-Kobeci (**Scheme 12**).²³ This was achieved in moderate to excellent yields to synthesise a range of *N*-alkyl anilines, however this methodology has the obvious drawback of producing stoichiometric Ph_3PO as waste and so failing to take advantage of the full green credentials of borrowing hydrogen technology.

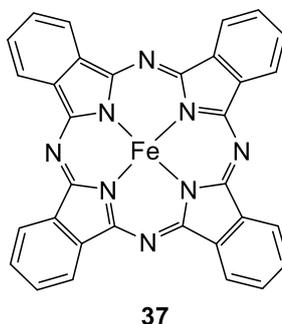
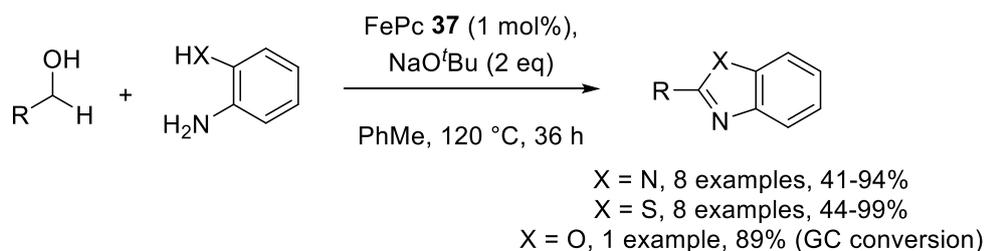
Another example is the direct alkylation of ammonia to produce primary amines from alcohols.²⁴ This reaction would obviously be greatly improved by the ability to use more convenient ammonia sources than NH_3 gas, however there are only two examples of this to date: work by Yamaguchi and Fujita, in which they demonstrated the amination of a wide-range of alkyl and benzyl alcohols using aqueous ammonia²⁵ and using ammonium salts.²⁶



Scheme 12

So far, all the work discussed has featured the use of ruthenium or iridium catalysts to carry out borrowing hydrogen reactions, which is largely representative of the literature. However, there is literature on the use of less expensive, first-row transition metals to carry out the same reactions.⁹ Interesting work exists on the use of manganese²⁷, copper²⁸, nickel²⁹ and cobalt³⁰, however iron deserves particular attention due its larger presence in the literature.

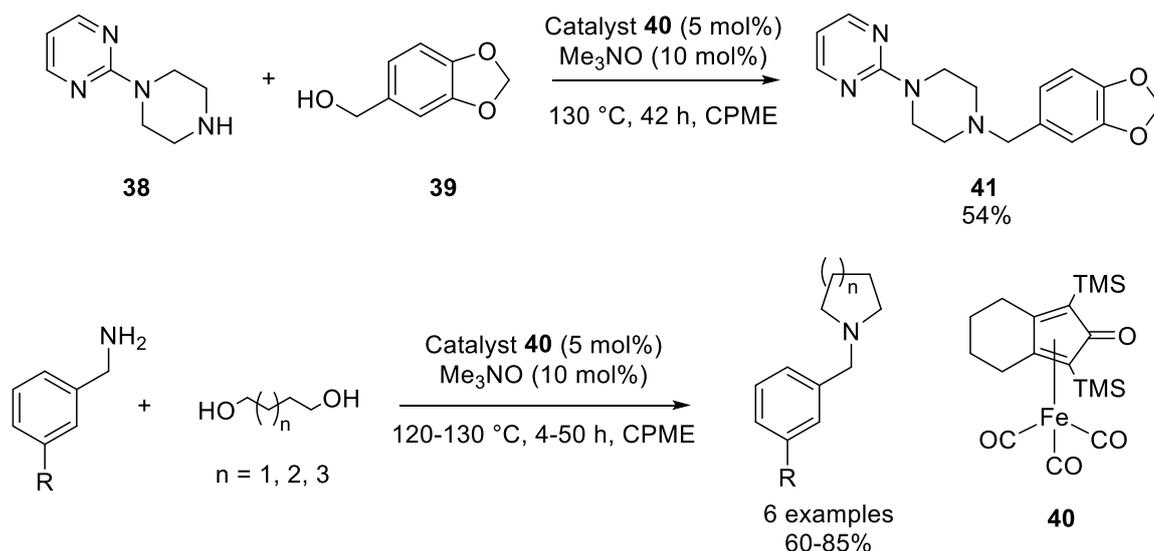
Early work on iron-catalysed borrowing hydrogen reactions by Singh *et al.* demonstrated the use of comparatively inexpensive iron phthalocyanine (**37**) for the synthesis of various benzimidazoles, benzothiazoles and benzoxazoles along with the alkylation of a range of aminopyridines and aminopyrimidines, using exclusively primary alcohols in each case (**Scheme 13**).³¹ The latter alkylations generally offered good yields for benzylic alcohols, but yields when using aliphatic alcohols were poor, as were those for the benzazole syntheses.



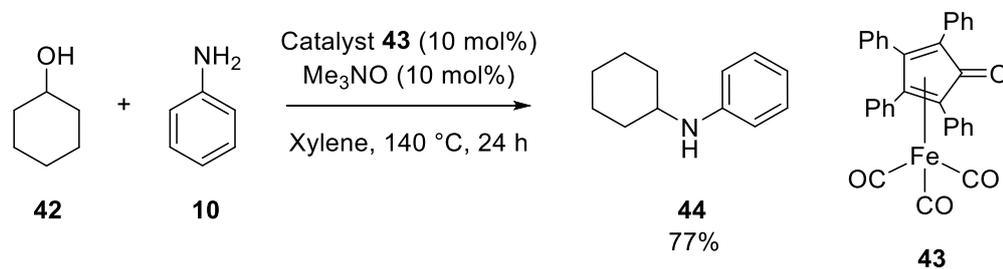
Scheme 13

Later work by Feringa and Barta expanded the range of substrates to achieve good yields with aliphatic alcohols, but secondary alcohols still gave very poor yields.³² Alongside a synthesis of the drug Perebedil **41**, demonstrating tolerance of their catalyst **40** for a range of heteroatom environments, they also used its activity towards aliphatic alcohols to achieve the synthesis of a variety of heterocycles from primary amines and the corresponding diol (**Scheme 14**).

Success with secondary alcohols was achieved by Wills *et al.* who used catalyst **43**, an iron tricarbonyl similar to Feringa's (**Scheme 15**).³³ They were able to alkylate aniline with cyclohexanol to obtain their desired product in 77% yield, as well as demonstrating their catalyst's competency with *n*-hexanol and a range of benzyl alcohols. However, as in Feringa's work above, their catalyst does require the use of trimethylamine *N*-oxide as an additive in order to form the active species by carrying out a decarbonylation, generating trimethylamine (and carbon dioxide) as waste.

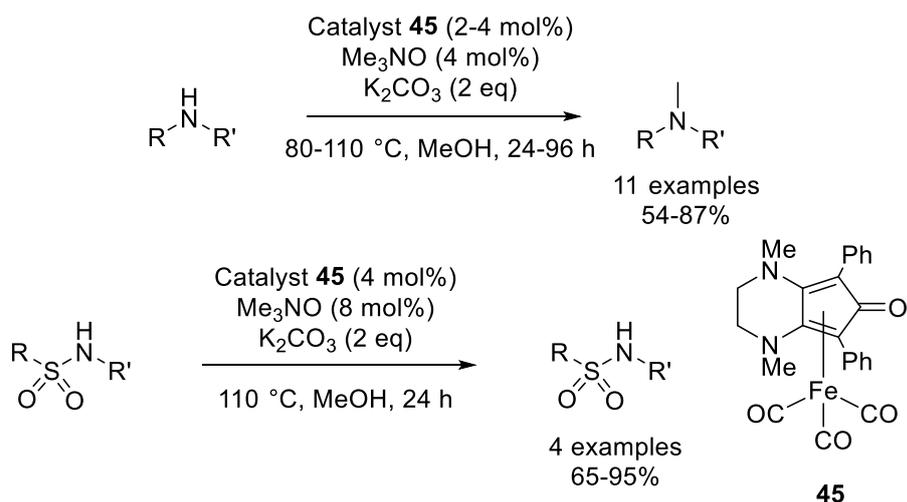


Scheme 14



Scheme 15

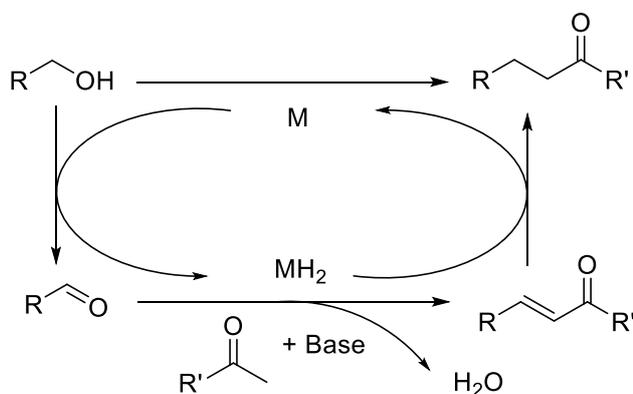
Finally, work by Morrill *et al.* used iron tricarbonyl complex **45** to carry out *N*-methylations onto amine and sulphonamides using methanol as an alkylating agent, demonstrating competence with both primary and secondary benzylic and aliphatic amines (**Scheme 16**).³⁴ Methylation is a highly important transformation in organic synthesis and is also considered to be a highly challenging reaction to carry out using borrowing hydrogen chemistry due to methanol being significantly harder to oxidise than other alcohols.



Scheme 16

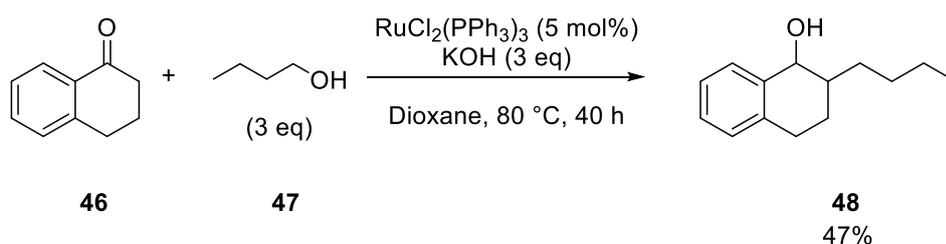
1.3 C-Alkylation Reactions

It is obviously possible to imagine the use of borrowing hydrogen methodology to facilitate a range of other reactions which feature carbonyl compounds as a reactant. An example which has been the subject of significant work in the literature is alkylation using carbonyl nucleophiles, proceeding via the aldol condensation (**Scheme 17**). In this case the *in situ* oxidation occurs as seen previously to form the carbonyl reactant, which then undergoes a standard aldol condensation with a ketone reaction partner, via its enol form. The product from this is the enone, which then receives the hydrogen abstracted by the catalytic species to form the desired ketone product.



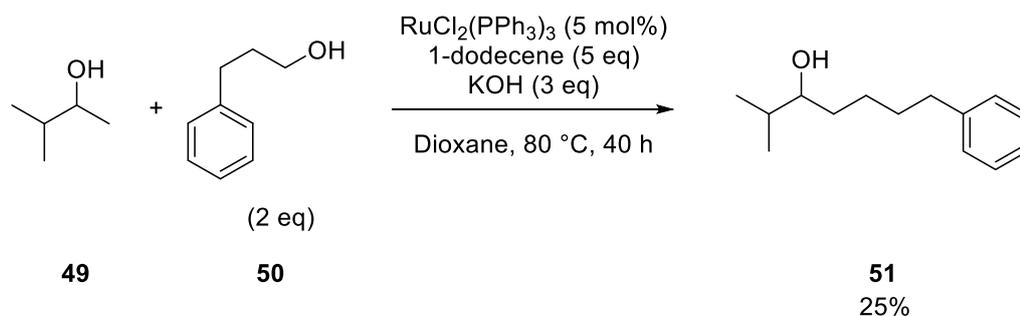
Scheme 17

An early example of these reactions was provided by Cho and Shim.³⁵ They achieved the alkylation of a variety of ketones with both primary benzylic and aliphatic alcohols, observing both the ketone product and the alcohol as a product of a further reduction, with the hydrogen for this coming from the excess of alcohol in the reaction. Optimising in favour of the alcohol, and using $\text{RuCl}_2(\text{PPh}_3)_3$ as their catalyst they obtained 13 examples in 43-85% yield. A specific example worth highlighting is their alkylation onto 1-tetralone **46** (**Scheme 18**), as it is the only reaction reported in which the alkylation occurs onto a methylene position, rather than a methyl.



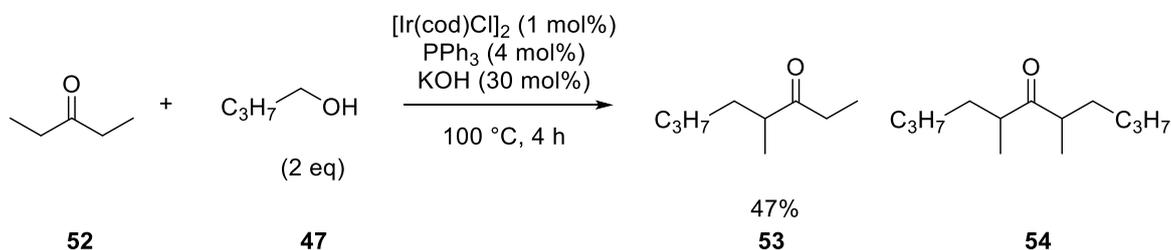
Scheme 18

Cho subsequently demonstrated the use of the same catalyst to carry out the β -alkylations of secondary aromatic and aliphatic alcohols with primary alcohols.³⁶ Again the reactions reported were generally of good to excellent yield, but those carried out using two aliphatic alcohols were problematic, with the worst yield being observed for the alkylation of 3-methyl-2-butanol **49** with 3-phenyl-1-propanol **50** (**Scheme 19**). Interestingly, when 3-phenyl-1-propanol was being used to alkylate 4-phenyl-2-butanol the yield obtained was 58%, more than double that achieved when alkylating onto the branched alkyl alcohol. Another drawback in this method is the significant amount of additives required, adding 5 equivalents of 1-dodecene as a sacrificial hydrogen donor to the 3 equivalents of KOH already used in the earlier work.



Scheme 19

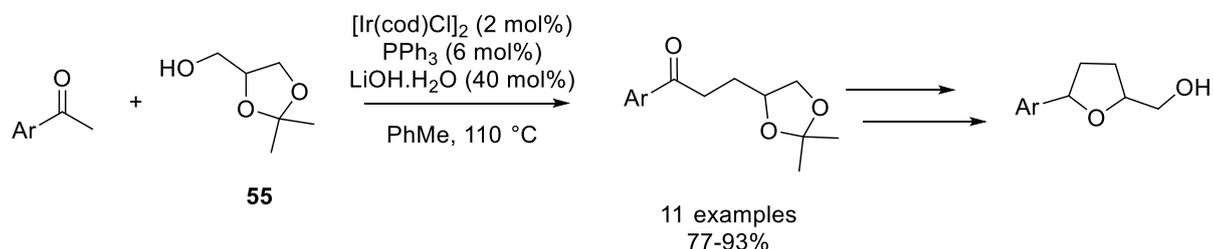
Examples also exist where the product is produced in the ketone form, for example work by Ishii *et al.*³⁷ They tuned their choice of ligands and base and catalyst in order to obtain α -alkylation of ketones, obtaining all but one of their products in good to excellent yield. The exception was the alkylation of 3-propanone (**Scheme 20**). The authors do not give details of the remaining mass balance or speculate as to the cause of this low yield, but an obvious possibility is over-alkylation, yielding the symmetrical product **54**. The absence of a solvent in this reaction should also be highlighted, due to the restraints it places on more general syntheses using potentially solid reactants, as previously discussed. In addition, no functional groups are present in any of their example compounds, aside from phenyl rings, and the alcohols and ketones involved in the aldol condensation itself.



Scheme 20

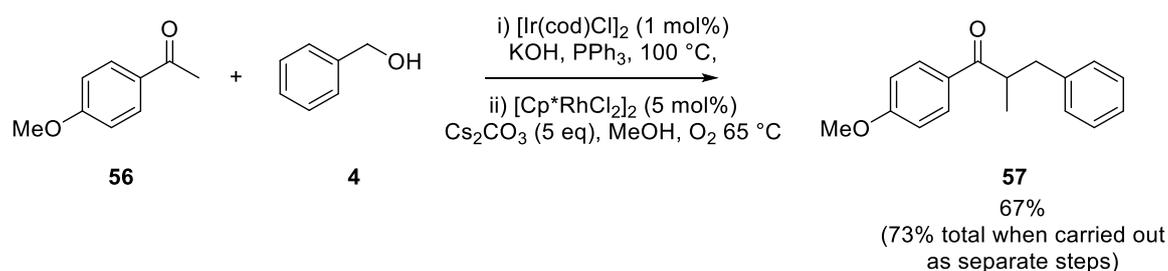
The tolerance of a wider range of substrates is displayed in work by Rueping and Phapale, where aryl ketones were alkylated with solketal (**55**) (**Scheme 21**).³⁸ This was achieved with a variety of substituted acetophenones using $[\text{Ir}(\text{cod})\text{Cl}]_2$, including in the presence

of halides and ethers. Acetylthiophene was also used as an example as a heteroaromatic compound, alongside several bicyclic compounds, and good to excellent yields were maintained throughout. They subsequently carried out a reduction of the ketone and cyclisation to obtain the substituted tetrahydrofuran.



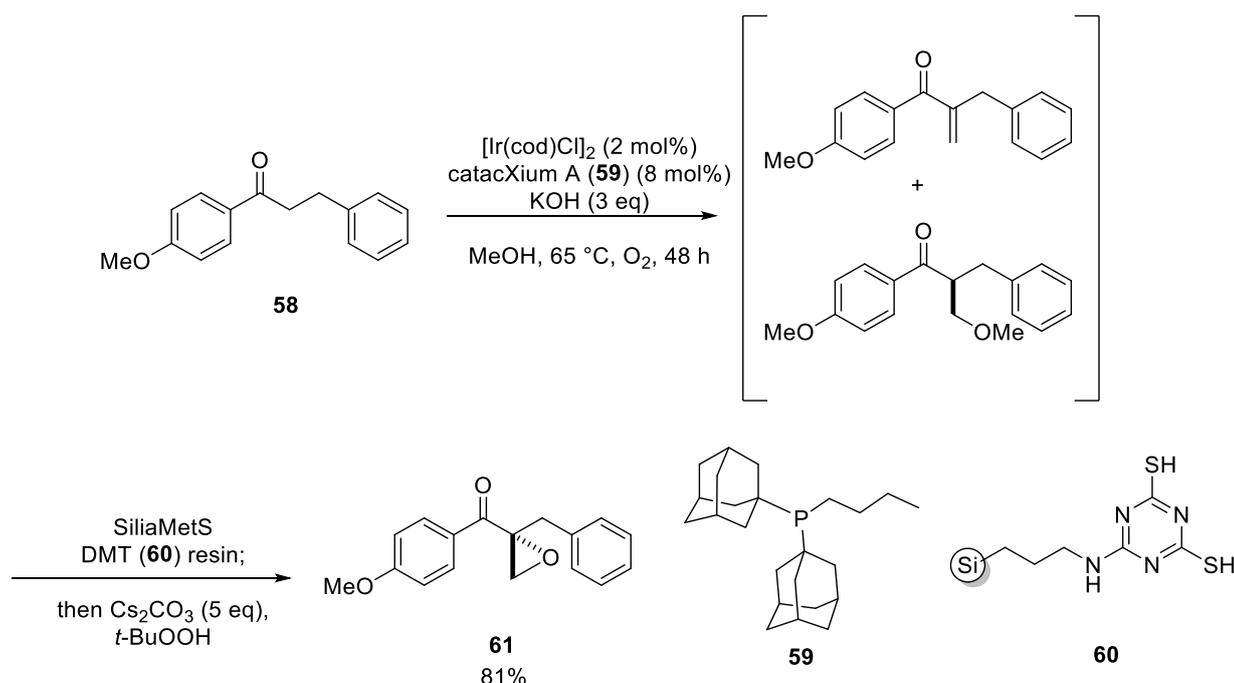
Scheme 21

Donohoe *et al.* demonstrated the α -methylation of aryl ketones at methylene carbons to form branched products.³⁹ As previously discussed, methylation is considered one of the more challenging transformations to carry out using borrowing hydrogen methodology; however in this case the authors report difficulty in forming branched ketones using more hindered alcohols, blaming steric interactions in the aldol intermediates formed. This is achieved at the cost of requiring 5 equivalents of Cs_2CO_3 as additive and, more troubling, an atmosphere of O_2 , which is strongly discouraged in larger-scale reactions due to the risk of explosion. A highlight of the work is a series of one-pot reactions which carry out an alkylation and then a methylation (**Scheme 22**). Although a small reduction of yield was observed in some cases when compared to the overall yield of both steps, having the ability to carry out both steps without reaction work-up or handling is a valuable tool.



Scheme 22

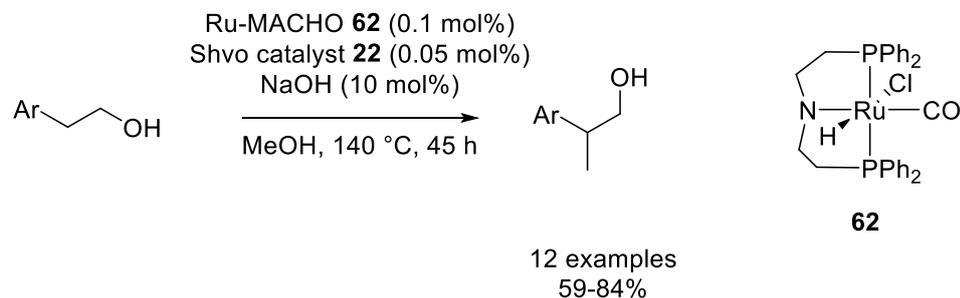
In subsequent work, Donohoe *et al.* were able to expand their synthesis of branched ketones beyond the addition of a simple methyl group.⁴⁰ This was achieved by interrupting the borrowing hydrogen process so that the alkene formed by the aldol condensation reaction was not reduced by their catalyst but attacked by a nucleophile to undergo a conjugate addition (**Scheme 23**). This was carried out using bulky ligands, in particular catacXium A ((adamantyl)₂PBu), which allowed the modulation of the rates of hydrogen abstraction and hydrogen returning. They demonstrated the use of a variety of nucleophiles, such as alkyl peroxides and enones formed in subsequent borrowing hydrogen reactions.



Scheme 23

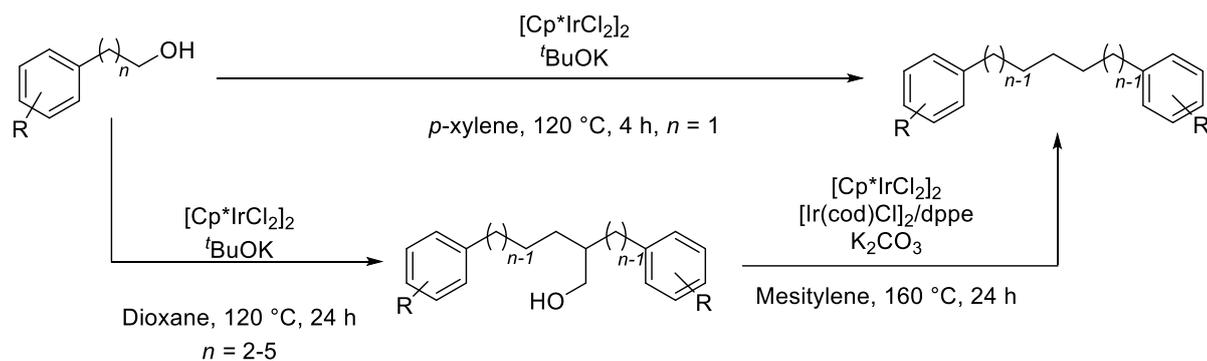
Good selectivity against self-reaction was demonstrated by Beller *et al.*, who published their procedure for the selective methylation of 2-arylethanol, using methanol.⁴¹ This was achieved by the use of two catalysts in their reaction, with Ru-MACHO **62** acting exclusively to oxidise the arylethanol. Their methodology was demonstrated across a range of aromatic rings and in the presence of ethers, halides and heteroatoms (**Scheme 24**). The authors highlight that this method is a significant improvement on the previous most rapid entry to these compounds, via the hydroformylation and subsequent reduction

of styrene. In comparison, Beller's method avoids the use of explosive H₂ gas, and toxic CO, and the high pressures and associated costly equipment.



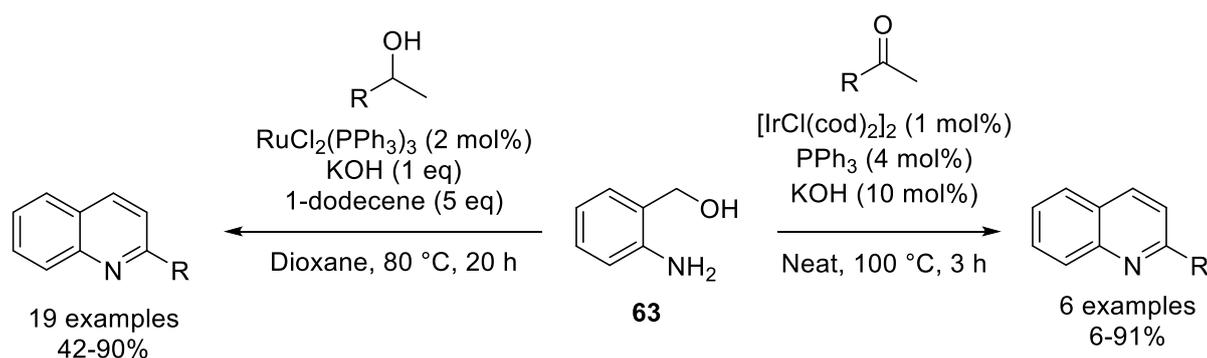
Scheme 24

Both a single reaction and an alternative two-step process were employed by Ishii *et al.* in the synthesis of α,ω -diarylalkanes by coupling various aryl n -alkyl alcohols (**Scheme 25**).⁴² The two-step presented is more suited to the synthesis of compounds from alcohols with chains longer than 2-phenylethanol. These products are alternatively synthesised by methods such as Grignard addition to α,ω -dihaloalkanes and Friedel-Crafts acylations, both of which are improved upon by the use of borrowing hydrogen methodology. This change in synthetic strategy allows the usage of less reactive and more easily obtained starting materials, and reduces safety concerns associated with the use of alkylmetal reagents in the case of the Grignard reaction and may allow milder reaction conditions in the case of Friedel-Crafts reactions.



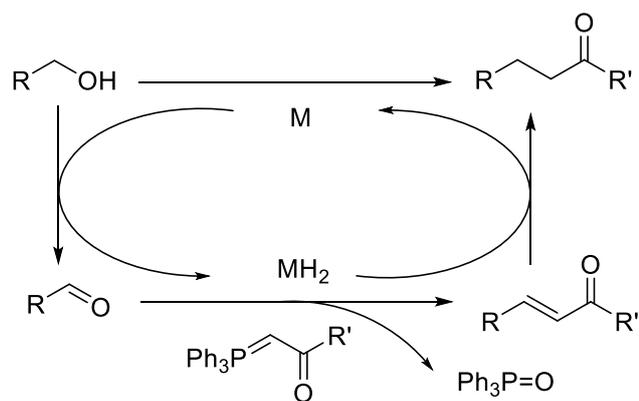
Scheme 25

These methods have also been used to synthesise heterocycles, for example the synthesis of quinolines from 2-aminobenzyl alcohol was demonstrated separately by the groups of Shim⁴³ and Ishii,⁴⁴ using ruthenium- and iridium-based catalysts respectively. Shim *et al.* used $\text{RuCl}_2(\text{PPh}_3)_3$, while Ishii's group used $[\text{IrCl}(\text{cod})]_2$ with PPh_3 as an additive and were able to reduce the amount of KOH used in their reaction to 0.1 eq, compared to Shim's 1.0 eq (**Scheme 26**). In Shim's case the cyclisation was carried out using alcohol compounds and therefore required the use of 1-dodecene as a hydrogen acceptor, while Ishii used ketones.



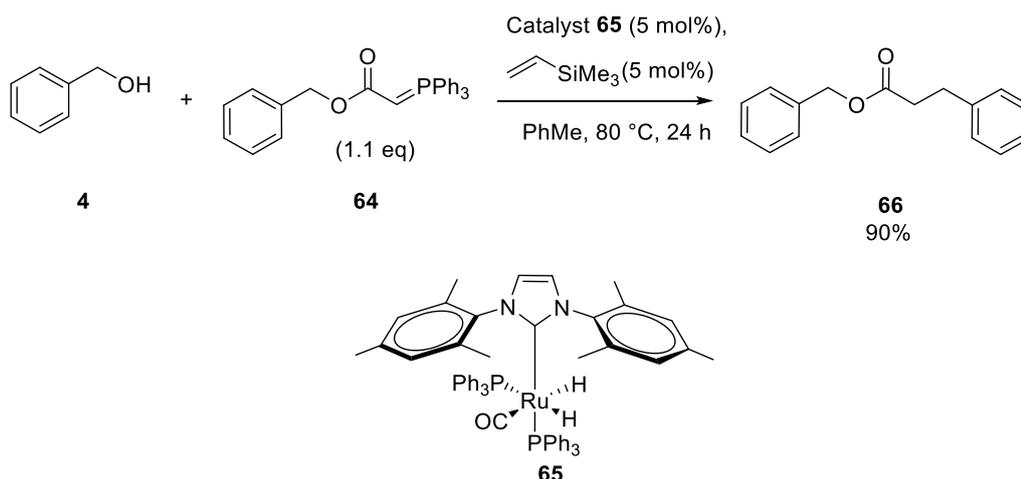
Scheme 26

Although a significant quantity of the borrowing hydrogen mediated *C*-alkylations in the literature proceed by aldol condensation reactions, it is also worth briefly highlighting alternate reaction pathways that have been demonstrated. One example is the Wittig reaction (**Scheme 27**). This proceeds similarly to a borrowing hydrogen aldol condensation, with the exception that the coupling partner is a phosphorus ylide, leaving $\text{Ph}_3\text{P}=\text{O}$ as a waste product, obviously taking away some of the green credentials of borrowing hydrogen technology.



Scheme 27

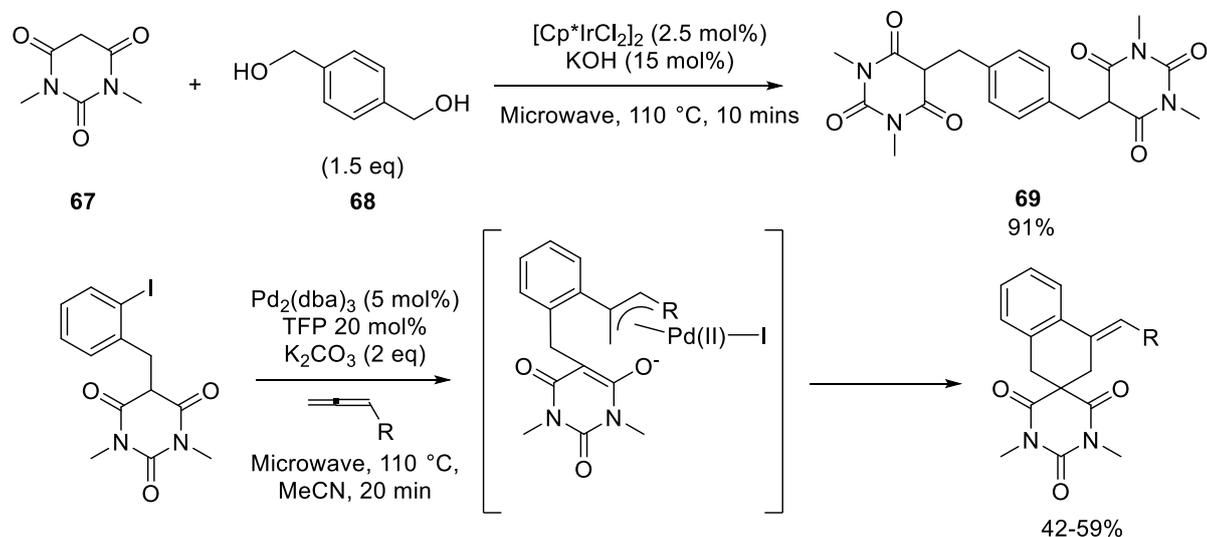
Several examples of the application of borrowing hydrogen methodology to Wittig reactions come from the group of Williams, such as the reaction of benzyl alcohol **4** with benzyl ester ylide **64** at 80 °C (**Scheme 28**).⁴⁵ In these reactions they included vinyltrimethylsilane as a hydrogen acceptor in order to allow the initial dehydrogenation of catalyst **65**.



Scheme 28

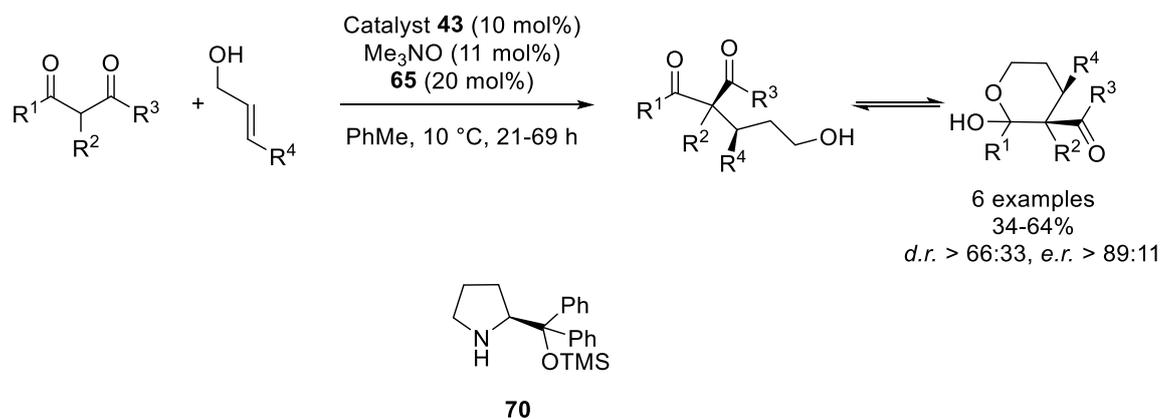
Knoevenagel reactions have also been shown to be possible using borrowing hydrogen methods. One interesting example comes from Grigg, where initial alkylation of 1,3-dimethylbarbituric acid **67** is carried out using $[\text{Cp}^*\text{IrCl}_2]_2$ under microwave conditions.⁴⁶ Good to excellent yields were achieved in the presence of ethers and halides, and a diol

was successfully used to bridge two molecules of the barbituric acid (**Scheme 29**). In the case that 2-iodobenzyl alcohol is used as the alkylating agent, the authors continue the synthesis by Pd-catalysed allene insertion and finally spirocyclisation to form the final barbiturate product.



Scheme 29

Finally, as with *N*-alkylation reactions, there has been work carried out to catalyse *C*-alkylation borrowing hydrogen reactions using less expensive metals than the iridium and ruthenium seen so far. The work by Morrill *et al.* discussed earlier also featured methylation onto a wide range of α -ketone positions as well as onto indoles and oxindoles using an iron-based catalyst, **45**.³⁴ Subsequent work by the same group has also achieved the methylation of 2-arylethanol, similar to the work by Beller *et al.* discussed earlier, but using their iron-based catalyst and avoiding the ruthenium used in the earlier work.⁴⁷ Extremely mild conditions were used by Rodriguez *et al.* who were able to carry out a range of enantioselective alkylations onto allylic alcohols using a cascade with iron catalyst **45** and organocatalyst **70**, at temperatures below room temperature (**Scheme 30**).⁴⁸

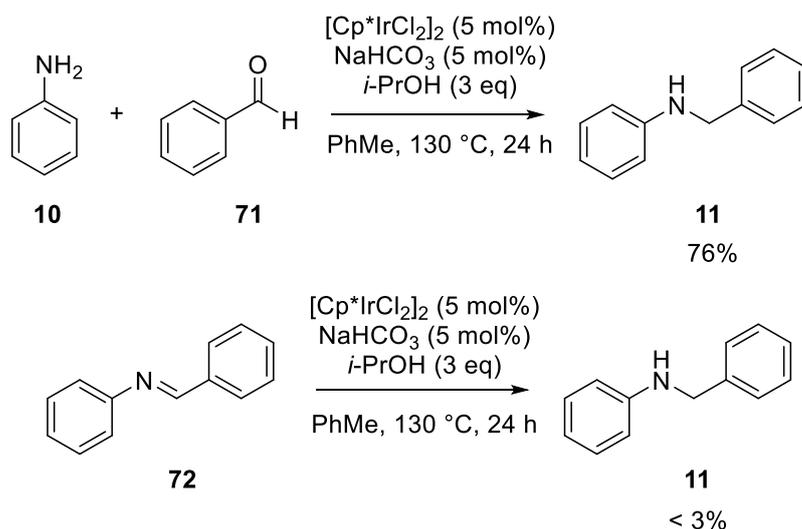


Scheme 30

Outside of iron chemistry, examples using cobalt catalysts to alkylate unactivated esters and amides⁴⁹ and secondary alcohols⁵⁰ are provided by the Kempe group, and Beller *et al.* have demonstrated the alkylation of ketones with primary alcohols using a manganese catalyst.⁵¹

1.4 Mechanistic Studies

Considerable work has been carried out within the literature to determine the mechanism responsible for these reactions, focusing on the alkylation of amines and alcohols by [Cp*IrCl₂]₂. Specifically, Yamaguchi used this catalyst along with NaHCO₃ and 2-propanol as a hydrogen donor in toluene at 130 °C to alkylate aniline with benzaldehyde and obtained the reduced product in good yield. But when an attempt was made to reduce benzylideneaniline, an intermediate in the previous reaction, using the same system, the product was observed in only trace amounts (Scheme **31**).⁵²



Scheme 31

This was taken as evidence that the final reduction step must take place while the imine is coordinated to the iridium catalyst, and a mechanism was proposed for the reaction (**Figure 1**).

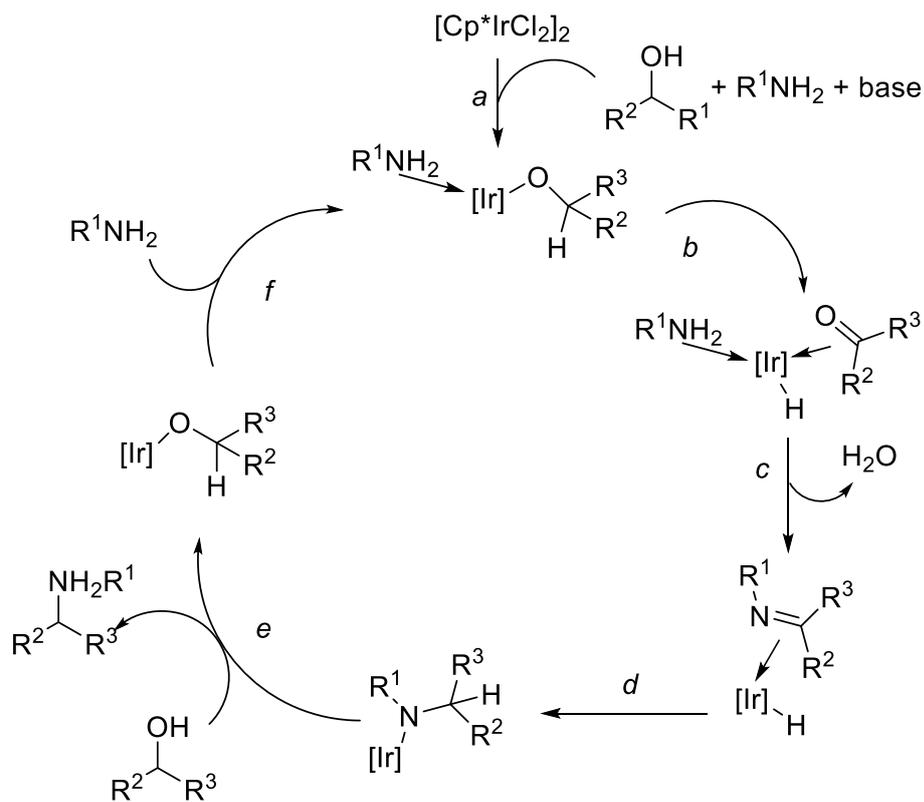


Figure 1

This cycle begins with the formation of the active catalyst by the bonding of iridium to the alkoxide species and coordination to the amine (*a*). The reaction then proceeds with elimination of the alkoxide's β -hydrogen, generating an iridium hydride species (*b*), and condensation between the newly formed carbonyl and the coordinated amine to form an imine, while remaining coordinated to the iridium (*c*). The imine is then reduced by inserting into the iridium-hydride bond (*d*) and released by exchanging with a new equivalent of the alcohol (*e*). Coordination of a new amine molecule returns the active catalyst (*f*). In this study no kinetic data was considered, so there is no indication as to which of the proposed steps is rate determining. Though not discussed in this work, it should be expected that several of the steps of this mechanism exist in equilibrium; specifically the formation of the imine, and steps which transfer a hydrogen between the metal centre and starting material and product. The formation of the amine is not however, which leads to overall formation of product.

Subsequent mechanistic investigations have been carried out and several alternate mechanisms for the same process have been suggested. Crabtree *et al.* proposed a mechanism in which the carbonate ion is directly coordinated to the iridium species instead of simply deprotonating the alcohol compound, after DFT calculations showed it to lower energy barriers to the reaction (**Figure 2**).⁵³

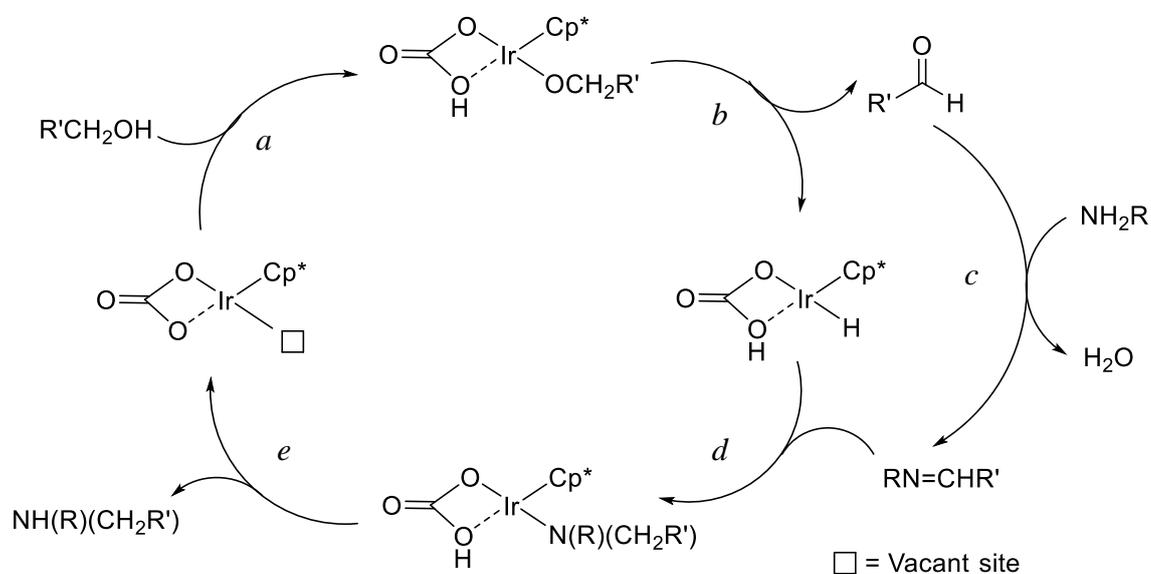


Figure 2

In this mechanism the carbonate deprotonates the alcohol as before but remains with the iridium as the newly formed alkoxide coordinates (*a*). The resulting carbonyl species is then released (*b*), condenses with an amine in solution outside the iridium's coordination sphere (*c*), and imine is coordinated again (*d*). The iridium's hydride is transferred to the imine, reducing it, and the product is released, freeing a coordination space and regenerating the active catalyst (*e*). The authors note the release of the amine as the rate-determining step.

DFT calculations were also used as the basis for the mechanism suggested by Zhao and co-workers, which was the first investigation to consider both inner and outer coordination sphere pathways (**Figure 3**).⁵⁴

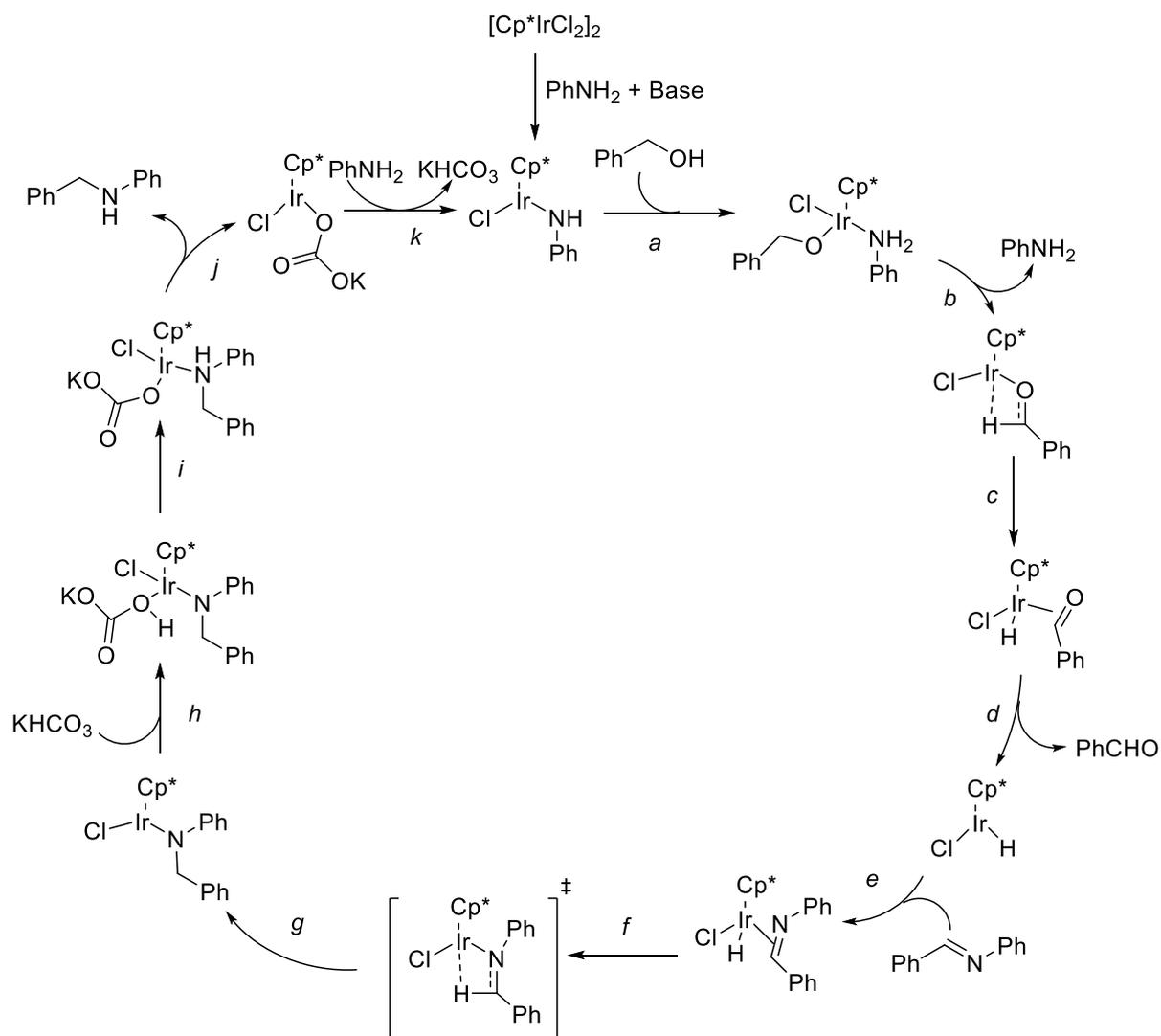


Figure 3

Here the catalytically active species is formed by the substitution of one of the precatalyst's chloride ligands with a molecule of aniline, which is then protonated by the alcohol molecule as it adds to the metal centre as an alkoxide (*a*). The amine is released into solution (*b*), and the alkoxide is oxidised to the carbonyl compound, generating the iridium hydride (*c*); this is proposed by the authors to be the rate determining step in the reaction. The aldehyde is also released (*d*), and condenses with the amine away from the catalyst, as in Crabtree's mechanism, to form the imine which recoordinates to the iridium (*e*). The iridium is dehydrogenated, transferring its hydride to the imine (*f*), as does the potassium carbonate which the authors postulated coordinates (*h*) and acts as a proton transfer agent (*i*), as they calculated this route to have the lowest Gibbs' free energy. This differentiates this mechanism from both Crabtree's, where the carbonate remains coordinated and Yamaguchi's, where it does not coordinate at any point. The amine product is finally released (*j*) and the potassium carbonate is displaced by another molecule of amine (*k*).

Finally, Madsen *et al.* proposed a mechanism with data drawn from both DFT studies and experimental evidence from a Hammett study, which suggested a positive charge was built up during the reaction's transition state, and an investigation into the reaction's kinetic isotope effect.⁵⁵ From these they concluded that the reaction's rate determining step was the carbonyl formation, the hemiaminal formation, or the elimination of water, contrasting with Crabtree's proposal but potentially in agreement with Zhao's.

In Madsen's mechanism, the reactants remain coordinated to the iridium centre for the entirety of the reaction, in opposition to the others discussed here (**Figure 4**). It is suggested that once bound the alkoxy transfers a proton to the amine, forming the carbonyl (*a*), which is then attacked by the amine to form a hemiaminal species (*b*). Dehydration of the hemiaminal forms the imine (*c*), and the water formed is released and another molecule of amine takes its place (*d*). A hydrogen is lost from the new amine species to the imine (*e*), and a molecule of the alcohol reactant provides the final hydrogen atom to form and release the amine product, reforming the iridium-alkoxy catalyst (*f*).

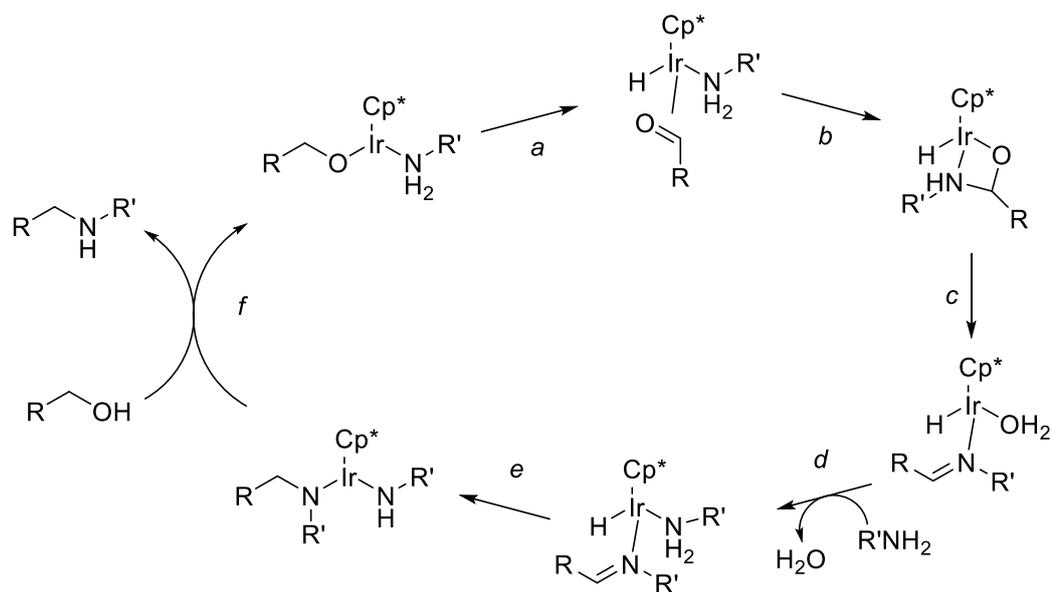


Figure 4

It is also worth noting that in this final mechanism there is no requirement for the potassium carbonate utilised in the others. This has been supported by work carried out within the Marsden group, which found that for the *N*-alkylation of piperidine with benzyl alcohol catalysed by $[\text{Cp}^*\text{IrCl}_2]_2$, the reaction rate was not altered by the addition or complete removal of base.⁵⁶ In the work from the Marsden group it was also found that the amount of the active catalytic species in this reaction, $[\text{Cp}^*\text{IrCl}_2]$, increased with the square root of the concentration of the precatalyst dimer; in agreement with Madsen and co-workers' calculations of the energy related to the monomer-dimer equilibrium.

1.5 Previous and Proposed Work

Previous work in the Marsden group led to the development of a family of catalysts, based on the knowledge gained from mechanistic studies that monomeric complexes may be more active than the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer, and that the presence of a vacant coordination site may be the source of catalyst sensitivity to poisoning.⁵⁶ These new catalysts, of the general structure shown in **Figure 5**, bore amine tethers, which coordinated to the metal centre.

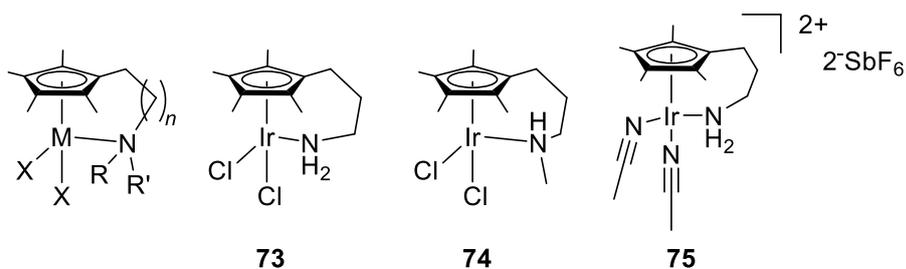
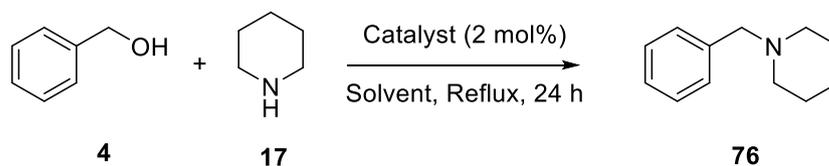


Figure 5

These complexes were synthesised with both rhodium and iridium centres and with tethers consisting of 2-4 carbon chains, with and without substituents on its amine and with a variety of other ligands. These were tested as catalysts for alkylation of amines with alcohols via borrowing hydrogen reactions, and it was observed that length of side-chain was fundamental to the action of the catalyst, and that catalysts with iridium centres and chloride ligands provide the greatest activity. Catalyst **69** and **70** were observed to have the greatest activity of these neutral compounds and gave excellent results when compared to $[\text{Cp}^*\text{IrCl}_2]_2$ when tested in a variety of solvents, particularly polar solvents (**Figure 6**).

Using catalyst **73** more than 20 substrates were used, including aryl, heteroaryl and alkyl compounds, with primary and secondary alcohols and amines, displaying tolerance for a wide range of functional groups, including halides, nitriles, ethers, esters, amides, sulphonamides and carbamates. Catalyst **73** was shown to be effective at loadings as low as 0.1 mol%, still achieving quantitative yields after 24 h. It was observed that selectivity of reactions towards the synthesis of either mono- or di-alkylation reactions outcome could be influenced by the choice of catalyst **73** or **74** for the reactions, as well as by altering the reactions stoichiometry (**Table 1**).



Conversion of Reaction After 24 h

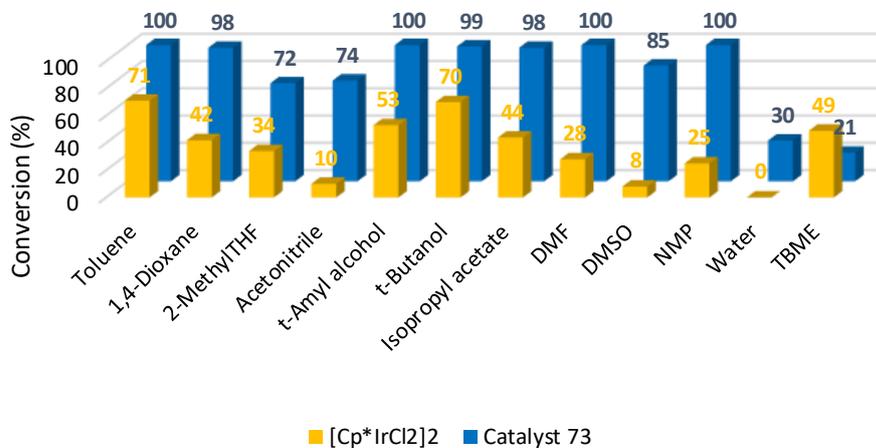
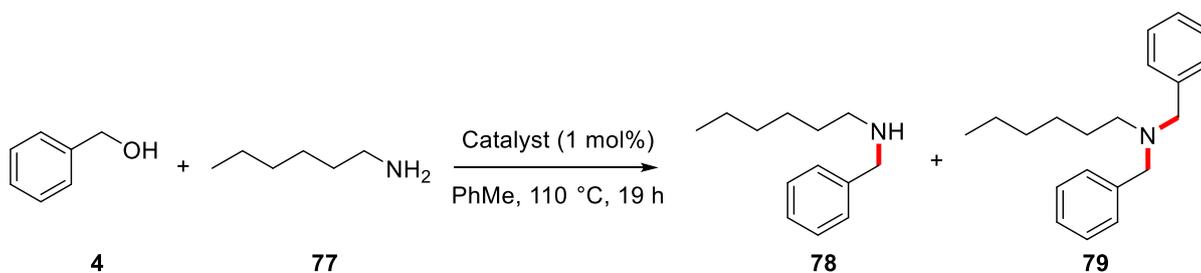


Figure 6 (conversions determined via GC with internal standard)



Catalyst	Amine : Alcohol	Product 78 (%)	Product 79 (%)
73	1:1	64	32
74	2:1	99	-
73	1:2	-	84
74	1:1	91	-

Table 1 (isolated yields)

It was also observed that catalysts of this family are completely selective against alkylation at aniline positions. It was suggested that this was due to the imine formation

in these reactions not being metal-templated, and an investigation was carried out into the mechanism of this family of catalysts.

Finally, cationic catalysts were synthesised, with **71** being the best performing; when tested against a range of solvents it was shown to be generally even more effective than **69** (Figure 7).

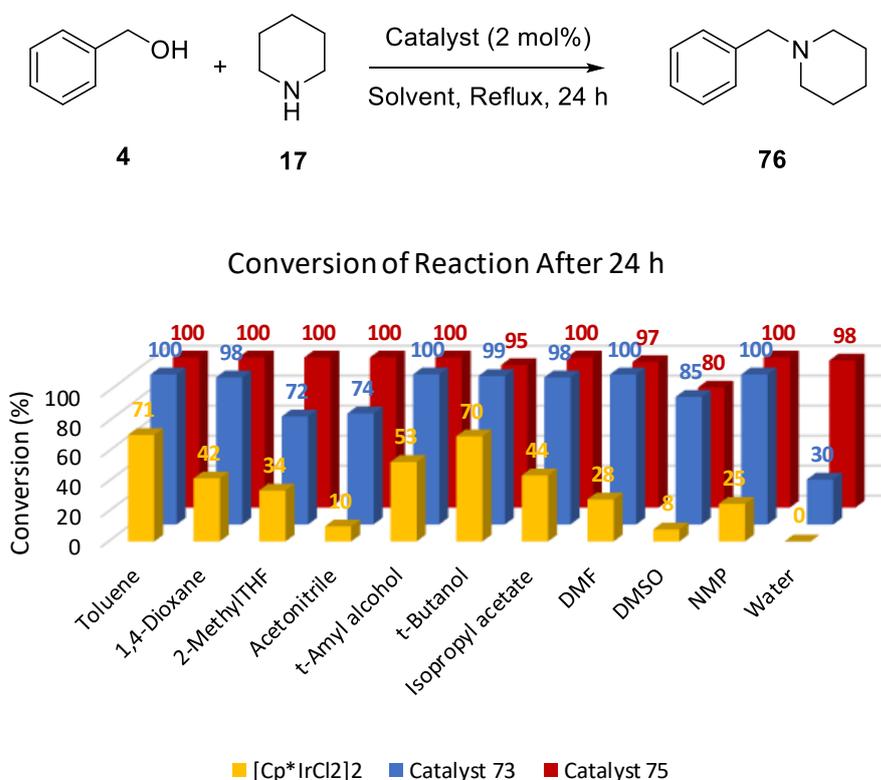


Figure 7 (conversions determined via GC with internal standard)

This family of catalysts have clearly shown great promise for carrying *N*-alkylation reactions, and this work will continue this research to examine a greater range of substrates, with particular focus on those with more than one possible site of reaction to determine the catalysts' selectivities beyond that already seen against anilines. Investigations will also be carried out into further optimisation of the catalysts' structure, and their synthesis. Finally, it is worth noting that none of the catalysts developed within the Marsden group have previously been tested to determine their potential utility as catalysts for carrying out *C*-alkylation reactions via hydrogen borrowing methodology.

As has been shown in the earlier review of the literature, this is an important subset of borrowing hydrogen reactions, and so we shall attempt to carry these out using our catalysts, and determine the scope for these reactions if successful.

Chapter 2: Borrowing Hydrogen *N*-Alkylation Reactions on Polyfunctional Compounds

2.1 Introduction

The synthesis of compounds bearing multiple heteroatoms is of industrial relevance as this is a feature of many pharmaceutical products and synthetic intermediates. For example, the local anaesthetic cinchocaine **80** and the antihistamine promethazine **81** both contain multiple nitrogen-containing functional groups (**Figure 8**). Traditionally these compounds present two problems to hydrogen borrowing methodology; firstly, it can be necessary to use protecting groups on one or more nitrogen atoms in order to control the reaction's regiochemical outcome. Secondly, some of the substrates and products involved in the synthesis of these compounds can coordinate or chelate to the catalyst being used, poisoning it and prematurely stopping the reaction. The latter case was observed in work by Leonard *et al.*, in which the alkylation of piperazine **82** with ethylene glycol **83** was unsuccessful.⁵⁷ The authors suggest that this is due to the large number of possible bidentate binding sites through which **82** could coordinate to the catalyst (**Scheme 31**). This was supported by showing that the catalyst was inactive in the presence of added **82** when attempting the alkylation of piperazine **85** with ethylene glycol, which was previously carried out in good yield.

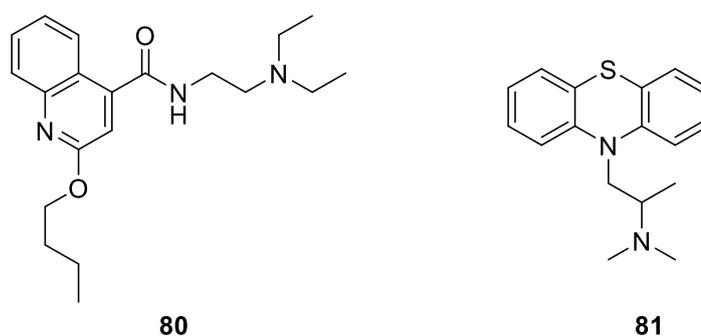
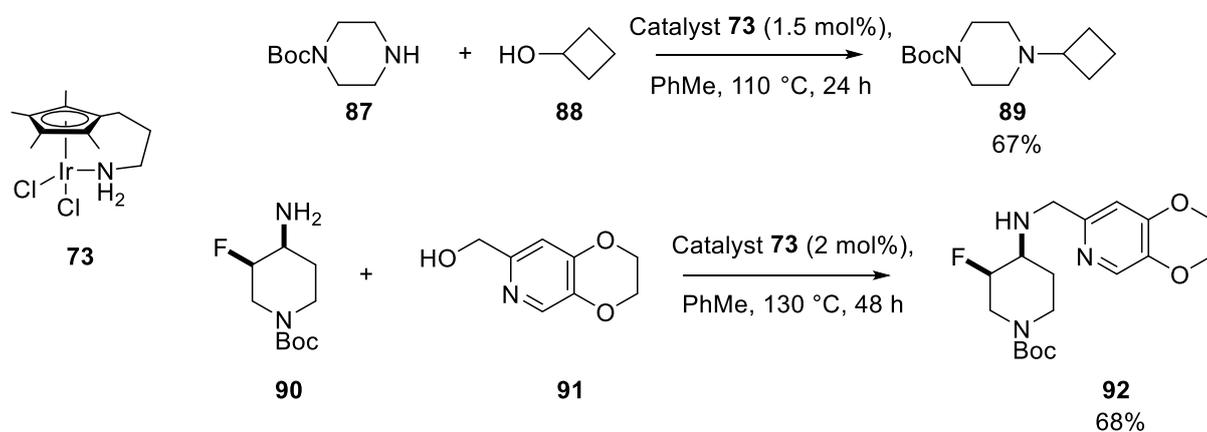
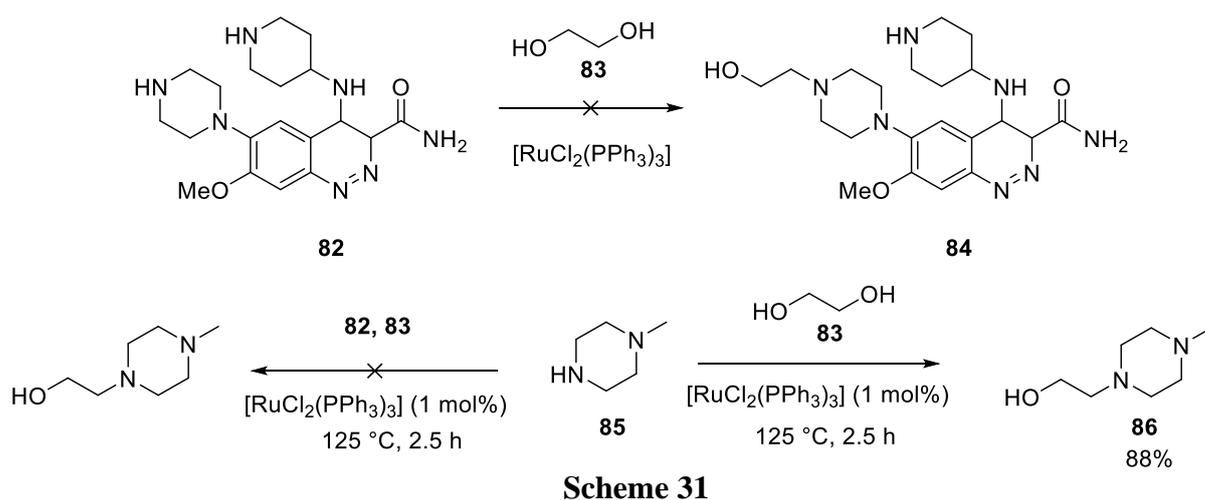


Figure 8

Previous work carried out within the Marsden group has proven the efficacy of catalyst **73** in carrying out amine alkylations via hydrogen borrowing methodology using a variety of substrates.⁵⁶ These included a significant variety of substituents aside from the amine and alcohol groups involved in the reaction, but only in a small number of cases did these examples include diols or diamines, which would present multiple possible sites of reaction. Two examples which were explored are the alkylation of *N*-Boc-piperazine **87** with cyclobutanol **88** and the alkylation of *N*-Boc-4-amino-3-fluoropiperidine **90** with dioxane **91** (Scheme 31).

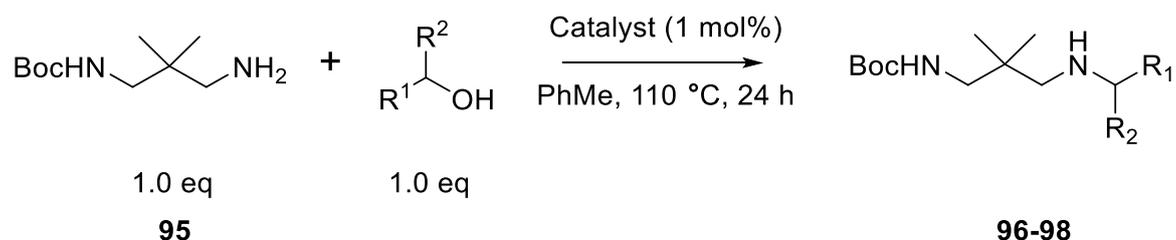


Both these reactions proceeded in good yield, however the Boc protecting group obviously removed the possibility of unintended alkylation in each case. The use of

Catalyst **73** outperformed the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer in the case of benzyl alcohol and hexanol and was slightly worse for the reactions with 1-phenylethanol. As would be expected, the alkylations with benzyl alcohol were the most effective, due to the electronically activated benzylic position, accelerating the oxidation of the alcohol. Despite sharing this advantage, the reactions with 1-phenylethanol were the worst performing. It was suspected that this was due to the oxidised intermediate in this reaction being a ketone, which will react more slowly with an amine than the aldehyde formed by the less favoured oxidation of hexanol. Similar reactions were then also carried out with the more sterically hindered *N*-Boc-2,2-dimethylpropanediamine, and at an increased concentration, to examine the potential for this to increase reaction conversion (**Table 3**).

Regarding the reactivity of the individual alkylating agents these results followed much the same pattern as shown in **Table 2** above. It can be seen however that $[\text{Cp}^*\text{IrCl}_2]_2$ has now performed better than **73** in the reaction with hexanol, and catalyst **73** performed better with 1-phenylethanol. In the case of the benzyl alcohol, there was little difference between the two, and the yield was only slightly increased by the doubling of concentration. It is also interesting to note that in all cases the yield obtained was increased compared to the reactions with the less sterically demanding diamine **91**.

To better differentiate the activities of the two catalysts, the reactions with benzyl alcohol were chosen as model reactions and the catalyst loading was dropped to 0.1 mol%. These reactions were monitored over time by GC using a mesitylene internal standard, with particular attention being paid to the initial rates of reaction. In the case of diamine **91**, catalyst **73** showed a final conversion more than 3 times that of catalyst the dimer, and a significantly higher initial rate of reaction (**Figure 9**).



Alcohol	Yield with [Cp*IrCl ₂] ₂ (%)	Yield with Catalyst 73 (%)
R ¹ = Ph, R ² = H	 96 70, 68 (1 M) (Conversion: 74, 75) 78, 80 (2 M) (Conversion: 83, 85)	 96 71, 73 (1 M) (Conversion: 78, 76) 75, 76 (2 M) (Conversion: 79, 82)
R ¹ = Ph, R ² = Me	 97 24, 29 (1 M) (Conversion: 28, 36) 45, 41 (2 M) (Conversion: 51, 49)	 97 33, 36 (1 M) (Conversion: 38, 40) 53, 57 (2 M) (Conversion: 60, 63)
R ¹ = Pent, R ² = H	 98 67, 71 (1 M) (Conversion: 75, 76) 76, 77 (2 M) (Conversion: 82, 84)	 98 52, 54 (1 M) (Conversion: 58, 59) 67, 70 (2M) (Conversion: 76, 74)

Table 3 (isolated yields and NMR conversions, reactions performed in duplicate)

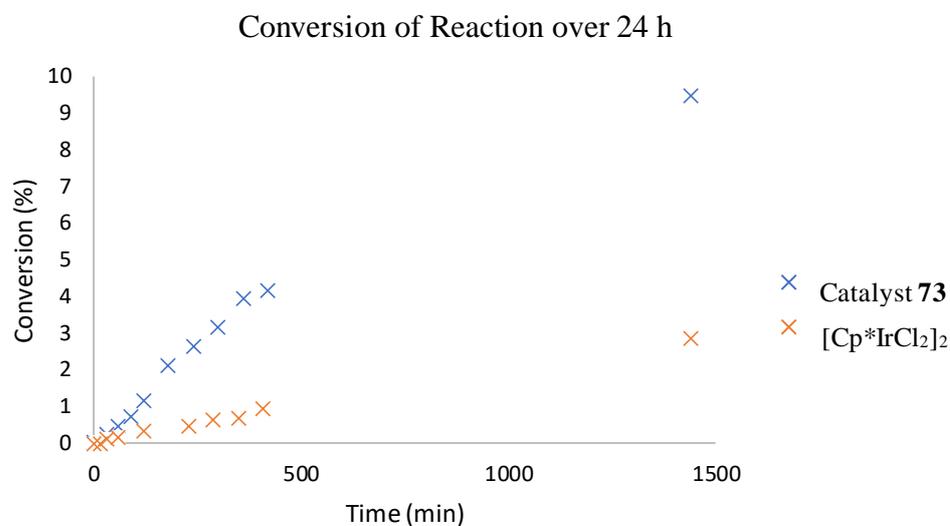
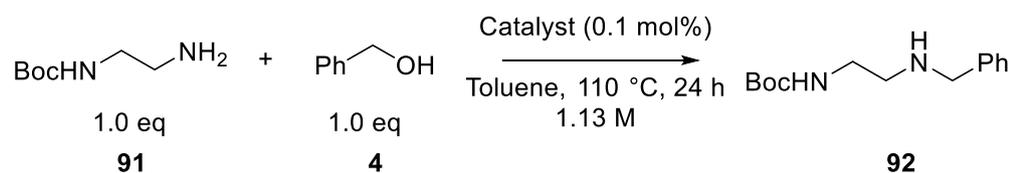
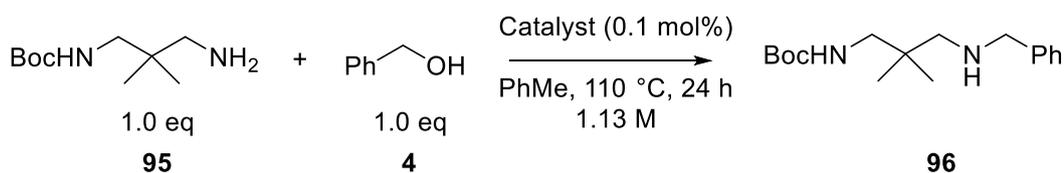
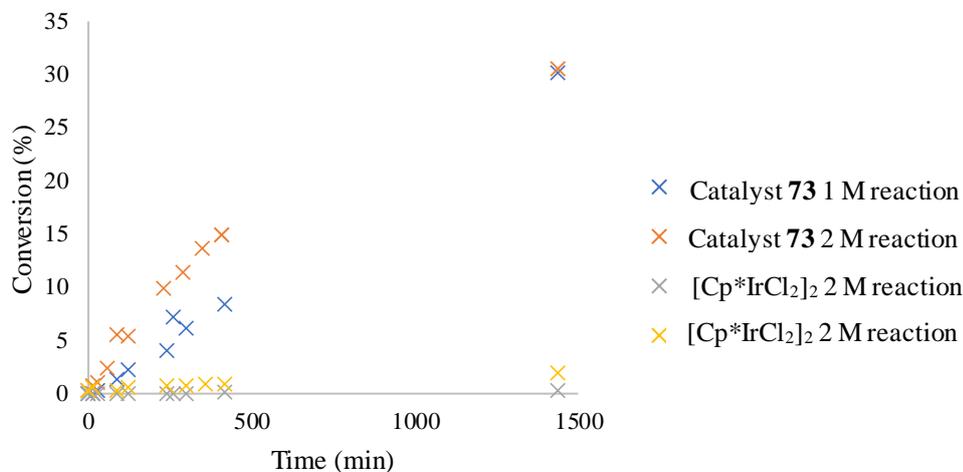


Figure 9 (conversions determined via GC with internal standard)

The lower loading reaction carried out on diamine **95** also demonstrated a higher activity from catalyst **73**, but in this case it was much more pronounced (**Figure 10**). It is interesting that both reactions catalysed by **73** reached roughly the same final conversion of 30% after 24 hours, but the more concentrated reaction had a significantly higher initial rate of reaction, which is potentially suggestive of catalyst poisoning by chelation of the diamine species.



Conversion of Reaction Over 24 h

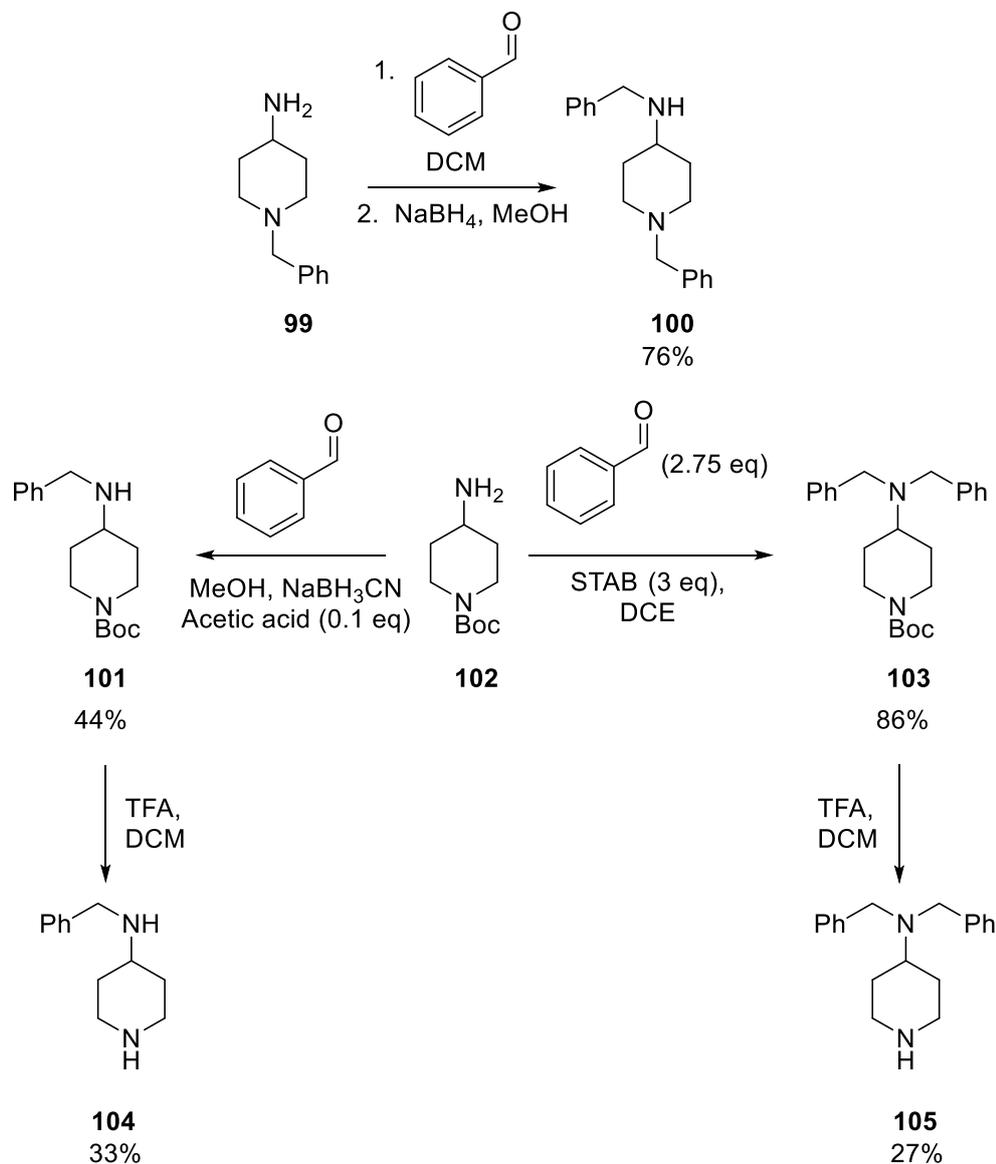


2.3 Selectivity with Unprotected Diamines and Diols

As previously mentioned, the use of protecting groups in synthetic routes is intrinsically inefficient, so experiments were carried out to determine whether any of the catalysts under examination displayed selectivity between different non-protected amines. 4-Aminopiperidine was chosen as a representative diamine, as the substituents on its secondary amine are sterically constrained by being in a ring, so that it is less sterically hindered than most secondary amines. Therefore, differentiation between it and the primary amine would be highly challenging and have to be at least partially on the basis of electronic differences.

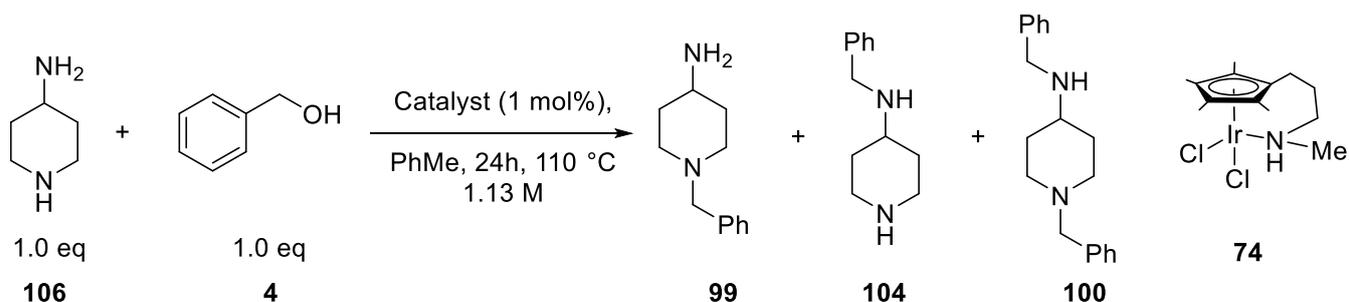
In order to facilitate analysis by GC, authentic samples of the various possible products from this reaction (**99**, **100**, **104** and **105**) had to be synthesised. Diamines **99** and **102** are commercially available, and reductive aminations with benzaldehyde and subsequent deprotections can be used to reach the remaining desired products.

After GC calibrations had been carried out for the starting materials and potential products, the alkylation of 4-aminopiperidine **106** with benzyl alcohol **4** was attempted using catalysts **73** and **74**, and $[\text{Cp}^*\text{IrCl}_2]_2$ (**Table 4**). Catalyst **70** was also developed in the Marsden group, and has previously shown selectivity towards selective monoalkylation of primary amines.



Scheme 33

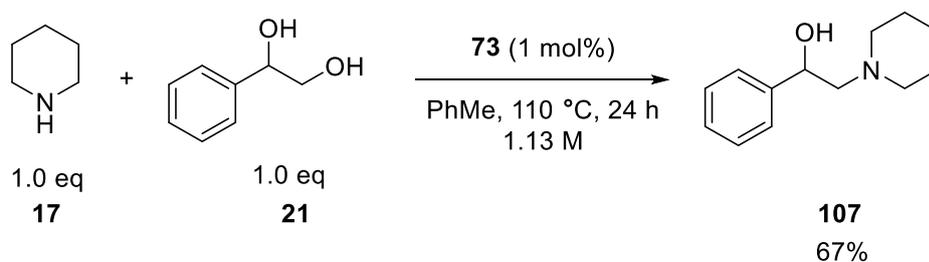
These results show good selectivity for monoalkylation on the primary amine from all the catalysts tested. $[\text{Cp}^*\text{IrCl}_2]_2$ achieved the highest selectivity, producing negligible amounts of any other products, while **74** gave the highest conversion, at the cost of somewhat increased production of side-products. The fact that catalysts **73** and **74** produced the same total amount of all product species (cumulatively 62%) fits with the observation made in previous work that the substitution on the amine tether does not affect the catalyst's activity, but only makes it more selective.⁵⁶



Catalyst	Yield of 99 (%)*	Yield of 104 (%)*	Yield of 100 (%)*	Remaining SM (%)*
73	2	42	18	31
74	2	54	6	25
$[\text{Cp}^*\text{IrCl}_2]_2$	1	47	1	43

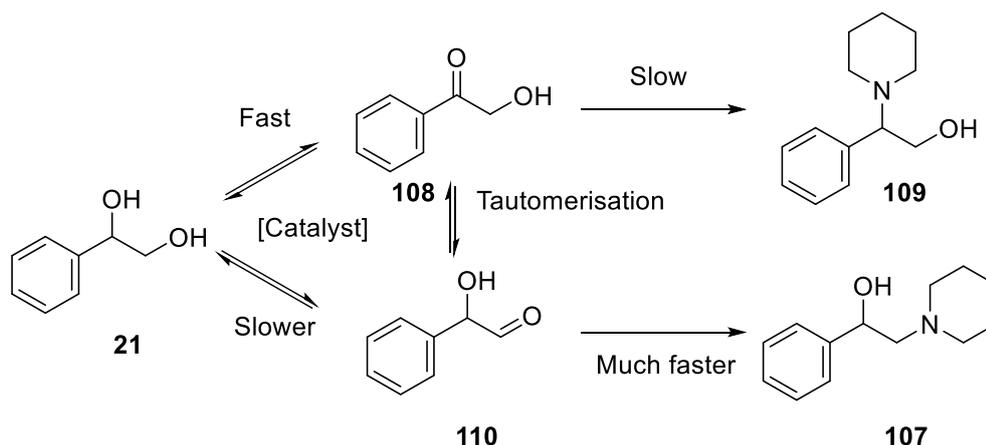
Table 4 (conversions determined via GC with internal standard)

Similarly, a reaction was carried out to examine the outcome of attempting to alkylate piperidine **17** with diol **21** (Scheme 34). In this case the only product observed was alkylation of the with the primary alcohol, with a good yield.



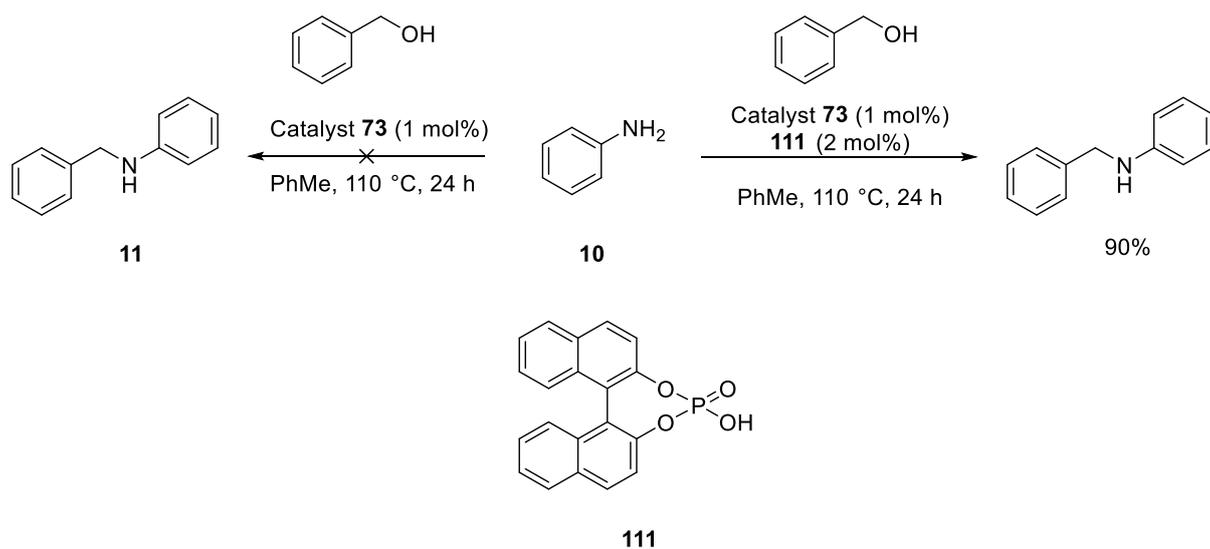
Scheme 34

Diol **21** is also a significantly challenging substrate to attempt to achieve selectivity with, as the oxidation of the secondary alcohol is encouraged by the electron-donating effect of the adjacent phenyl ring. Evidently this was outweighed by the superior reactivity of the aldehyde which results from the oxidation of the primary alcohol compared to that of the ketone which results from oxidation of the secondary alcohol. We may attribute the complete lack of alternative products either to the reversible nature of the oxidation or to tautomerisation of the oxidised species. (**Scheme 35**).



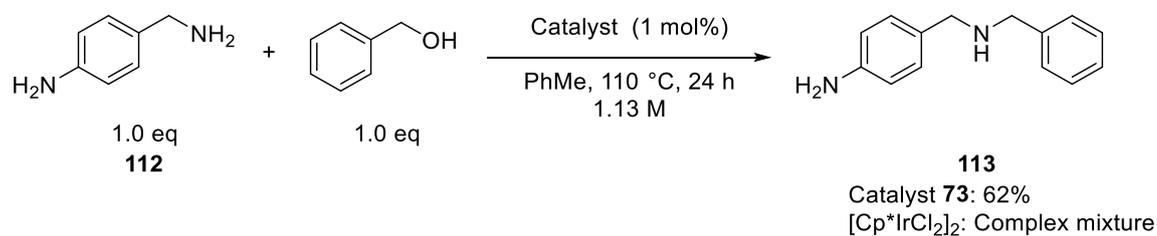
Scheme 35

Previous work in the Marsden group also found that catalyst **73** will not catalyse the *N*-alkylation of anilines unless an acid is present (**Scheme 36**), in contrast to $[\text{Cp}^*\text{IrCl}_2]_2$, which generally shows more activity towards anilines than the corresponding benzylamine.⁵⁶



Scheme 36

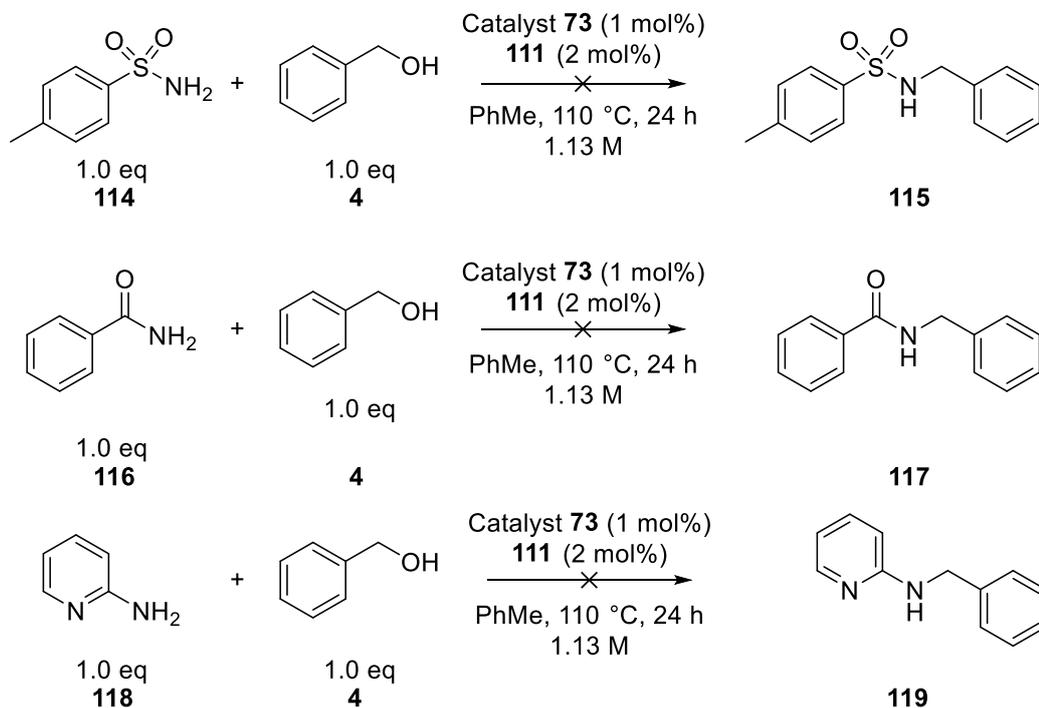
This raised the possibility of exploiting this selectivity to carry out selective *N*-alkylations, for example onto the benzylic position of 4-aminobenzylamine **112**. When we carried out this reaction with catalyst **73**, we were pleased to observe only formation of the desired product with **113**, while a complex mixture resulted from using $[\text{Cp}^*\text{IrCl}_2]_2$ (**Scheme 37**). In the latter case, LCMS peaks were visible which corresponded to both a single and a double alkylations.



Scheme 37

Reactions were also carried out investigating whether other compounds with more electron-poor nitrogen atoms would be alkylated under similar conditions. It was hoped

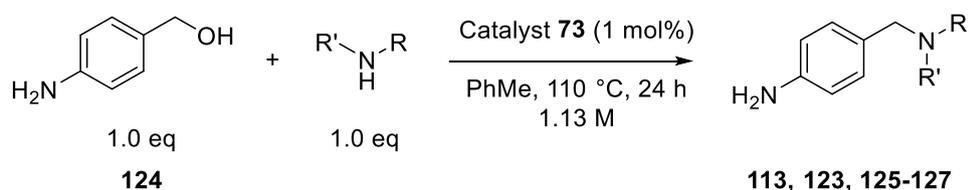
that these alkylations would not occur, thereby demonstrating an even greater selectivity in alkylation site, and this was proven to be the case (**Scheme 38**).



Scheme 38

This suggested that, even in the presence of our acidic additive **111**, there is a minimum level of nucleophilicity required of a nitrogen atom in order for it to be alkylated by our catalyst. Returning to 4-aminobenzylamine **112** as our substrate, the scope of alcohols which were tolerated by the reaction was examined (**Table 5**).

Another class of substrates which are viable for use in *N*-alkylation reactions as a result of catalyst **73**'s selectivity are those which bear an alcohol and an aniline on the same compound, for which we would predict oligomerisation if a reaction was attempted using another catalyst, such as $[\text{Cp}^*\text{IrCl}_2]_2$. To investigate the possibility to exploit this, another screen was carried out, alkylating various amines with 4-aminobenzyl alcohol **124** (Table 6).



Entry	Amine	Isolated Yield (%)	Product
1		38 (Conversion: 44)	
2		12 (Conversion: 17)	
3		66 (Conversion: 71)	
4		33 (Conversion: 37)	
5		36 (Conversion: 42)	

Table 6 (isolated yields and NMR conversions)

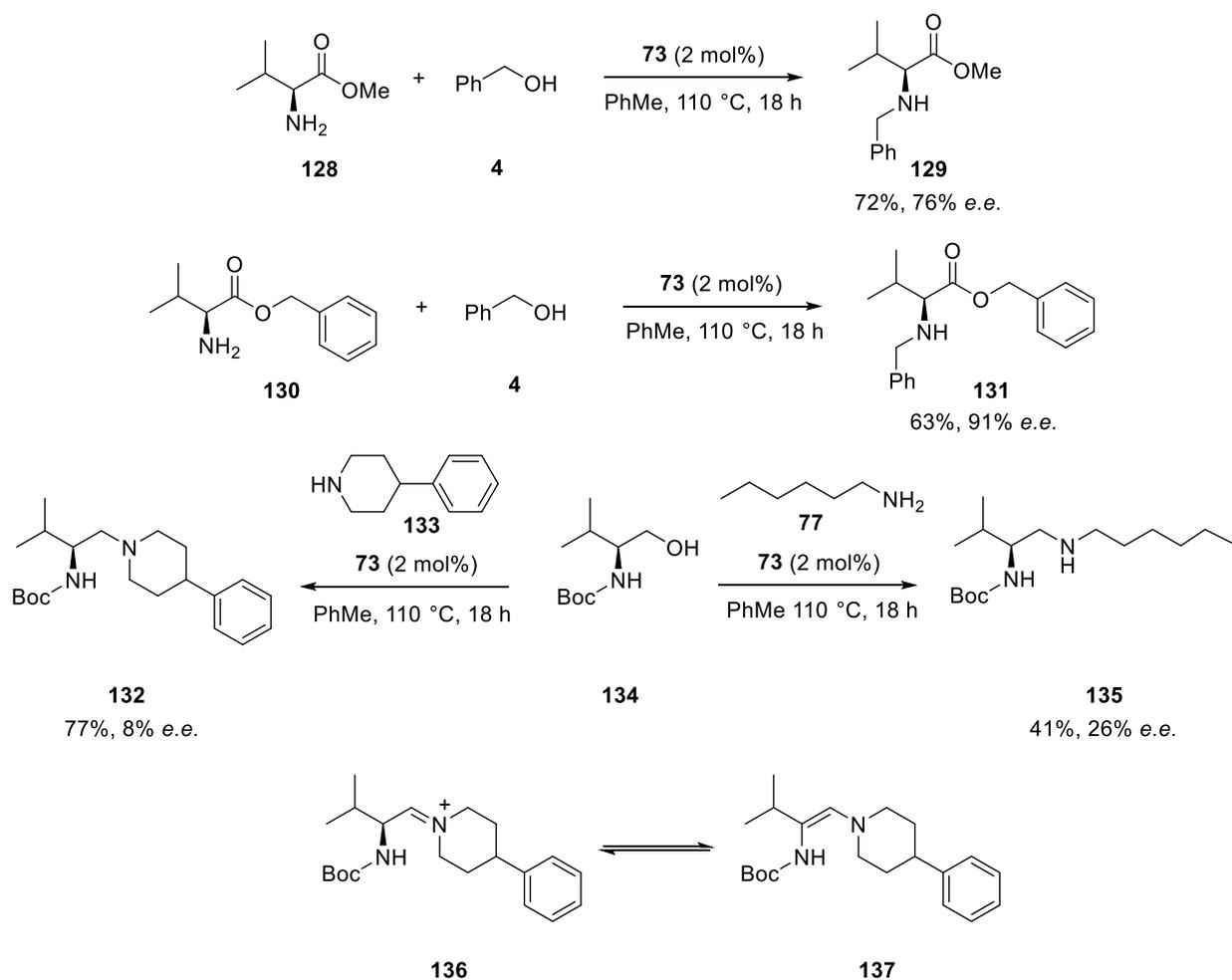
Generally, these reactions also proceeded in adequate yields. The introduction of a second heteroatom into the compound to be alkylated (entry 2) caused a large fall in yield,

although in previous work it achieved a good yield when being alkylated with benzyl alcohol with catalyst **73**, so it was not obvious why the aniline group should be so damaging to this reaction. It was not expected that cyclohexylamine (entry 3) would outperform piperidine (entry 1) to the extent seen here, as in previous work alkylating with benzyl alcohol, they achieved similar yields.⁵⁶ Benzylamine (entry 4) had performed significantly worse than piperidine in the same earlier work (60% vs 82%), but with 4-aminobenzyl alcohol a roughly equal result was achieved, which was not notably altered by the addition of an extra methylene when testing 2-phenylethylamine (entry 5).

In summary, though catalyst **73** does tolerate these aniline substrates, and has been shown previously not to alkylate at the aniline position, these reactions do provide lower yields than comparable reactions carried out in the absence of aniline groups. It is possible that, while not being alkylated, the presence of the aniline allows compound **124** to act as a chelator, potentially contributing to catalyst poisoning.

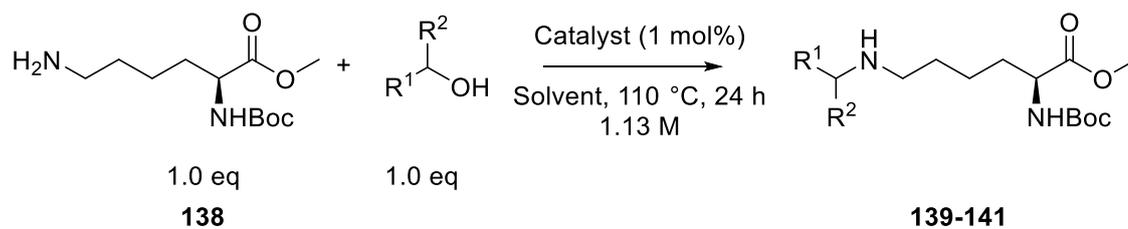
2.4 Alkylation of Amino Acids

Previously work with catalyst **73** has shown its competency in carrying out alkylations using both *O*-protected valine (**128** and **130**) and *N*-protected valinol (**132**) (**Scheme 39**).⁵⁶ In both cases, good yields could be obtained, and good enantiopurity was observed with the valine compounds, but not with the valinol. The loss of enantiopurity in the latter case is likely due to the migration of the imine double bond formed as part of the catalytic cycle to form enamine **137**, racimising the chiral centre. However, it could be argued that valine is one of the easier amino acids to attempt these reactions with, as the isopropyl side chain does not contain any additional heteroatoms which could coordinate to the catalyst, for example.



Scheme 39

Therefore, the scope of catalyst **73** for alkylating amino acids was further examined by attempting alkylation reactions on the residue amine of *N*-Boc-lysine methyl ester **138** (**Table 7**). The reactions were carried out in toluene which had been used so far, and DMF, which as a polar solvent, was expected to be more effective at solubilising **138**.

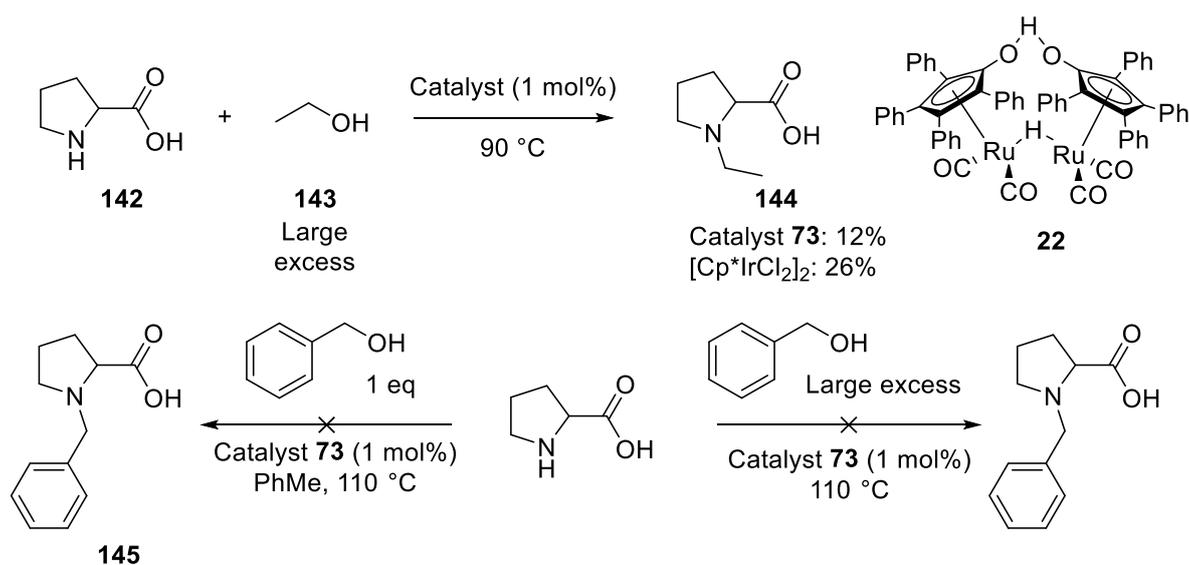


Alcohol	Yield with Catalyst [Cp*IrCl ₂] ₂ (%)	Yield with Catalyst 73 (%)
$R^1 = \text{Ph},$ $R^2 = \text{H}$	<p>139</p> <p>12 (DMF), (Conversion: 17)</p> <p>6 (PhMe) (Conversion: 10)</p>	<p>139</p> <p>10 (DMF), (Conversion: 16)</p> <p>0 (PhMe) (Conversion: 0)</p>
$R^1 = \text{Ph},$ $R^2 = \text{Me}$	<p>140</p> <p>11 (DMF), (Conversion: 15)</p> <p>6 (PhMe) (Conversion: 11)</p>	<p>140</p> <p>0 (DMF), (Conversion: 0)</p> <p>0 (PhMe) (Conversion: 0)</p>
$R^1 = \text{Pent},$ $R^2 = \text{H}$	<p>141</p> <p>9 (DMF), (Conversion: 15)</p> <p>7 (PhMe) (Conversion: 12)</p>	<p>141</p> <p>8 (DMF), (Conversion: 11)</p> <p>0 (PhMe) (Conversion: 0)</p>

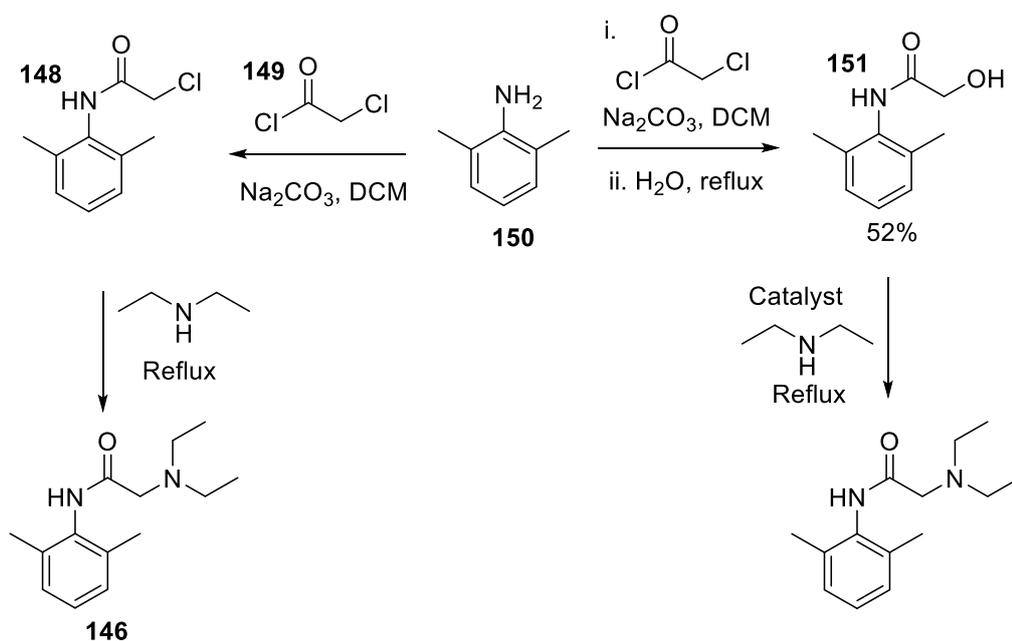
Table 7 (isolated yields and NMR conversions)

It is immediately clear that these alkylations were not nearly as successful as those carried out on the protected valine and valinol compounds, with the final reaction mixtures containing mostly starting material. The most obvious reason for this is that the catalysts were being poisoned by coordination of **138**, with the additional coordination from the residue's amine group allowing for more effective chelation than from amino acids and amino alcohols with hydrocarbon residues. $[\text{Cp}^*\text{IrCl}_2]$ had fully outperformed **73** in these reactions. In particular it was surprising that catalyst **73** provided no product at all in toluene, as it has already been demonstrated to be effective in this solvent.

Recently, Feringa *et al.* published the first general methodology for the catalytic *N*-alkylation of unprotected amino acids, utilising hydrogen borrowing catalysis.⁵⁹ These reactions were carried out using a large excess of the alcohol as the reaction solvent, using catalyst **22**. It was decided to replicate these conditions using our own catalysts, choosing two reactions with proline **142** in which particularly good results were reported. Feringa *et al.* reported a quantitative yield when ethanol was used as the alkylating reagent, and 68% with benzyl alcohol. Using the same reactions conditions with **73** and $[\text{Cp}^*\text{IrCl}_2]_2$, similar results were not achieved (**Scheme 40**).

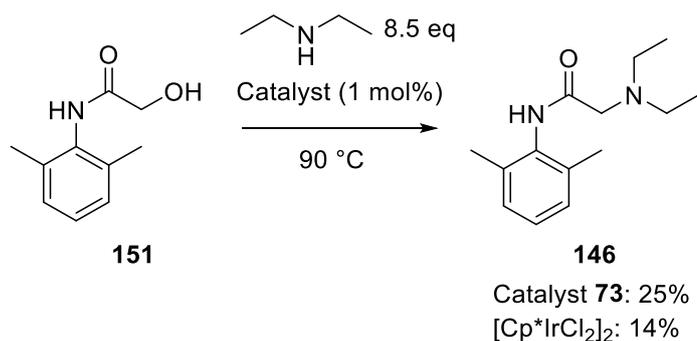


Scheme 40



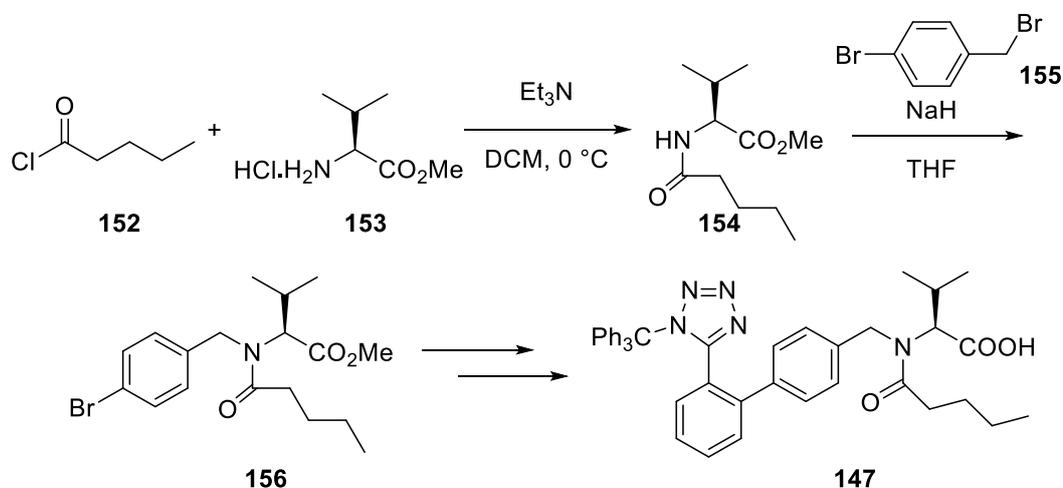
Scheme 41

The formation of **146** from **151** was attempted using catalyst **73** and $[\text{Cp}^*\text{IrCl}_2]_2$. Initially this was carried out under the usual conditions of equimolar amounts of both reactants in toluene, but only starting material was observed, likely due to the low boiling point of diethylamine (56 °C) resulting in the majority of that reagent not being present in the liquid phase with the catalyst and starting material **151**. This was more successful, when the reaction was carried out in neat, excess diethylamine (**Scheme 42**). Catalyst **73** was found to be more effective in this reaction than the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer, however 25% is still unlikely to be synthetically useful. This low yield could be attributed to the potential for the starting material **151** to coordinate to the catalyst and poison it.

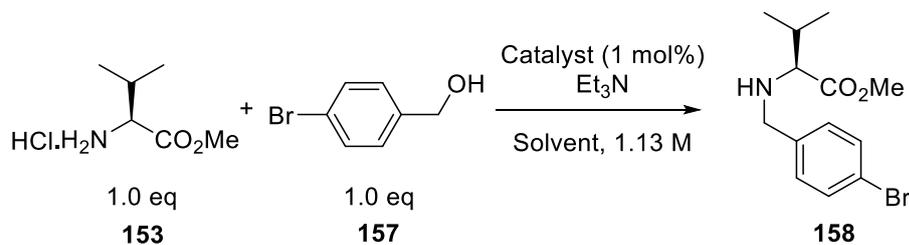


Scheme 42

The beginning of one synthetic route to valsartan **147** is shown below (**Scheme 43**).⁶¹ It was hoped that by simply changing the order of the first two reactions 4-bromobenzyl bromide **155** could be replaced with 4-bromobenzyl alcohol, which is significantly less hazardous.^{62,63}



Accordingly, the results of attempts to alkylate **153** with 4-bromobenzyl alcohol **157** using both catalysts and in toluene and DMF are shown in (**Table 8**).



Solvent	Yield with catalyst 73 (%) (Conversion: %)	Yield with catalyst [Cp*IrCl₂]₂ (%) (Conversion: %)
Toluene	13 (Conversion: 19)	6 (Conversion: 12)
DMF	13 (Conversion: 17)	11 (Conversion: 14)

Table 8 (isolated yields and NMR conversions)

Again, catalyst **73** has outperformed the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer, but both yields are disappointing and unlikely to be useful on a production scale without significant optimisation.

2.6 Conclusion

In conclusion, catalysts developed in the Marsden group, particularly catalyst **73**, have been used to carry out alkylations on a variety of polyfunctionalised compounds, in most cases improving on the performance of the commercially available $[\text{Cp}^*\text{IrCl}_2]_2$ dimer. In the case of *N*-Boc protected diamines, **73** was shown to be significantly more active, emphasised by its ability to carry out reactions at loadings as low as 0.1 mol%.

All catalysts tested showed good selectivity towards the alkylation of primary amines in compounds also containing secondary amines. The commercially available $[\text{Cp}^*\text{IrCl}_2]_2$ displayed the highest selectivity, while **74** produced the highest quantity of the desired primary alkylation. Similarly, catalyst **73** was very effective in selectively carrying out reactions at primary alcohols in the presence of secondary alcohols, producing no unwanted products. It was suggested that this could be attributed to reversibility of the parts of the reaction and this could be tested by carrying out a reaction using an enantiopure starting material and the comparing the *e.e.* of the final product. Catalyst **73** was also shown to be completely selective against alkylations onto aniline functions in all reactions attempted, allowing for selective alkylations onto 4-aminobenzylamine and using 4-aminobenzyl alcohol using a range of aryl, and linear and cyclic reactions partners.

Both catalysts tested struggled to alkylate the amino group on a protected lysine species in polar or non-polar solvent. It is suspected that this is due to poisoning of the catalyst, which could be tested by spiking a reaction which the catalysts are known to be capable of carrying out with the lysine species. They were however able to alkylate proline with ethanol, albeit using a large excess of ethanol and with $[\text{Cp}^*\text{IrCl}_2]_2$ giving a superior yield to **73**, supporting the hypothesis that the failure of the reactions with lysine species was due to coordination from their second nitrogen atom.

Finally, both catalysts were able to be used in routes towards the synthesis of the drugs lidocaine and valsartan. In both cases catalyst **73** gave a better result but would still require significant optimisation in order to be viable in an industrial setting.

Chapter 3: Optimisation of *N*-Alkylation Reactions with Respect to TON

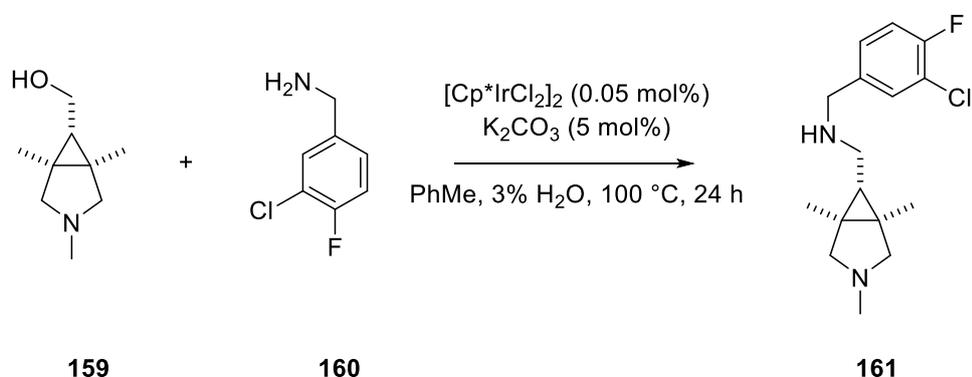
3.1 Introduction

The turnover number (TON) of a catalyst represents the number of times each individual molecule of catalyst completes one catalytic cycle, based on the yield of the reaction, and can be calculated by:

$$TON = \frac{\text{Yield (\%)}}{\text{Catalyst loading (mol\%)}}$$

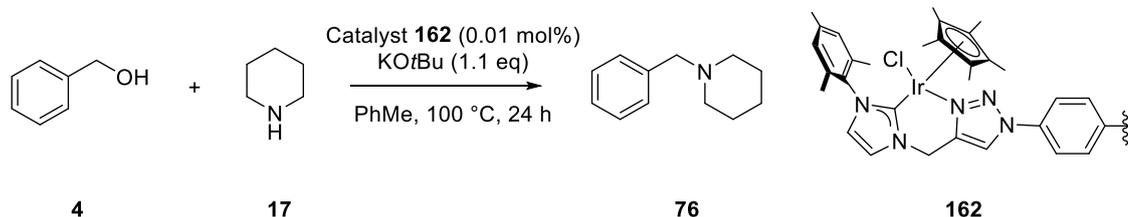
TON is a measure of the activity of a catalyst, and is particularly important in industrial processes where efficiency is economically required. This is most relevant in cases such as catalyst **73**, where the catalyst itself is expensive, due to both the cost of materials, particularly iridium, and the synthesis required to produce it.

Generally, catalysts for borrowing hydrogen reactions have a low TON and high loadings of precious metals are required to bring the reaction to completion.⁵⁷ Some positive examples do exist in the literature however; for example chemists working at Pfizer were able to obtain a TON of 1700 in the synthesis of a GlyT1 inhibitor, using a catalyst loading of 0.05 mol% (**Scheme 44**).⁶⁴



Scheme 44

A significantly higher TON has been achieved by Messerle *et al.*, who used heterogeneous borrowing hydrogen catalyst **162** to alkylate a series of anilines with various alcohols.⁶⁵ On the simple reaction of benzyl alcohol **4** and piperidine **17**, they recorded a yield of 42% at a loading of 0.01 mol%, a TON of 4200 (**Scheme 45**).

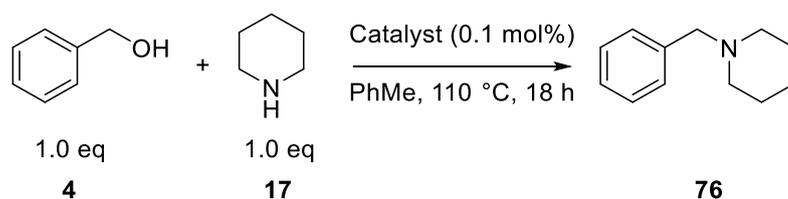


Scheme 45

Previous work within the Marsden group on borrowing hydrogen reactions catalysed by **73** had explored loadings as low as 0.1 mol%, which achieved quantitative conversion after 24 hours, corresponding to a TON of 1000. Accordingly, we decided to investigate the scope for demonstrating TONs above this level.

3.2 Optimisation of Catalyst Loading for TON

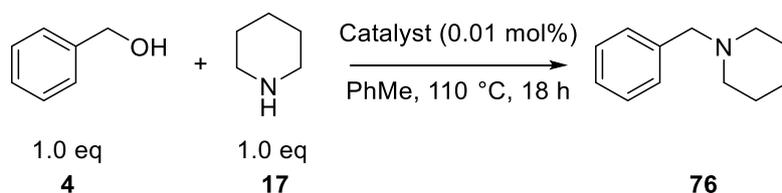
The investigation begun by carrying out a series of *N*-alkylations to determine the competency of both catalyst **73** and [Cp*IrCl₂]₂ at lower loadings and with a range of reaction concentrations and solvents, starting with a loading of 0.1 mol%; a factor of ten lower than previous reactions (**Table 9**). For this the alkylation of piperidine **17** with benzyl alcohol **4** was used as our model reaction, as it had been previously proven to be high yielding.



Concentration of starting material (M)	Catalyst	Toluene	DMF	NMP
0.33	Catalyst 73	92% (TON: 920)	38% (TON: 380)	49% (TON: 490)
	[Cp*IrCl ₂] ₂	3% (TON: 30)	1% (TON: 10)	2% (TON: 20)
1.33	Catalyst 73	94% (TON: 940)	67% (TON: 670)	72% (TON: 720)
	[Cp*IrCl ₂] ₂	5% (TON: 50)	2% (TON: 20)	4% (TON: 40)
4.0	Catalyst 73	96% (TON: 960)	69% (TON: 690)	81% (TON: 810)
	[Cp*IrCl ₂] ₂	4% (TON: 30)	6% (TON: 60)	3% (TON: 30)

Table 9 (conversions determined by GC with internal standard)

The results of this screening showed a more pronounced preference for catalyst **73** over [Cp*IrCl₂]₂ than previous reactions at 2 mol%, when catalyst **73** achieved a quantitative yield compared to 72% with [Cp*IrCl₂]₂.⁵⁶ There also appeared to be a general preference for toluene over NMP, and for NMP over DMF, though the influence of the solvent choice varied. It was believed that the relatively large ratio of catalyst to reactant was still a limiting factor in these reactions; obviously the highest TON that can be achieved in a reaction with 0.1 mol% catalyst loading is 1000, which is relatively low in the context of those previously discussed. As such, the investigation moved on to look at reactions with 0.01 mol% catalyst loadings (**Table 10**).

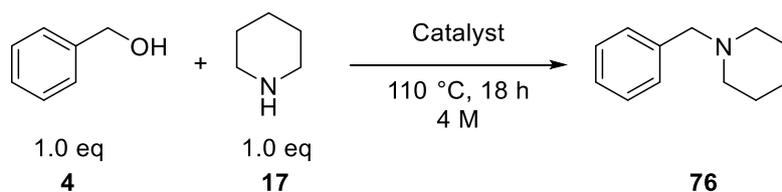


Concentration of starting material (M)	Catalyst	Toluene	DMF	NMP
0.33	Catalyst 73	1% (TON: 100)	1% (TON: 100)	*
	[Cp*IrCl ₂] ₂	*	*	*
1.33	Catalyst 73	1% (TON: 100)	2% (TON: 200)	4% (TON: 400)
	[Cp*IrCl ₂] ₂	*	*	1% (TON: 100)
4.0	Catalyst 73	1% (TON: 100)	1% (TON: 100)	1% (TON: 100)
	[Cp*IrCl ₂] ₂	*	*	*

*No observed product

Table 10 (conversions determined by GC with internal standard)

It was immediately obvious that this loading was too low to be tolerated by catalyst **73**. However, the fact that the catalyst did not achieve a yield equivalent to roughly the same TON as in the previous experiments, suggested that the relationship was not simply a smaller amount of catalyst catalysing proportionally less reactions. In order to determine the optimal level of catalyst loading another set of reactions was therefore carried out, probing points between these two loadings, in this case carrying out all reactions at a concentration of 4 M (**Table 11, Figure 11**).



Catalyst loading (mol%)		Toluene	DMF	NMP
0.013	Catalyst 73	5% (TON: 385)	13% (TON: 1000)	3% (TON: 231)
	[Cp*IrCl ₂] ₂	< 1% (TON: < 77)	< 1% (TON: < 77)	< 1% (TON: < 77)
0.02	Catalyst 73	4% (TON: 200)	11% (TON: 550)	25% (TON: 1250)
	[Cp*IrCl ₂] ₂	< 1% (TON: < 50)	< 1% (TON: < 50)	1% (TON: 50)
0.04	Catalyst 73	86% (TON: 2150)	90% (TON: 2250)	51% (TON: 1275)
	[Cp*IrCl ₂] ₂	8% (TON: 200)	2% (TON: 50)	4% (TON: 100)

Table 11 (conversions determined by GC with internal standard)

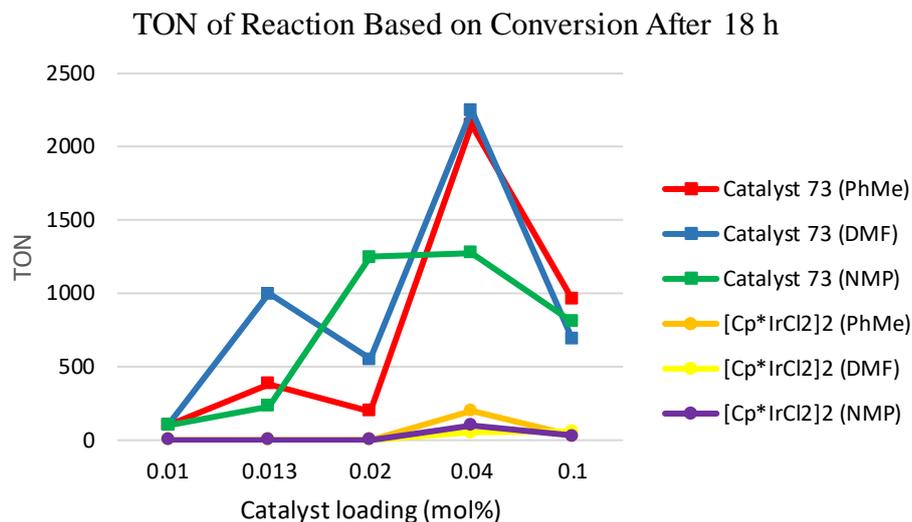


Figure 11

Figure 11 shows that TON peaked at around a loading of 0.04 mol% for all reactions with catalyst **73**, and in the case of reactions carried out in toluene and NMP for $[\text{Cp}^*\text{IrCl}_2]_2$, after which there is a sharp drop off in performance. The best TON achieved with catalyst **73** was 2250 in DMF, compared to a peak of 200 for $[\text{Cp}^*\text{IrCl}_2]_2$, clearly demonstrating the superiority of our catalyst in this context.

Two possible explanations were hypothesised for the sharp drop-off seen in the performance of catalyst **73** below loadings of 0.04 mol%. One possibility is that it could be due to a low level of impurity in our reactants or solvent which is capable of poisoning the catalyst – if the level of impurity was similar to the catalyst loading we would expect a rapid decrease in activity at that level as all catalyst in the reaction is inactivated.

Another possibility becomes apparent if the rate equations for the individual steps in the *N*-alkylation reaction are examined (**Figure 12**). It can be seen that the hydrogenated catalyst species **D** must complete a full cycle of the reaction in order to reform the catalyst **B** and oxidise another molecule of the alcohol **A**. As such, the upper limit of the combined concentrations of the intermediates **C** and **F** is equal to the initial concentration of **B**. It is also obvious that the concentration of **D** in the reaction can never exceed the initial concentration of **B**. An equation can therefore be written for the maximum possible rate of the third step of this reaction as:

$$\text{Rate} = k_3[\mathbf{B}]^2$$

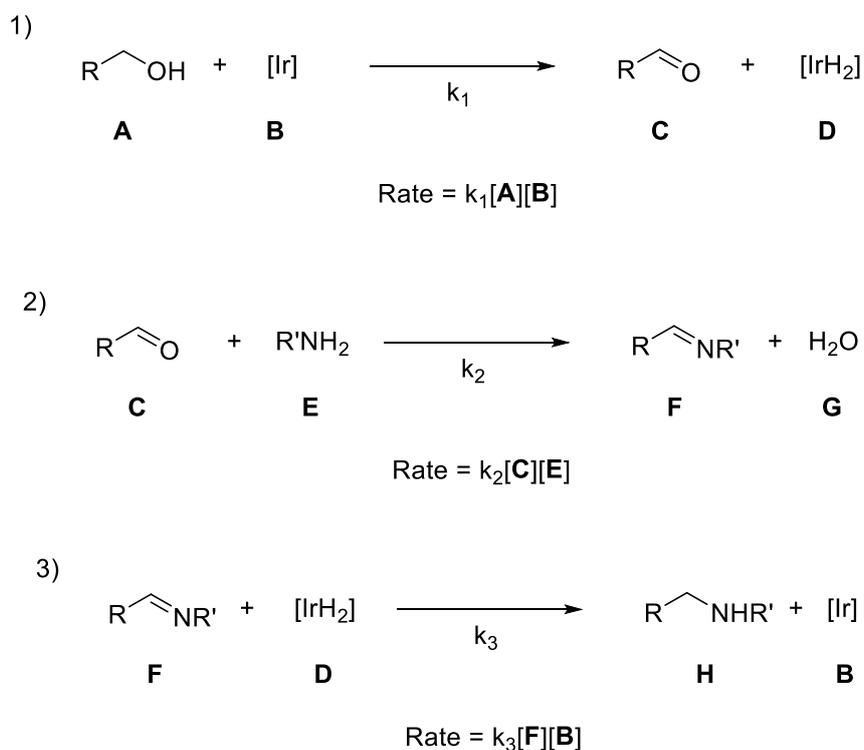
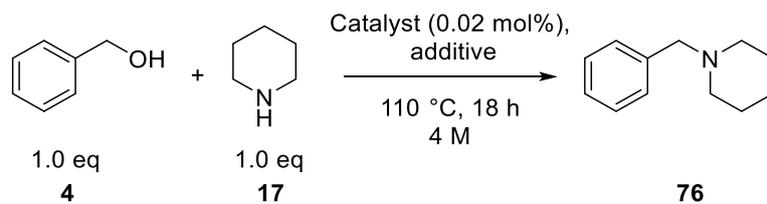


Figure 12

This means that while the rates of steps **1** and **2** are dependent on the initial catalyst concentration, the rate of step **3** is dependent on the square of that concentration and is therefore much more sensitive to changes in it. Step **1** is generally the rate limiting step of this reaction, however, depending on the ratio of k_1 to k_3 , step **3** could be expected to become rate limiting below a critical level of catalyst concentration, indicated by the sharp drop-off in **Figure 11**.

Previous work with catalyst **73** also found that its activity could be slightly increased by the addition of a small amount of weak acid or water, or an equivalent of weak base.⁵⁶ Accordingly a final screening of both catalysts in different solvents was carried out, using additives to attempt to achieve a higher TON (**Table 12**, **Figure 13**). These reactions were carried out with a catalyst loading dropped to 0.02 mol%, as in the case of catalyst **73** in toluene and DMF there was little room for increase in yield at a loading of 0.04 mol%.



Additive		Toluene	DMF	NMP
1.0 eq DIPEA	Catalyst 73	3% (TON: 150)	8% (TON: 400)	8% (TON: 400)
	[Cp*IrCl ₂] ₂	< 1% (TON: <50)	< 1% (TON: <50)	4% (TON: 200)
0.1 eq AcOH	Catalyst 73	16% (TON: 800)	8% (TON: 400)	34% (TON: 1700)
	[Cp*IrCl ₂] ₂	2% (TON: 100)	< 1% (TON: <50)	1% (TON: 50)
0.1 eq H ₂ O	Catalyst 73	1% (TON: 50)	5% (TON: 250)	13% (TON: 650)
	[Cp*IrCl ₂] ₂	< 1% (TON: <50)	< 1% (TON: <50)	2% (TON: 100)

Table 12 (conversions determined by GC with internal standard)

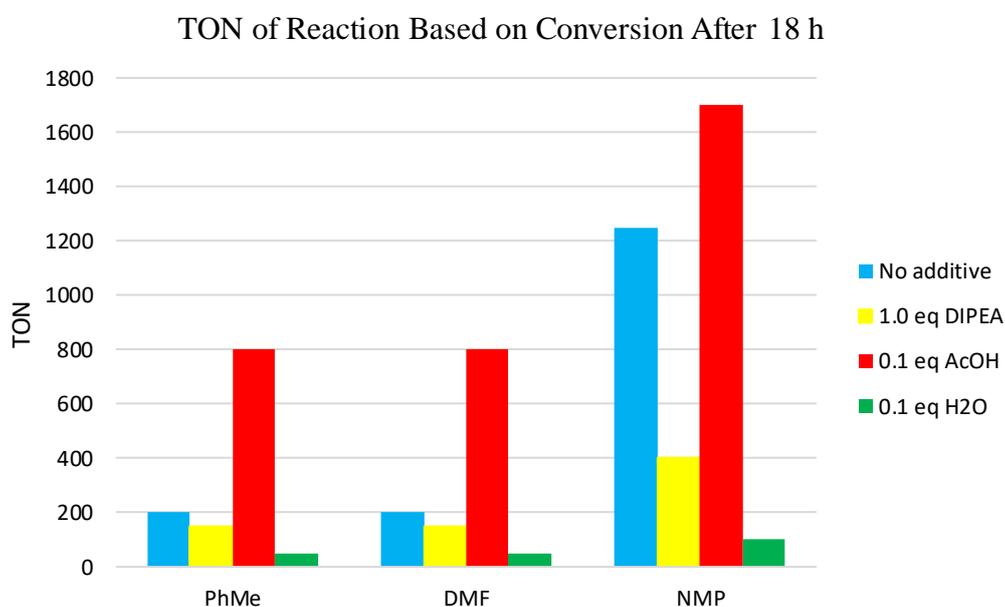


Figure 13

From the results for reactions with catalyst **73**, it can be seen that for every solvent the addition of 0.1 eq of AcOH achieves the highest TON, with the second-best result being the unadulterated reaction. It was also consistent that the worst result was from the reaction which has had 0.1 eq of H₂O added. The scale of the differences between effects of the additives however, appeared to be highly solvent dependent. Once again catalyst **73** dramatically outperformed [Cp*IrCl₂]₂, but there is similarity between the two sets of data in that both achieved their highest TON in NMP with an AcOH additive.

3.3 Conclusion

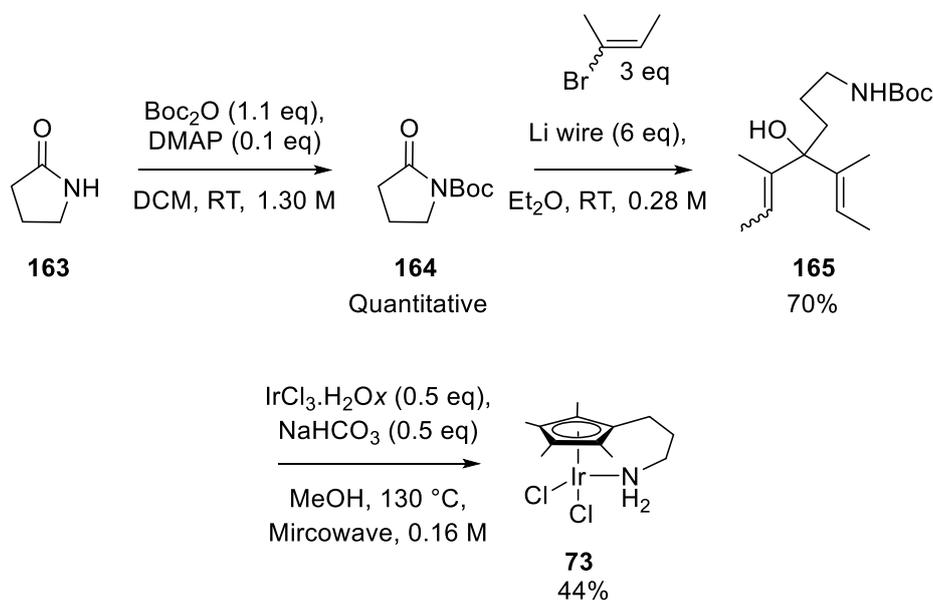
Optimisation of our *N*-alkylation reaction methodology has been carried out with regards to TON in order to make it more applicable in an industrial context, using the reaction between benzyl alcohol and piperidine as our model. It was discovered that below a critical level of catalyst concentration catalyst **73** rapidly ceases to be competent in the catalysis of this reaction, causing TON to drop at a greater rate than the catalyst concentration. Two possible mechanisms were hypothesised for this, and in future work one of these could be validated or invalidated by repeating these reactions with materials of known, varying purity grades.

Optimising the methodology with regards to catalyst concentration, solvent choice, reaction concentration, our best TON of 2250 was found using catalyst **73** in DMF, with 0.04 mol% catalyst loading in a 4 M reaction. By comparison, the best result achieved with [Cp*IrCl₂]₂ was 200; demonstrating a greater than ten-fold superiority of our catalyst. This places our result significantly above examples seen using [Cp*IrCl₂]₂ in other literature studies, but not above all examples of borrowing hydrogen catalysts.^{64,65} It has also been demonstrated that the presence of a small amount of AcOH increases the TON of the reaction. Future work is still needed to determine the generality of this methodology beyond our model reaction.

Chapter 4: Catalyst Syntheses

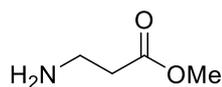
4.1 Introduction

Previous work in the Marsden group investigated the synthesis and testing of a variety of catalysts for carrying out *N*-alkylations via borrowing hydrogen, wherein the catalysts were synthesised using one main route.⁵⁶ In order to synthesise catalyst **73**, bearing a 3 carbon tether between its Cp* ring and amine moiety, the route shown in **Scheme 45** was used. A Boc-protected 2-pyrrolidinone **163** was attacked by two equivalents of a vinyl lithium species formed *in situ*, to yield a diene **165**,⁶⁶ which was then heated to 130 °C in a microwave reactor to obtain catalyst **73**.

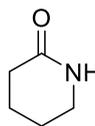


Scheme 45

To produce catalysts with a 2-membered tether β -alanine methyl ester **166** was used, and 2-piperidone **167** was used to synthesis those containing a 4-membered tether.

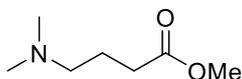


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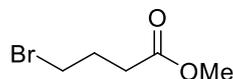


167

Variants on these catalysts were produced, which contained a rhodium centre by using RhCl₃.3H₂O in the final step, and which were alkylated on their amine group, by starting from, for example, *N,N*-dimethyl ethyl 4-aminobutyrate **168** synthesised from ethyl 4-bromobutyrate **169**. Chiral catalysts were also synthesised by using 2-pyrrolidinones which bore chiral centres on their tether.



168



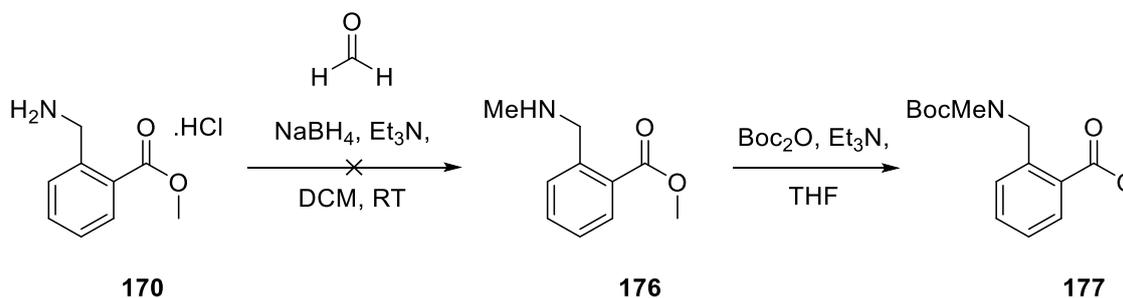
169

It was decided to explore the synthesis of further catalysts of this family by considering the possibility of placing an aryl ring within the tether. This would impose a degree of conformational constraint, and further research could be considered based upon whether this had a positive or negative impact on the catalyst's performance.

4.2 Attempted Synthesis of Variant Catalysts

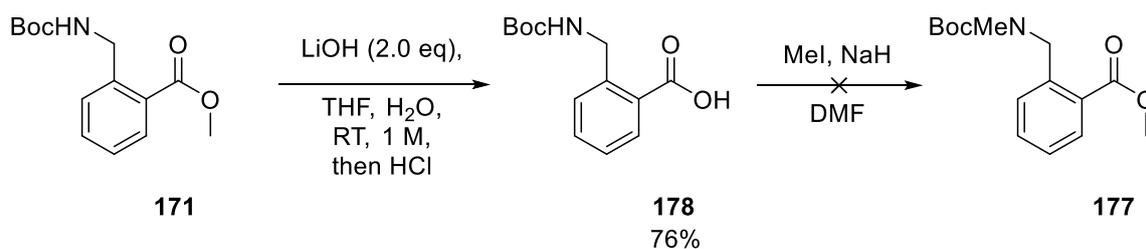
The synthesis of proposed catalyst **173** was targeted, using a similar route to the established synthesis of our catalyst with a 4-membered tether (**Scheme 46**).

easily synthesised (**Scheme 48**). However, this was also unsuccessful, and cyclisation product **174** was once again observed in the reaction mixture from the attempted reductive amination.



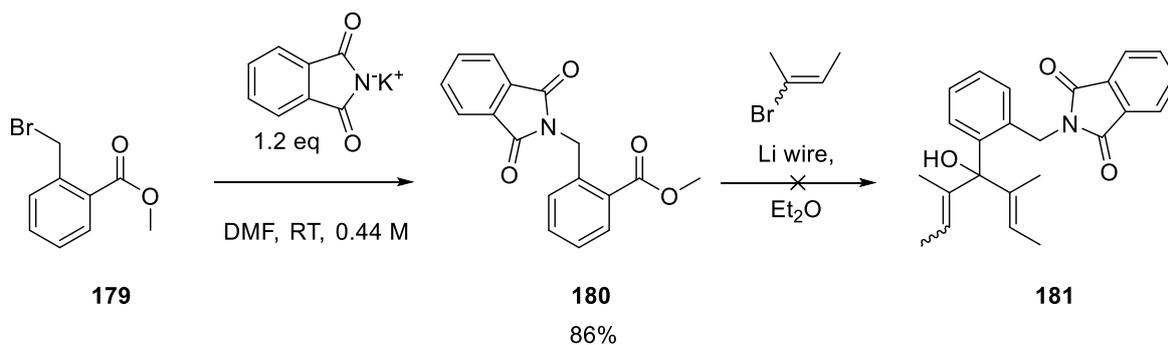
Scheme 48

To prevent this cyclisation, it was decided to saponify ester **171** before methylating the amine and reforming the ester in one pot (**Scheme 49**). When this was attempted, ¹H NMR showed a complex mixture as the product of the second reaction, which no longer contained the expected benzyl peak from the desired product.



Scheme 49

As a final effort, it was decided to change to a different protecting group strategy. Starting from the benzyl bromide **179** protection as a phthalimide was carried out. Subsequent reaction under our vinyl lithium conditions yielded a complex mixture, which contained none of the desired product (**Scheme 50**).



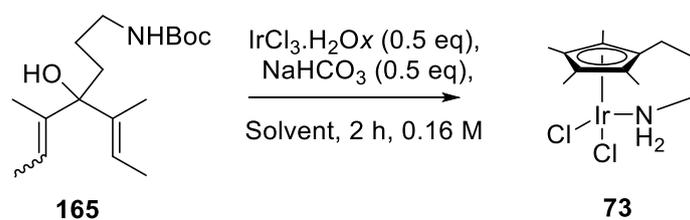
Scheme 50

At this point our attempts to synthesis a new catalyst were abandoned and instead the design of an improved synthesis of catalyst **73** was prioritised.

4.3 Alternative Synthesis of Catalyst **69**

Our investigation was turned towards the final step in the synthesis of catalyst **73**, which uses a microwave reactor with MeOH as solvent being heated significantly above its boiling point. Neither the use of microwave heating nor the pressurised vessel required for this reaction are conducive to this catalyst synthesis being scaled up, so a series of metallation reactions was carried out at atmospheric pressure. These were carried out for two hours, in a range of solvents, at those solvents' boiling points, and the final conversion observed by LCMS analysis of the crude reaction mixture (**Table 13**).

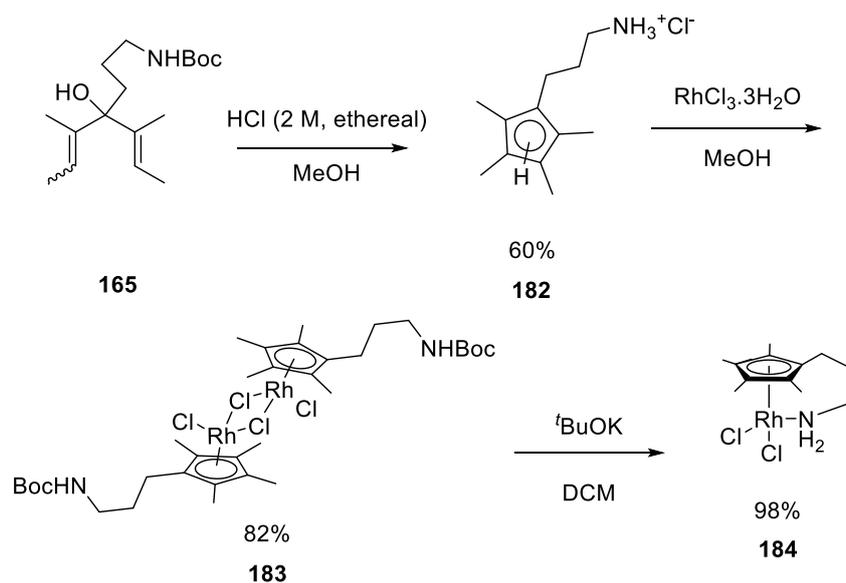
These results showed the general trend that higher conversions were achieved by reactions carried out in more polar solvents, however there did not appear to be any correlation between reaction temperature and conversion. More importantly, none of these methods were superior to the 44% yield obtained in our usual method of MeOH in a microwave, the closest being NMP at 190 °C and 30% conversion.



Solvent	Temperature (°C)	Conversion (%)
MeOH	60	18
<i>t</i> -Amyl Alcohol	95	8
1-Methoxy-2-Propanol	115	12
DMF	150	14
NMP	190	30
PhMe	110	0
Isopropyl Acetate	80	0
Anisole	150	7
2-Me-THF	80	23

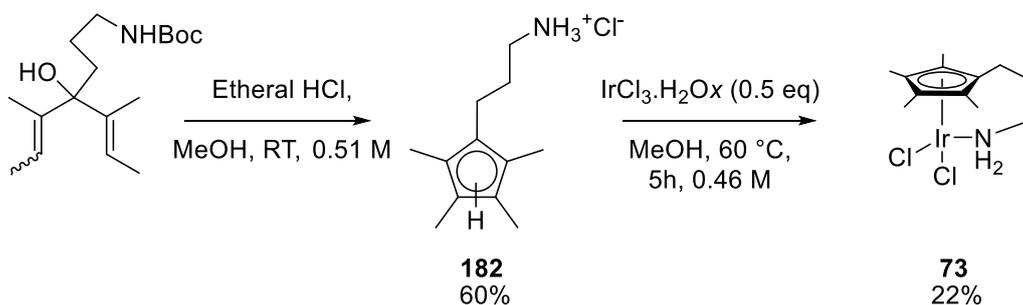
Table 13 (conversion determined by LCMS analysis)

Work by Ito *et al.* has shown that compound **184** was synthesised from diene **165**, by separate cyclisation and deprotection, and coordination steps (**Scheme 50**).⁶⁶ This was previously attempted within the Marsden group⁵⁶, but at the time the formation of diene **182** was unsuccessful.



Scheme 50

However, when the reaction was repeated diene **182** was successfully obtained in 60% yield. The next step of the synthesis was carried out, heating the reaction to 60 °C for five hours, at which point we were pleased to observe the formation of catalyst **73** in place of the expected dimeric compound (**Scheme 51**).



Scheme 51

This combined yield for these two steps was 12%, which is significantly lower than the previous synthesis, and indeed lower than when the cyclisation, deprotection and coordination were carried out in one step in MeOH (**Table 14**). However, in the cases of both of these reactions, these are only preliminary investigations, and it is possible that they can be optimised

to find a route which is both more scale-up friendly and at least as high-yielding as the existent route.

4.4 Conclusion

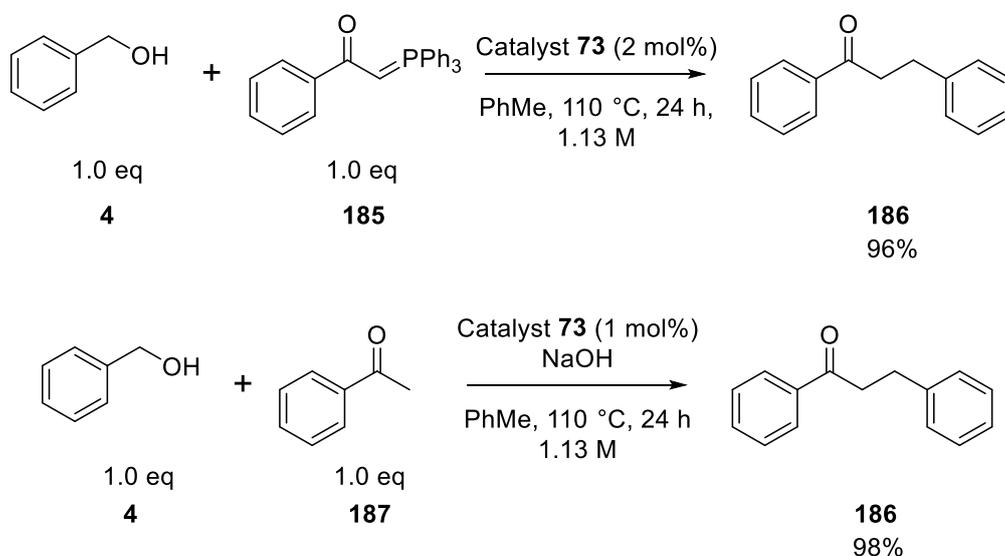
Varied attempts have been made to synthesise an analogue of catalyst **73** which contained a phenyl ring within its tether but have been impeded in each route due to intramolecular cyclisation and failure to reproduce the addition of vinyl lithium into the precursor to our alternate ligand.

Investigations were carried out into the synthesis of catalyst **73** using conditions which would be more amenable to being carried out on a larger scale. Replacing the final step in its synthesis with a reaction at atmospheric pressure, rather than the usual high-pressure microwave reaction, gave varied results but none were as high-yielding as the original synthesis. Catalyst **73** was also synthesised by an alternate route which included the cyclised and deprotected diene **73** as an intermediate, but this too gave a poor overall yield. In the second case there is significant scope for further optimisation and development of a more scalable process.

Chapter 5: Hydrogen Borrowing Methodology for C-C Bond Forming Reactions

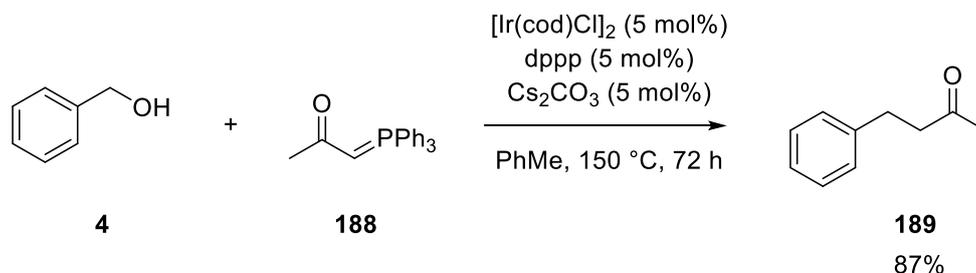
5.1 Introduction

Up to this point, all work using our family of catalysts has focused on the *N*-alkylation of amines using alcohol compounds. However, as discussed in Chapter 1, the literature contains many examples of hydrogen borrowing methodology being used to facilitate other reactions. It was therefore decided to proceed by attempting simple aldol and Wittig reactions incorporated into borrowing hydrogen sequences, using catalyst **73** (Scheme 52).



Scheme 52 (isolated yields)

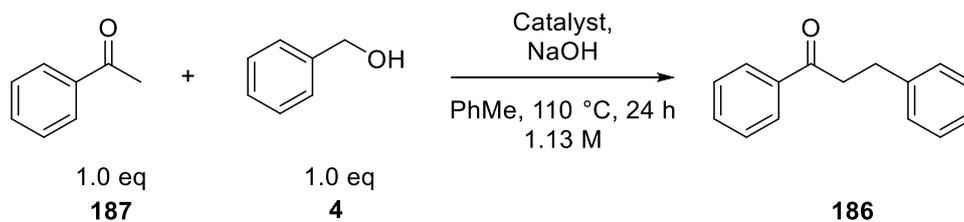
Both of these reactions performed well, providing product **186** in excellent yield in both cases. They are largely comparable to results seen previously in the literature, for example, although we could not find any examples of the first reaction in the literature, work by Williams *et al.* synthesised compound **189** from the corresponding ylide in 87% using Ir[(cod)Cl]₂ after triple the reaction time and at a significantly higher temperature (Scheme 53),⁶⁷ and Venkatasubbaiah, *et al.* obtained the same yield after 24 hours using their palladacycle catalyst in similar conditions via the aldol reaction route.⁶⁸



Scheme 53

The sequence incorporating the aldol reaction obviously exploits the strengths of this methodology more effectively than those with Wittig reactions (carbonyl compounds being significantly more synthetically accessible and commercially available than these ylide compounds, and not generating the stoichiometric triphenylphosphine oxide waste), so it was decided that our investigation should focus on them.

As done previously for *N*-alkylation reactions, a series of reactions were carried out with decreasing catalyst loadings, to determine differences in activity between catalyst **73** and $[\text{Cp}^*\text{IrCl}_2]$ (Table **14**). We were encouraged to see that, in these reactions too, catalyst **73** outperformed $[\text{Cp}^*\text{IrCl}_2]$, with our catalyst's activity dropping off less rapidly as loading was decreased. Although the difference between the two catalysts was less extreme than when catalysing *N*-alkylations, both were competent at a significantly lower loading.



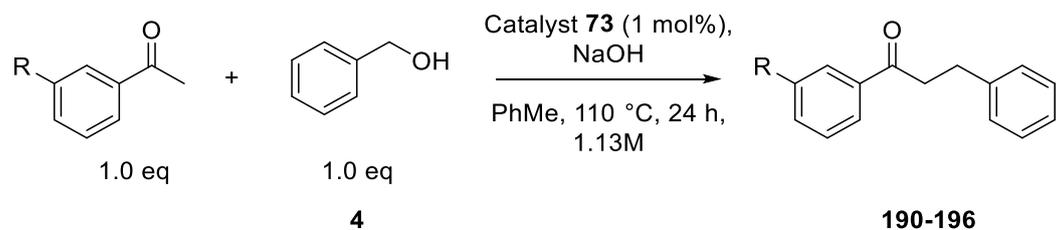
Catalyst loading (mol%)	Conversion with Catalyst 73 (%)*	Conversion with $[\text{Cp}^*\text{IrCl}_2]_2$ (%)*
1	> 98	> 98
0.5	> 98	> 98
0.1	> 98	61
0.05	89	36
0.01	49	29

Table 14 (conversions determined by NMR with internal standard)

5.2 Substrate Scope

The potential scope of the reaction of the reaction was investigated, with regard to functional groups on the aromatic ring of each reactant. The first set of experiments, concerning functional groups on meta-functionalised acetophenones, are summarised in **Table 15**.

These reactions demonstrated a good tolerance for halides (entries 1 and 2), and methyl and methoxy groups (entries 6 and 7). Nitro and hydroxy groups gave poor results (entries 3 and 5); this was disappointing as catalyst **73** had previously been shown to be tolerant of these groups when present on benzyl alcohol compounds being used as reactants in *N*-alkylation reactions.⁵⁶ One consideration in this is the presence of the strong NaOH base, which was not present in our *N*-alkylation reactions; for example the phenol (entry 3), would have been mostly phenoxide in our reaction, which may have been more liable to poison the catalyst.

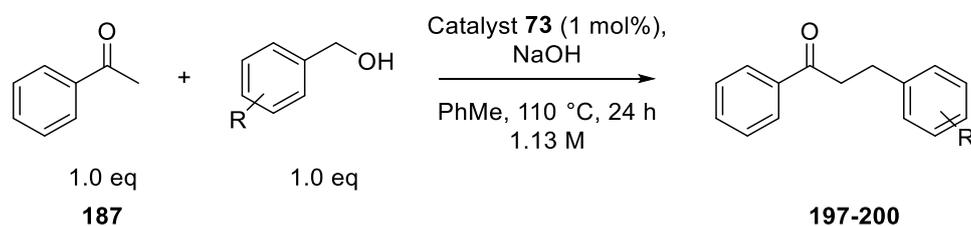


Entry	R	Isolated Yield (%)	Product
1	F	63 (Conversion: 66)	 190
2	Br	65 (Conversion: 69)	 191
3	OH	6 (Conversion: 8)	 192
4	NH ₂	94 (Conversion: 98)	 193
5	NO ₂	7 (Conversion: 10)	 194
6	Me	73 (Conversion: 78)	 195
7	MeO	78 (Conversion: 85)	 196

Table 15 (isolated yields and NMR conversions)

The impact of a strong base on the nitro-bearing substrate (entry 5) was less obvious; although nitroalkanes can be deprotonated to form nitronates, this would not be the case for a nitroaryl. The nitro group could also be a candidate for a side reaction in which it is reduced, but none of the anticipated products were observed, and it was not clear why this would occur here but not in an *N*-alkylation reaction. The positive result from the aniline (entry 4) was very pleasing and was another demonstration of catalyst **73**'s selectivity against alkylations on aniline positions.

A similar screening was carried out, this time varying the functionalisation on the aromatic ring of the benzyl alcohol. In this case, the position of the R group was also varied, to investigate the possible effects upon the reaction of the substituent's position on the ring. The results are shown in **Table 16**.



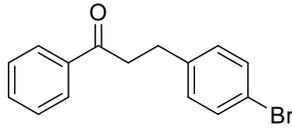
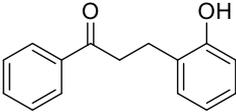
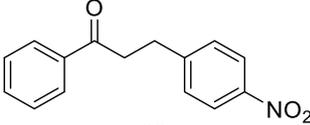
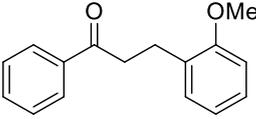
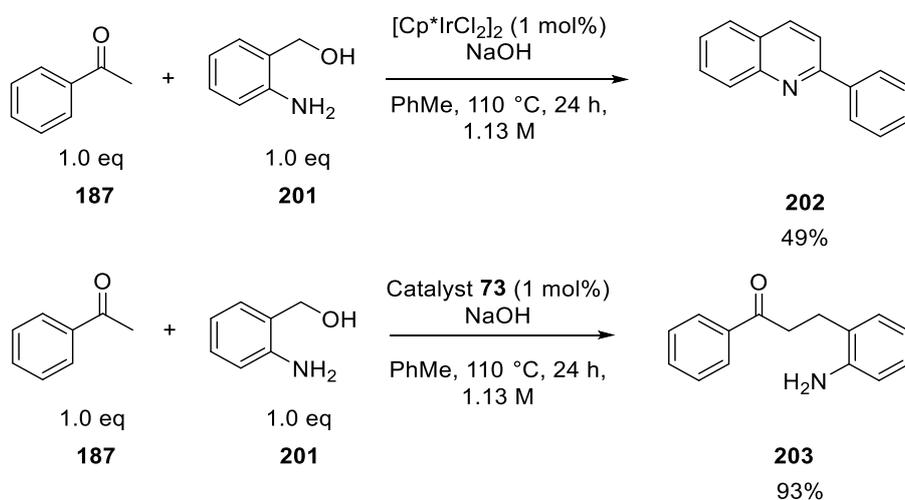
Entry	R	Yield (%)	Product
1	4-Br	47 (Conversion: 53)	 197
2	2-OH	7 (Conversion: 9)	 198
3	4-NO ₂	10 (Conversion: 13)	 199
4	2-OMe	76 (Conversion: 80)	 200

Table 16 (isolated yields and NMR conversions)

While the methoxy-bearing compound (entry 4) performed as well as when on the acetophenone ring, there was a significant drop in the tolerance for the bromo group (entry 1). There was also little difference in the yield for nitro or phenol compounds compared to when they are present on the other reagent, with them both performing poorly; likely due to the same reasons as previously.

However, the reaction between acetophenone and 2-aminobenzyl alcohol **201** was unusual and deserves special attention (**Scheme 54**). Previous work using a variety of ruthenium catalysts for this reaction resulted in subsequent cyclisation and oxidation yielding quinoline **202** in every case.⁶⁹

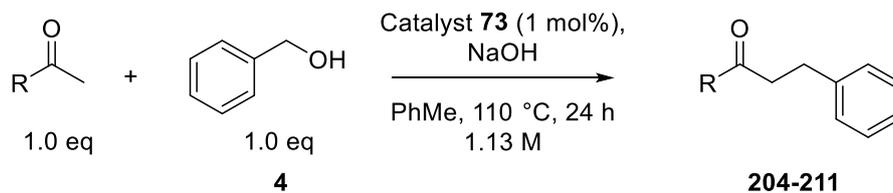


Scheme 54

However, when the same reaction was carried out using catalyst **73**, the dihydrochalcone **203** was the only observable product. This observation was confirmed by the presence of a pair of diagnostic triplets in the NMR for dihydrochalcone **203**, corresponding to its two methylene positions (although the amine protons are not observed in the NMR), as well as mass spectrometer data. It is believed that this may have been due to the previously discussed difference in mechanisms between catalyst **73** and the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer, whereby aniline positions are not nucleophilic enough to be alkylated by our catalyst. Therefore, our catalyst is able to access these aminodihydrochalcones where other borrowing hydrogen catalysts are not.

With this basic screening completed, consideration was given to expanding our examples to include different ring systems in the reacting partners. Once again, this began by varying the ketone reagents (**Table 17**).

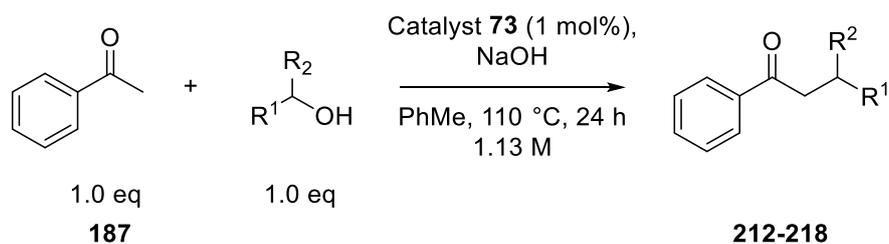
We were pleased to see that the catalyst was generally tolerant of different ring systems, with the major exception being the free N-H indole (entry 4). From the fact that when we synthesised an *N*-methylated indole (entry 5) the reaction proceeded in excellent yield, it was suspected that the poor yield for the unprotected indole was due to either catalyst poisoning by coordination to the nitrogen, or by the formation of the indole anion in the presence of the reaction's strong base, deactivating the substrate. The successful alkylation onto indanone with good yield (entry 6) was encouraging, as it demonstrated the possibility of carrying out alkylations onto methylene positions. The successful reaction with cyclohexyl methyl ketone (entry 7) was the most encouraging however, as it suggested that the reaction is general beyond the various aromatic ketones we had used so far. Following this, a reaction with Boc-protected acetylpiperidine was attempted, which also proceeded in good yield (entry 8). As discussed in previous chapters, protecting groups such as Boc are often required in industrial syntheses, so we were pleased to see that catalyst **73** tolerated them in this reaction context as well.



Entry	Ketone	Yield (%)	Product
1		47 (Conversion: 52)	
2		53 (Conversion: 56)	
3		68 (Conversion: 72)	
4		9 (Conversion: 11)	
5		96 (Conversion: 99)	
6		79 (Conversion: 84)	
7		56 (Conversion: 60)	
8		66 (Conversion: 72)	

Table 17 (isolated yields and NMR conversions)

Similar variations were also carried out on the alcohol reagent of the reaction (**Table 18**).



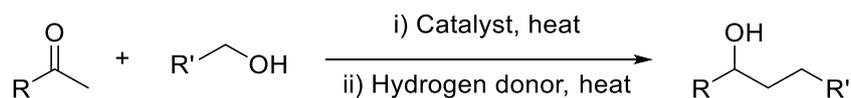
Entry	Alcohol	Yield (%)	Product
1		10 (Conversion: 14)	 212
2		71 (Conversion: 76)	 213
3		61 (Conversion: 66)	 214
4		12 (Conversion: 14)	 215
5		68 (Conversion: 72)	 216
6		77 (Conversion: 83)	 217
7		44 (Conversion: 49)	 218

Table 18 (isolated yields and NMR conversions)

The most obvious difference between these results and those shown in **Table 17** is that the catalyst was much more sensitive to the presence of pyridine when on the alcohol reactant, with the yield for the product dropping from 47% (entry 1, **Table 17**) to 10% (entry 1, **Table 18**) this could have been due to the hydroxy and the ring's nitrogen acting together to chelate to the catalyst as a bidentate ligand, poisoning it. However, there was a higher yield for the thiophene bearing product (from 53% in entry 2 **Table 17** to entry 2 **Table 18**), and the yields of the furan bearing compounds were comparable. A free N-H indole was problematic in these reactions too (entry 4), but a good yield was achieved in the case of 1-phenylethanol (entry 5), demonstrating that this method is general to secondary as well as primary alcohols. The reaction with an aliphatic alcohol (*n*-hexanol in this case, entry 6), demonstrated an even greater generality as it was now clear that straight chain alcohols were viable in reactions catalysed by catalyst **73**. A similar reaction was also carried out where the aliphatic alcohol was fluorinated, suggested by collaborators as being a common motif in pharmaceutical compounds (being used to improve metabolic stability, lipophilicity and target selectivity among others⁷⁰), and although a decrease in product formation was observed compared to the hydrocarbon chain, a moderate yield was still obtained.

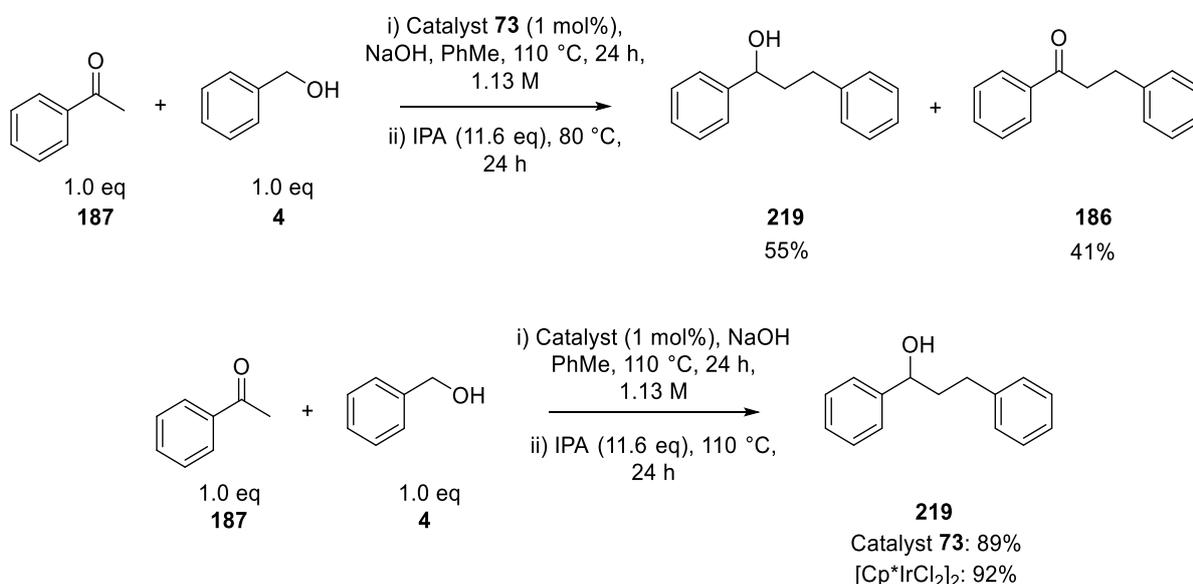
5.3 One Pot Reduction

Individually the use of hydrogen borrowing catalysts to carry out aldol alkylation reactions as seen previously and their use alongside an easily oxidised 'hydrogen donor' compound such as IPA to act as reducing agents are both well described in the literature.⁷¹ However, we were unable to find any examples where these two steps were combined in a 'one pot' reaction to carry out the alkylation and form the alcohol product directly after (**Scheme 55**), although the cross-coupling of alcohols to form the α -alkylated alcohol product is known.⁷² One-pot reactions carry the significant benefits of reducing the amount of material transfer required in an overall process (potentially removing the need for an extra vessel on a plant scale), and removing the need for any purification between reactions, both of which would be of value in an industrial setting. Therefore, the possibility of our proposed sequence was investigated.



Scheme 55

Firstly, the formation of **219** was attempted by using our standard conditions for the synthesis of dihydrochalcone **186**, followed by injection into the sealed vessel of 1 ml of IPA (bringing the total solvent volume to 2 ml) and subsequent heating to the boiling point of IPA (**Scheme 56**). This reaction achieved a yield of 55% of alcohol **219**, with the only other product observed being 41% of the ketone intermediate **186**, which was encouraging on our first attempt and proved that process was possible.



Scheme 56

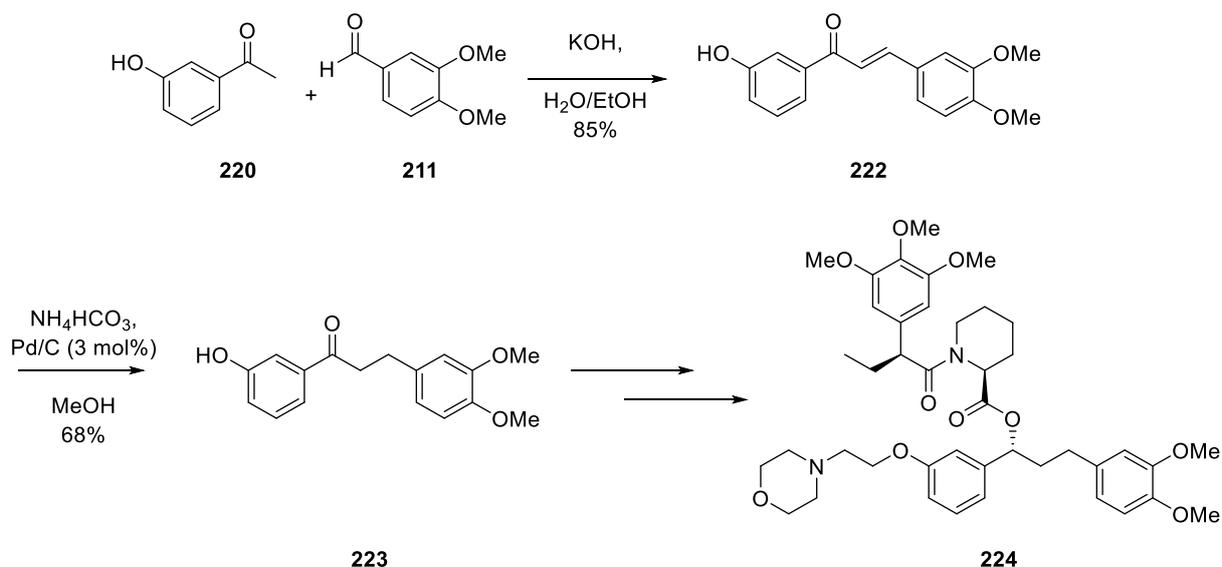
As our reactions were being carried out in sealed vials, it was decided to heat the second step of the process above the boiling point of IPA, to the usual temperature of 110 °C which had been used for reactions with catalyst **73**. A duplicate reaction was also carried out using $[\text{Cp}^*\text{IrCl}_2]_2$ as the catalyst.

With this change, it was observed that both reactions achieved excellent yields of the desired alcohol compound **219**, with very little difference between them (89% in the case of catalyst **73**, compared to 92% achieved with the $[\text{Cp}^*\text{IrCl}_2]_2$ dimer).

5.4 Synthesis of Biologically Relevant Compounds

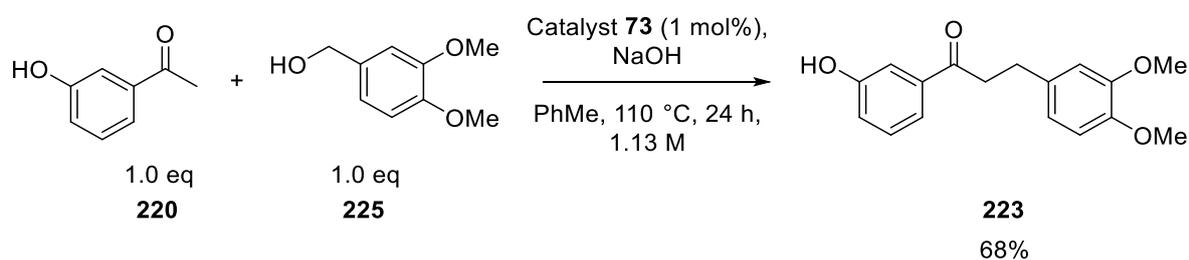
With this methodology in hand, we turned to look at possible applications of our catalyst in the synthesis of biologically relevant compounds. Following a literature search, several examples were found of compounds which had previously published syntheses which could be shortened by application of the reactions trialled in this chapter.

Our first attempt was to synthesis an intermediate in a recent synthesis of Shld.⁷³ Shld is a synthetic simplification of two immunosuppressant drugs, rapamycin and FK506, and is useful in the study of individual proteins, as it can be used to promote the production of a protein of interest in a genetically engineered cell.⁷⁴ In Jørgensen and Bols' work, compound **223** is synthesised as an intermediate towards the synthesis of the final compound Shld **224** (Scheme 57).



Scheme 57

Obviously, the aldol reaction and subsequent reduction used to obtain ketone **223** is suitable to be replaced with one step using our own methodology, also allowing synthesis from 3,4-dimethoxybenzyl alcohol **225** instead of the corresponding aldehyde **221**. Although it had been previously observed that hydroxy groups are problematic in our methodology, it was decided to attempt the reaction and we were pleasantly surprised to see that it proceeded in a yield of 68% (**Scheme 58**); although it could not be rationalised why the addition of methoxy groups on the benzyl alcohol would increase tolerance for the presence of a hydroxy on our acetophenone. By comparison, Jørgensen and Bols achieved a yield of 58% across their two steps, so our method had increased the overall yield as well as reducing the amount of purification and handling required.



Scheme 58

The synthesis of taccabulin compounds was investigated as another promising line of investigation. Taccabulins are a family of compounds with a dihydrochalcone skeleton, isolated from plants of the *Tacca* genus, several of which have previously been identified as having anti-cancer properties (**Figure 14**).⁷⁵ Spring *et al.* have demonstrated a general synthesis of various taccabulins, once again by carrying out an aldol condensation and subsequent reduction of the product's C=C double bond (**Scheme 59**).⁷⁶

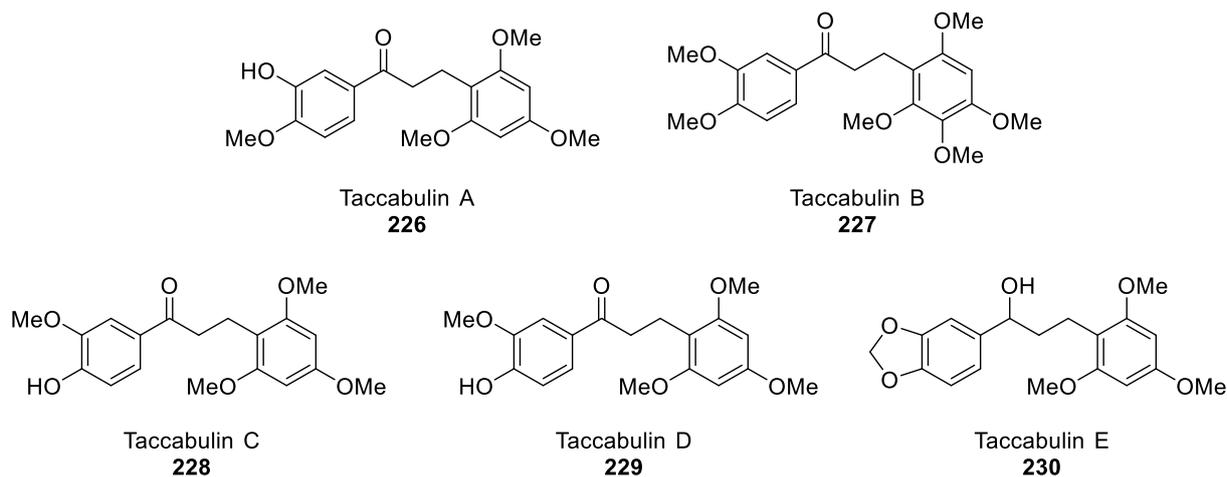
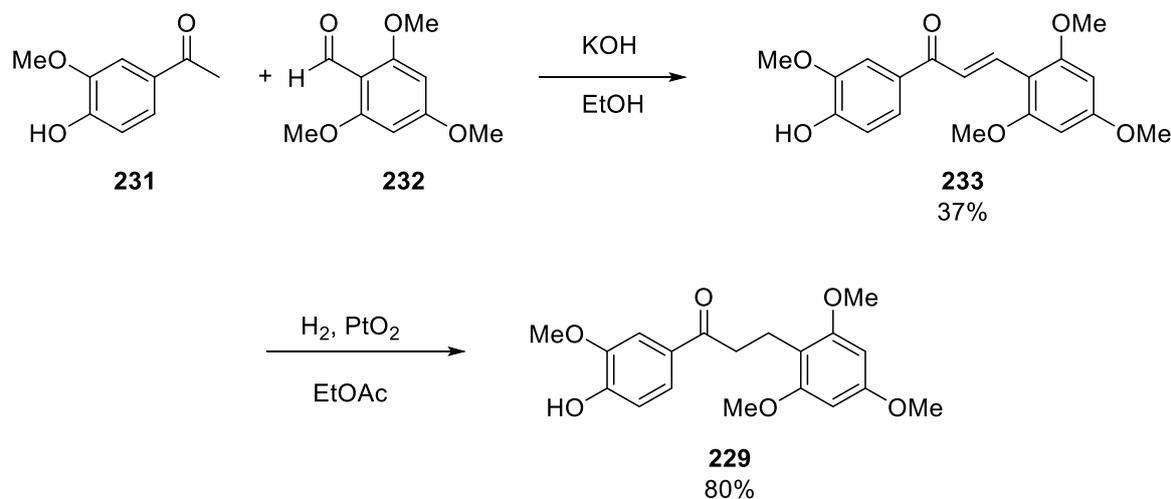
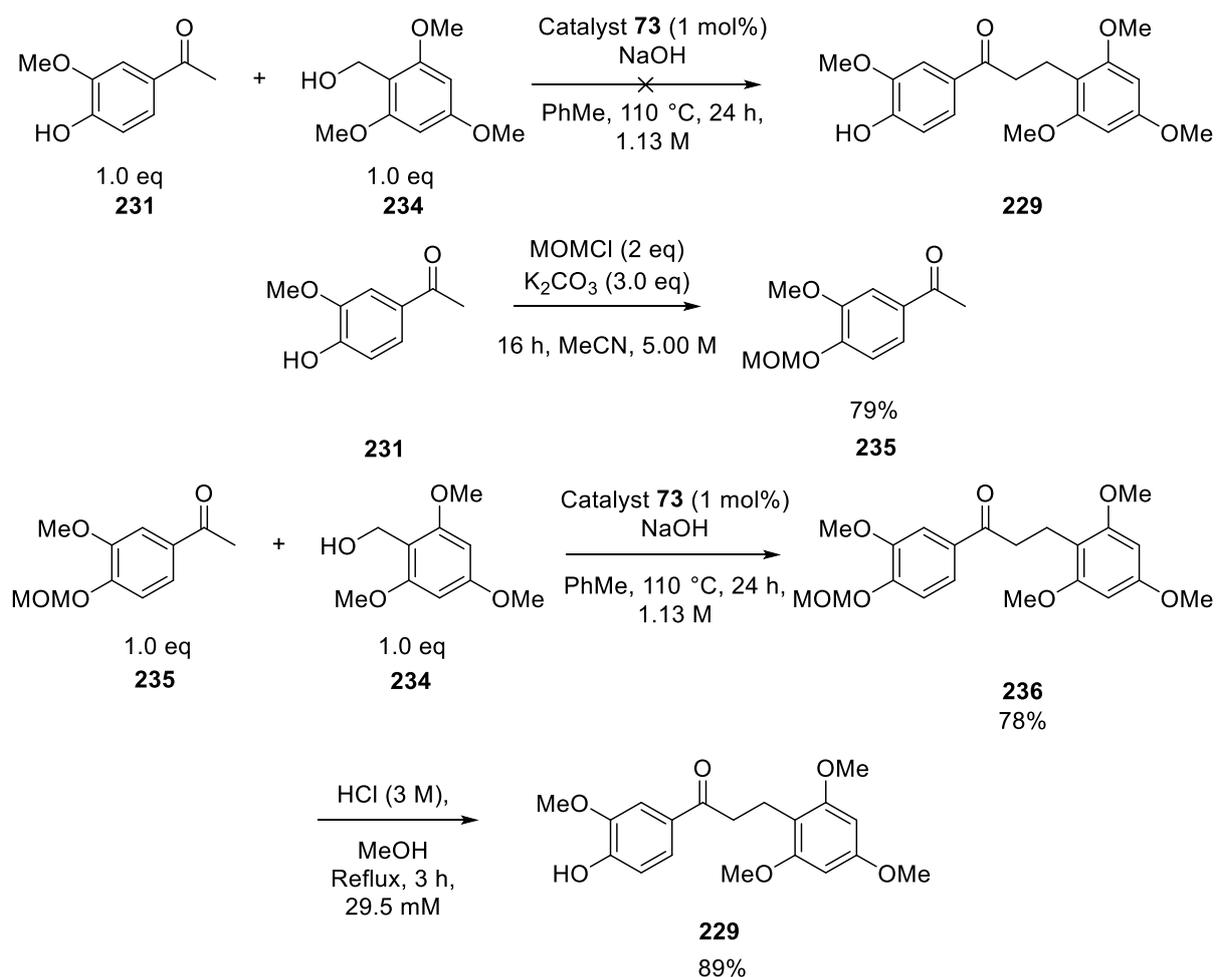


Figure 14



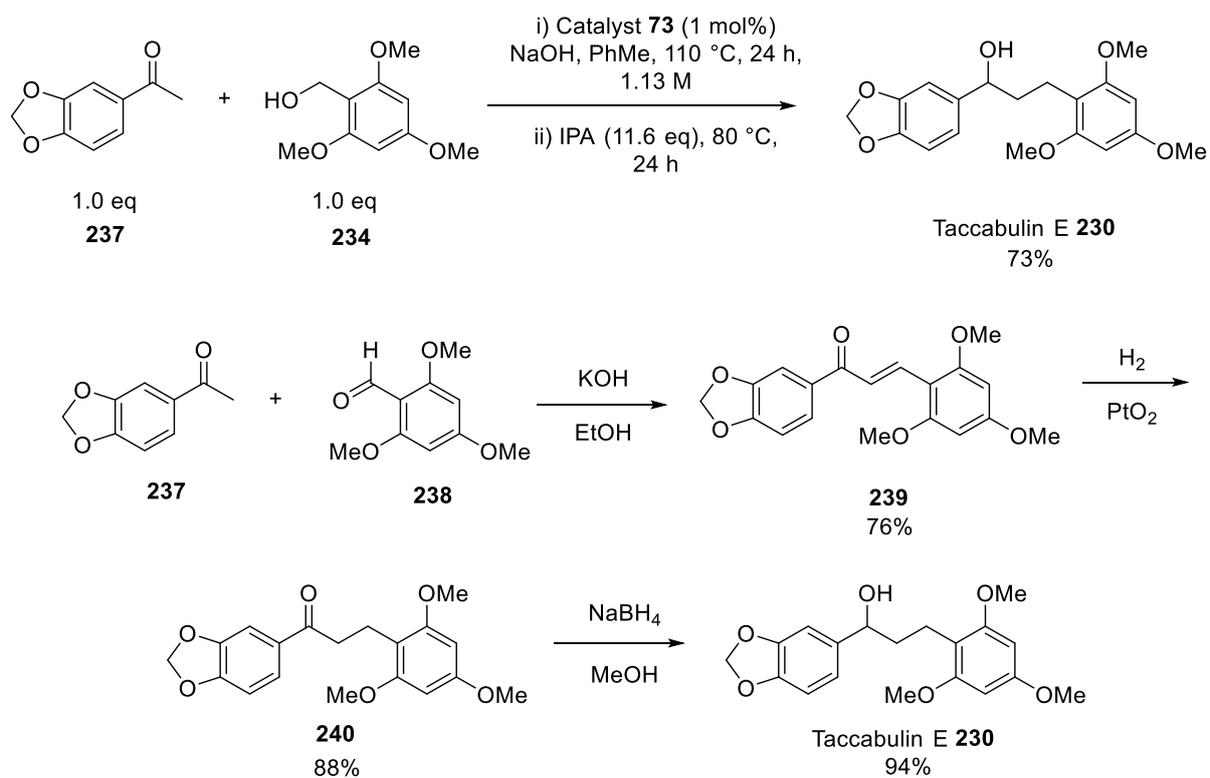
Scheme 59

Once again, this presented an opportunity for the removal of reduction step out of the synthesis by using a borrowing hydrogen aldol sequence. However, the synthesis was attempted from the obvious acetophenone **231** and benzyl alcohol **234** starting materials none of the desired product **229** was observed (**Scheme 60**). It was believed that this was due to the presence of the phenol group, so a protected acetophenone **235** was synthesised and used as a starting material. This allowed the synthesis of the product **236** in 78% yield, which was deprotected to obtain taccabulin D.



Scheme 60

The use of our one-pot method to synthesise taccabulin E **230**, which has an alcohol instead of a ketone, but helpfully does not have any phenol moieties, was also investigated. As a result, we were pleased to see that the reaction proceeded well, and our product could be obtained in 73% yield (**Scheme 61**). In Spring *et al.*'s work, taccabulin E was synthesised by aldol condensation of the corresponding ketone and alcohol, reduction of alkene **239** to **240** and reduction of that in turn to the natural product.⁷⁶ Our method has therefore avoided the use of the more reactive aldehyde species, and simplified the synthesis by removal of both reduction steps and the associated isolation and handling operations.



Scheme 61

To take advantage of our success it was decided to create a variety of ‘synthetic taccabulins’, consisting of reduced forms of those which bear a ketone, an oxidised taccabulin E analogue, and several of our own design (**Figure 15**). Although the reduced forms of these compounds could have been synthesised by use of our one-pot method, in practice each was synthesised as the ketone and then carried out a separate reduction, as it was intended to screen both the alcohol and ketone in all cases. The yields of the various steps in synthesising these compounds are given in **Table 19**.

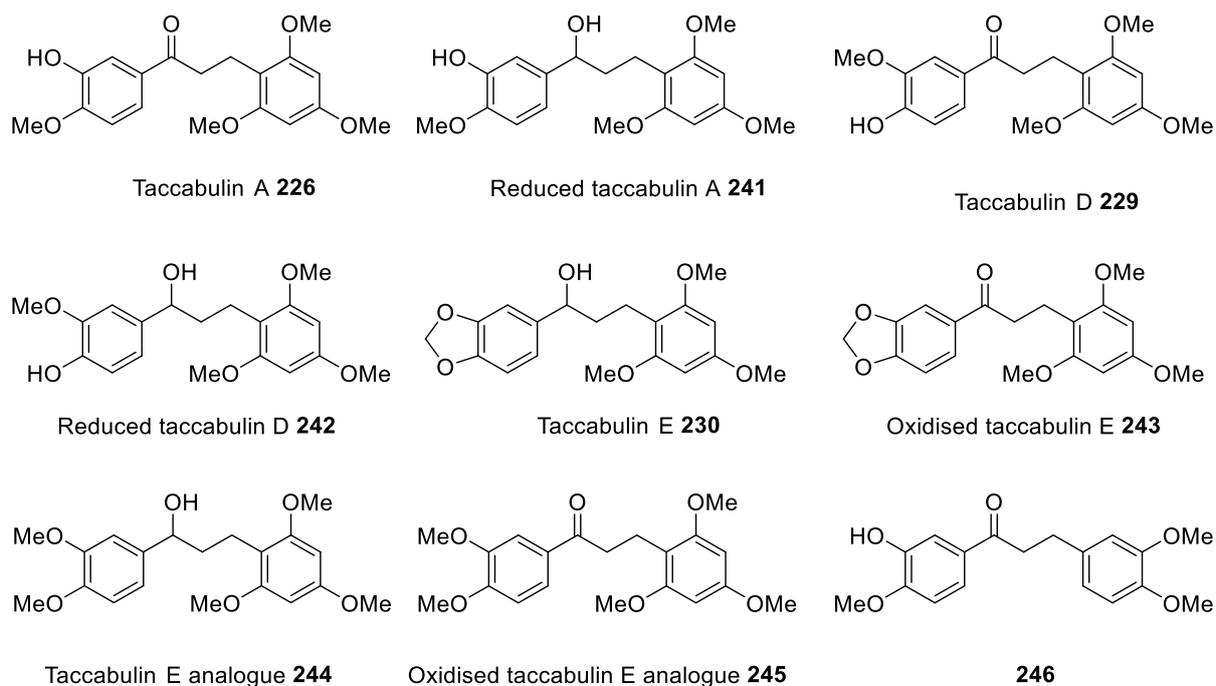
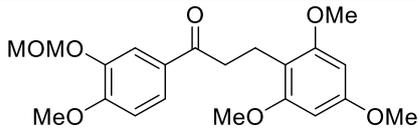
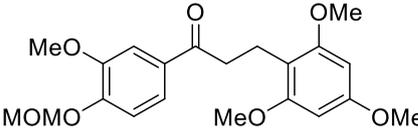
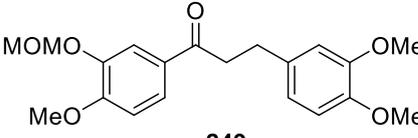


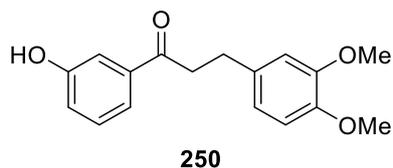
Figure 15

It was decided to screen our novel compounds for anti-cancer activity, along with taccabulins A, D and E as controls as these had already been tested in previous literature. A reduced, alcohol form of our previously synthesised Shld intermediate **223**, **250**, was also included in the screening. Screening was carried out against colon carcinoma colon cells (HCT116) by our collaborator Dr Farideh Javid at the School of Pharmacy, University of Huddersfield (**Table 20**). Also included in the table is data from previous work in the literature where a variety of taccabulin compounds were tested against HeLa breast cancer cells (though there is no guarantee that there would be similarity between the activity of a compound across these two tests).

Compound	Yield (%)		
	Aldol sequence	Deprotection	Reduction
Taccabulin A 226	 247	91 (226)	N/A
241	75 (Conversion: 81)		(241) 63
Taccabulin D 229	 248	76 (229)	N/A
242	78 (Conversion: 81)		(242) 83
Taccabulin E 230	(230) 73* (Conversion: 78)	N/A	N/A
243	80 (243) (Conversion: 84)	N/A	N/A
244	74 (244) (Conversion: 77)	N/A	86 (245)
245		N/A	N/A
246	 249	86 (235)	N/A
	83 (Conversion: 87)		

*Carried out as one-pot reduction

Table 19 (isolated yields and NMR conversions)



Entry	Compound	Activity against HCT116 (IC ₅₀ μM)	Activity against HeLa (IC ₅₀ μM) ⁷⁵
1	Taccabulin A	0.63	0.58
2	241	5.95	N/A
3	Taccabulin D	37.75	28.9
4	Taccabulin E	>50	>50
5	243	>50	N/A
6	244	23.95	N/A
7	250	>50	N/A
8	246	>50	N/A

Table 20

Previous work⁷⁷ has shown that taccabulins are cytotoxic to cancer cells via binding to the colchicine binding site and interfering with microtubule stabilisation, and docking carried out by Dr Martin McPhillie at the School of Chemistry, University of Leeds, has shown both enantiomers of our reduced taccabulin A analogue (**241**) fit this site (**Figure 16**, *S* enantiomer left, *R* enantiomer right).

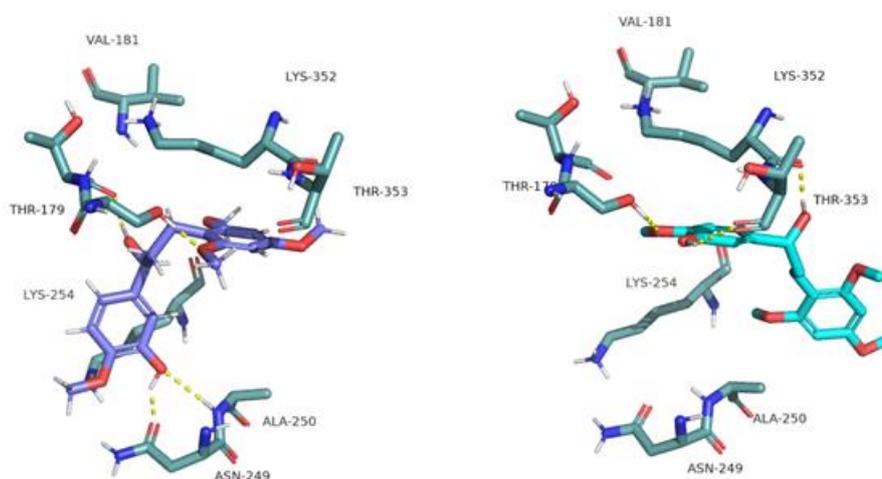


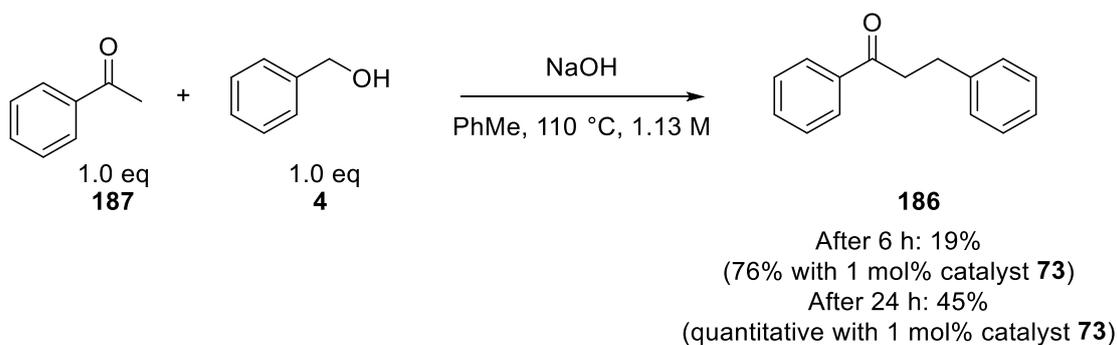
Figure 16

Although it is not necessarily true that similar levels of activity for the same compound across both cell lines would be expected, it was encouraging for the reliability of our results that taccabulin A (entry 1) was the most active in both cases, and no activity was observed for taccabulin E (entry 4) in either case. The most active of our novel compounds was **241**, the reduced form of the best performing compound overall, suggesting taccabulin A as a starting point for any further attempts to optimise activity. Of our novel compounds, activity was only observed for **241** (entry 2) and **223** (entry 6), so overall activity was exclusively seen for compounds with a 2,4,6-trimethoxybenzyl group on the ‘alcohol’ side of the compound, but not for every compound that did. It was surprising that the taccabulin E analogue **244** showed activity, but the oxidised form of taccabulin E **243** did not.

5.5 Investigation of Non-catalysed Reactions

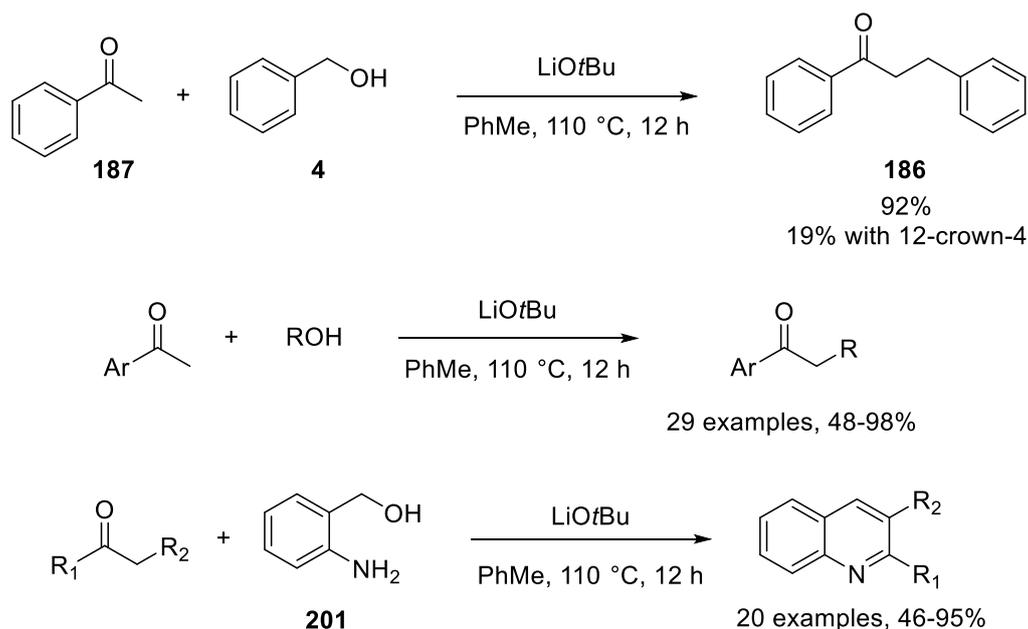
To a large extent, the literature describing these borrowing hydrogen aldol sequences do not explicitly demonstrate the superiority of the catalysed reaction over a non-catalysed control reaction, and it is generally accepted that it is necessary for a catalyst to be present for the reaction to take place.³⁷ To be thorough it was decided to carry out a control reaction using our model reaction of the alkylation of acetophenone **187** with benzyl alcohol **4**, and we were surprised to find a significant quantity of the ketone product **186** formed (**Scheme 62**). Although catalyst **73** carried out this reaction to a quantitative yield with a 1% loading, given the comparatively high cost of iridium and the several reaction steps needed to synthesis it, it was considered that it wasn’t generally economically reasonable to use it to achieve a little over a doubling of the reaction yield.

A reaction between **187** and **4**, which we stopped after only 6 hours, was also carried out to determine if the presence of the catalyst led to a higher initial rate of reactions. However, although this enhanced the difference between the yields achieved (19% when non-catalysed and 76% with 1 mol% of **73**), it was still felt that a four-fold increase in yield did not justify the usage of the catalyst in this reaction.



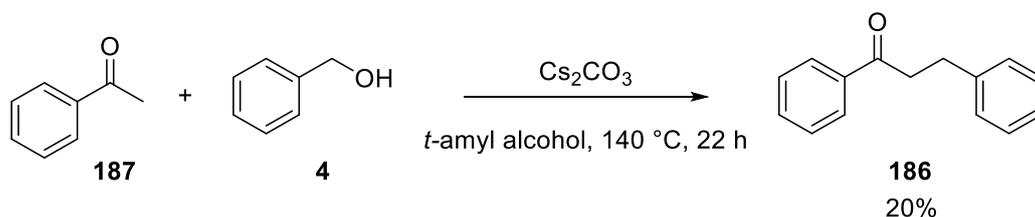
Scheme 62 (isolated yields)

The literature was reviewed to find previous references to similar reactions being carried out without catalysis and only a small number of papers were uncovered. It was also interesting to find that the majority of papers carrying out this borrowing hydrogen methodology do not acknowledge the potential non-catalysed reactions. Work by Xu *et al.*, initially aimed at investigation of copper catalysts for borrowing hydrogen aldol sequences, quickly found that the reaction could occur using only base (the reaction was actually hindered by the presence of $\text{Cu}(\text{OAc})_2$ or CuCl_2 , the two catalysts they did test)⁷⁸. In their specific case of the alkylation of **187** with **4** they record a yield of 90%, and tolerance of a good range of functional groups (**Scheme 63**). Their base screening identified $\text{LiO}t\text{Bu}$ as the most effective, and although they do not suggest a mechanistic pathway for the reaction, they do note that their yields drop significantly in the presence of 12-crown-4, a common lithium chelator. Interestingly, they also carried out a series of reactions demonstrating scope for reactions between 2-aminobenzyl alcohol **170** and obtained the corresponding quinoline as their product in each case. As our isolation of the dihydrochalcone intermediate in this reaction was previously attributed to our catalyst's non-reactivity with less nucleophilic anilines, it was surprising to see the quinoline products being formed in the absence of any catalyst.



Scheme 63

Later work on manganese complexes for hydrogen borrowing catalysis from Beller *et al.* also noted the possibility of formation of **186** by the reaction of benzyl alcohol **4** and acetophenone **187**, but in their case the base used was Cs_2CO_3 , which achieved a yield of only 20% after 22 h at 140 °C and consequently was not further investigated (**Scheme 64**).⁵¹



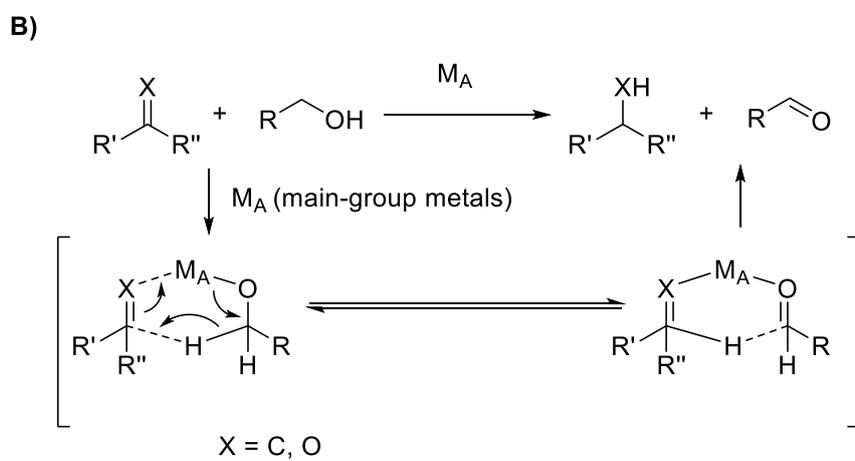
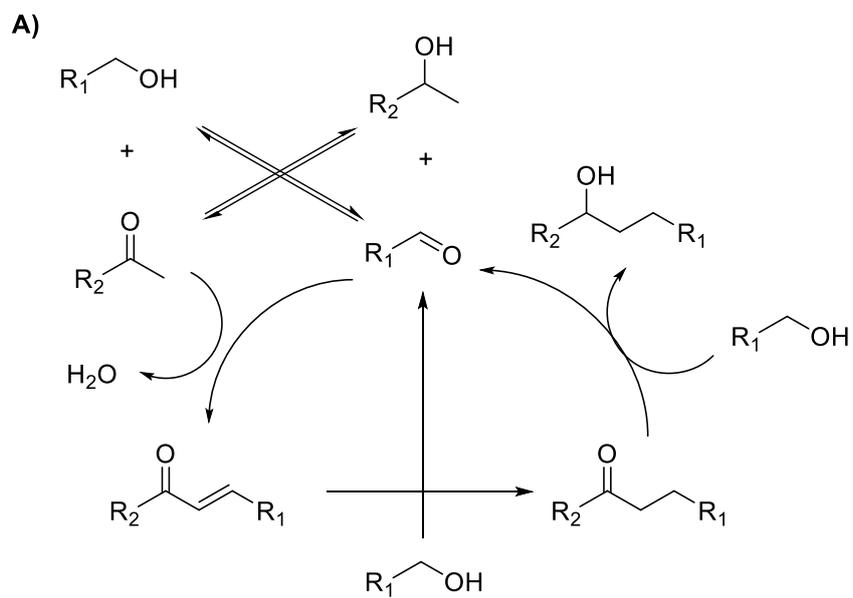
Scheme 64

This appeared to establish that the reaction is highly dependent on the choice of base. Work by Liu *et al.* demonstrated that both NaOH and KOH are suitable for carrying out these reactions and so NaOH was continued to be used in our investigations for more direct comparison with our catalysed reactions.⁷⁹ In their work, they also postulated a potential pathway for the reaction to take place, via the Meerwein–Ponndorf–Verley–Oppenauer (MPVO) redox process

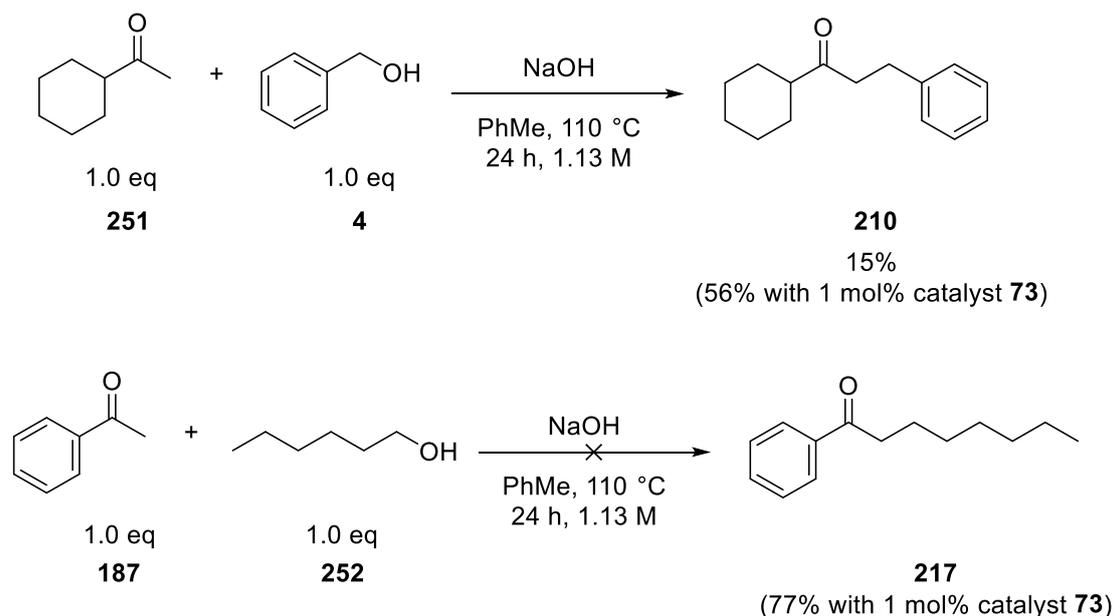
(**Scheme 65**) which suggests the potential for formation of both the ketone product and the corresponding alcohol, and indeed they demonstrated the ability to tune their reaction to obtain a majority of either.

In the first step of the reaction, shown in part **A**) of **Scheme 65**, aldehyde is generated by MPVO oxidation, the mechanism of which is shown in part **B**) where, in this case the sodium, acts to facilitate the transfer of a hydrogen atom between the alcohol and the ketone. The newly formed aldehyde is able to undergo a standard aldol condensation, and its C-C double bond is reduced by a further MPVO transfer to form another molecule of aldehyde. The ketone also has the potential to undergo a final MPVO reduction, generating another equivalent of aldehyde to take part in the aldol condensation.

In our own work the existence of the non-catalysed reaction has been observed in the case of the reaction of benzyl alcohol with acetophenone, however the literature examples discussed above described non-catalysed reactions with a wider range of substrates. Reactions were therefore carried out where one of the reactants did not feature an aromatic, which had been more challenging for our own catalyst than the benzyl alcohol and acetophenone pairing (**Scheme 66**).

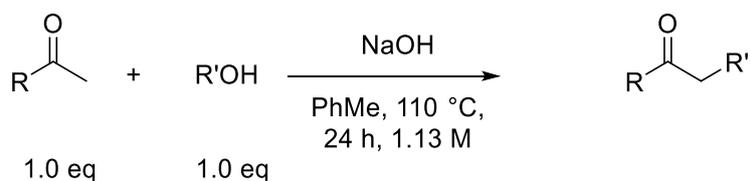


Scheme 65



Scheme 66 (isolated yields)

It was found that the reaction between benzyl alcohol **4** and cyclohexyl methyl ketone **251**, proceeded to only 5% conversion after 24 hours, compared to the fair yield achieved using catalyst **73**, while the formation of **217**, the product of alkylating acetophenone **187** with *n*-hexanol **252**, which had been obtained in a good yield using catalyst **73** was not observed. We were pleased to see that the presence of a borrowing hydrogen catalyst seemed to be required to carry out these reactions effectively when working with non-aromatic substituents and was required to see any product at all in the case of the non-aromatic alcohol. A wider screen of reactions containing a non-aromatic component was therefore carried out, both with catalyst **73** and without catalysis (**Table 20**).



252-256

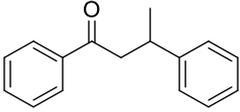
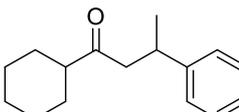
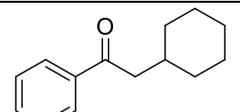
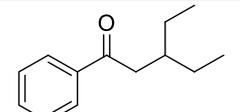
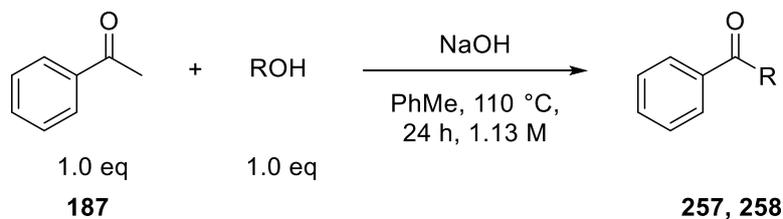
	R = Ph		R = Cy	
	With catalyst 73	Without catalyst	With catalyst 73	Without catalyst
R' = CH(CH ₃)Ph	 <p>253 68% (Conversion: 73)</p>	No product	 <p>256 17% (Conversion: 21)</p>	No product
R' = Cy	 <p>254 40% (Conversion: 45)</p>	No product	No product	No product
R' = CH(CH ₂ CH ₃) ₂	 <p>255 7% (Conversion: 10)</p>	No product	No product	No product

Table 20 (isolated yields and NMR conversions)

The most obvious result from this data set was that a catalyst was required to see any product formation when the alcohol is non-benzylic, in agreement with our previous observation. There was also a marked drop in yield when the ketone used was non-aromatic, with cyclohexyl

methyl ketone only forming a product with the one aromatic alcohol tested, and even then, only in the presence of our catalyst and in a low yield. A significant decrease in the yields obtained when using cyclohexanol or propan-3-ol was also noted; as the hydroxyl group in each case is in a generally comparable electronic environment, this difference was attributed to steric considerations. One final screening was carried out between acetophenone and other alcohol compounds, to explore the area around the more successful results seen so far (**Table 21**).

In entry **1**, results were seen for hydrocinnamyl alcohol which were largely similar to those achieved by catalyst **73** with *n*-hexanol and acetophenone (77%). Similarly, both reactions failed to yield any of the desired product when carried out without any hydrogen borrowing catalyst present. When the reaction was carried out using cinnamyl alcohol (entry **2**), the same product was obtained, and in approximately half the yield as in entry **1**. This suggested that the desired product was initially formed, but then subsequently reduced again by our catalyst, using another molecule of cinnamyl alcohol as a hydrogen donor. It was difficult to rationalise the dramatic decrease in yield from the reaction using cyclohexanol (**Table 20**) to that using cyclopentanol in **Table 21** (entry 3), but it is suspected that the complete failure of reactions with tetrahydro-4-pyranol (entry 4) was due to catalyst poisoning by chelation of the starting material.

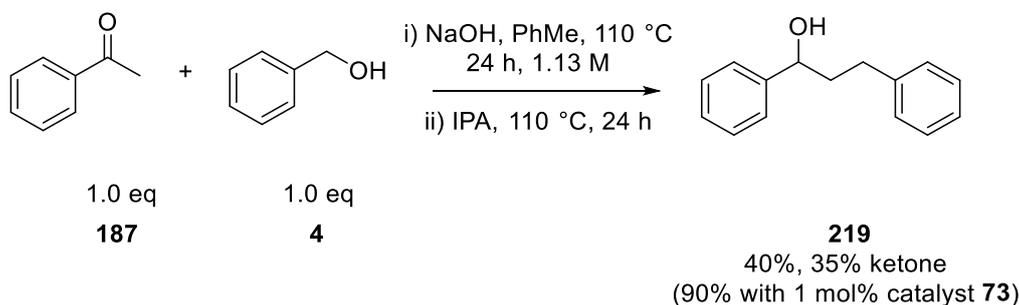


Entry	Alcohol	Yield (%)		
		Non-catalysed	[Cp*IrCl ₂] ₂ (1 mol%)	Catalyst 73 (1 mol%)
1		0	 257 67 (Conversion: 73)	 257 89 (Conversion: 93)
2		0	 257 35 (Conversion: 39)	 257 36 (Conversion: 42)
3		0	0	 258 7 (Conversion: 11)
4		0	0	0

Table 21 (isolated yields and NMR conversions)

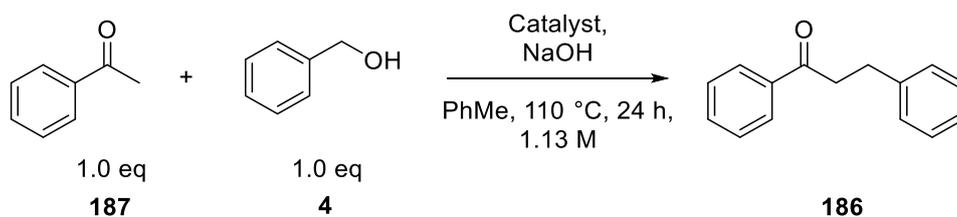
A repeat of our one-pot reduction with acetophenone **187** and benzyl alcohol **4** was also carried out, in the absence of a catalyst (**Scheme 67**). 24 hours after the addition of IPA, a 40% yield

of the desired alcohol **219**, and 35% of the ketone intermediate was observed, compared to the 90% of alcohol **219** which had obtained when the reaction was carried out using catalyst **73**.



Scheme 67 (isolated yields)

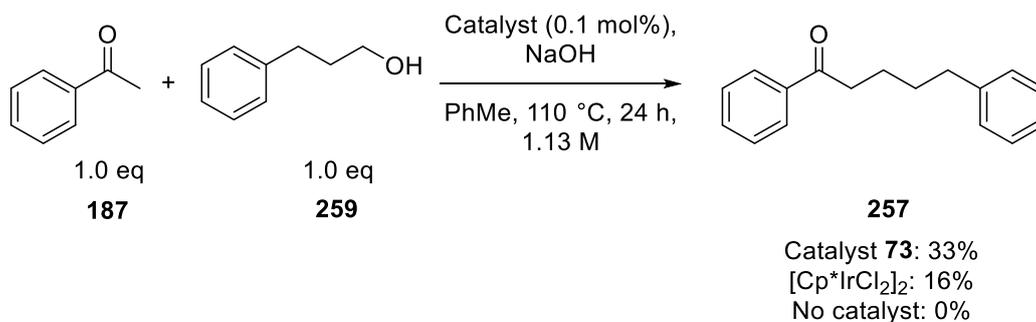
Now aware of the existence of this non-catalysed reaction, it was clear that our investigation needed to finish by turning back to the experiments investigating the conversions achieved with different levels of loading of catalyst **73** and $[\text{Cp}^*\text{IrCl}_2]_2$. The previously obtained results are reproduced in **Table 22**, along with the new information obtained for the same reaction when no catalyst was present. The obvious observation from the expanded data set is that the conversions obtained by both catalysts at loadings of 0.01 mol%, and at 0.05 mol% by $[\text{Cp}^*\text{IrCl}_2]_2$ are lower than or comparable to that obtained without using any catalyst at all. This suggested that the catalysts had no effect on the reaction at these concentrations, although for catalyst **73** at 0.05 mol% there was clearly still a significant contribution made by the catalyst. The results also suggested that even at a concentration of 0.1 mol%, the addition of $[\text{Cp}^*\text{IrCl}_2]_2$ was only responsible for a conversion of 16%, assuming that the reaction pathways did not interfere with each other. Additionally, although there is some precedence in the literature for this reaction being impeded by very low levels of catalyst, it was believed to be more likely that the recorded conversions of 29% and 36% for the reactions with the lowest concentrations of $[\text{Cp}^*\text{IrCl}_2]_2$ represent experimental error.



Catalyst loading (mol%)	Conversion with Catalyst 73 (%)*	Conversion with [Cp*IrCl ₂] ₂ (%)*
1	> 98	> 98
0.5	> 98	> 98
0.1	> 98	61
0.05	89	36
0.01	49	29
No catalyst added	45	

Table 22 (conversions determined by NMR with internal standard)

Therefore, to obtain a set of results which more accurately reflected the activities of the two catalysts at lower concentrations a new trial was carried out. We chose the alkylation of acetophenone **187** with hydrocinnamyl alcohol **259** as our new model reaction (**Scheme 68**), as it had already been shown to require the presence of a hydrogen borrowing catalyst to proceed.



Scheme 68 (conversions determined by NMR with internal standard)

Although both catalysts were found to still be competent at this loading, we were pleased to see that catalyst **73** still achieved a yield of 33%, double that of $[\text{Cp}^*\text{IrCl}_2]_2$.

5.6 Conclusions

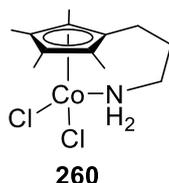
In conclusion, it has been successfully demonstrated that catalyst **73** was competent for the alkylation onto carbon centres via a hydrogen borrowing sequence incorporating aldol reactions, and generally outperformed $[\text{Cp}^*\text{IrCl}_2]_2$. More than 30 different substrates were prepared using catalyst **73**, with compounds including halides, anilines, ethers, phenols and a variety of heteroaromatic compounds. Alkylations were successfully carried out both onto and using both primary and secondary alcohols, aromatic and aliphatic compounds, and onto both methyl and methylene positions.

A method was developed for a one-pot aldol sequence alkylation and subsequent reduction to yield the corresponding alcohol product, which proceeds in excellent yield with either catalyst **69** or $[\text{Cp}^*\text{IrCl}_2]_2$. These combined methodologies were then used for the improvement of synthetic routes to a series of known compounds of biological interest, along with the synthesis of several novel compounds, which were tested for possible activity against colon carcinoma colon cells (HCT116). Here the naturally occurring taccabulin A was the best performing as was previously the case in literature studies of activity against HeLa breast cancer cells. The second-best performing was our reduced taccabulin A analogue **241**, though this was approximately ten times less efficacious.

Finally, the existence of a non-catalysed reaction was investigated, which had generally been under-reported in the literature. It was found that in the case of catalyst **73** and $[\text{Cp}^*\text{IrCl}_2]_2$ a significant proportion of the activity in simple alkylation reactions can be achieved without the use of a catalyst and examined the scope for this reaction. It was found that the non-catalysed reaction is much less effective when either the alcohol or ketone was aliphatic and the value of a catalyst in a series of these substrates was demonstrated, as was the superiority of catalyst **73** to $[\text{Cp}^*\text{IrCl}_2]_2$ in these cases.

Chapter 6. Future Work

There are a variety of options for further investigation to build on the work carried out here. Firstly, an analogue of catalyst **73** could be synthesised using a more common metal; the obvious candidate for this is cobalt which sits two rows above iridium in the periodic table. This proposed catalyst **260** could then be trialled in similar reactions to those developed and demonstrated here, in order to compare and eventually optimise the use of this less expensive catalyst.



Similarly, a future investigation could return to the work carried out here in chapter 4, to design new ligands to use in alternate catalysts of this family and study the relationship between their structure and the activity of the catalyst. There is also significant room for efforts to optimise the synthesis of catalyst **73** by our newly developed, more scale-up friendly route by experimenting with the conditions of the cyclisation and chelation reactions.

Further work could be carried out investigating the aldol-style hydrogen borrowing reactions which were the subject of chapter 5. For example, experiments could be carried out to determine whether catalyst **73** shows any useful selectivity when used in reactions with substrates bearing multiple alcohol or ketone moieties, or with substrates which contain both. These studies should also be carried with control reactions with a variety of bases in the absence of any catalyst to account for the uncatalysed reaction investigated here.

Finally, it may be of value to synthesis additional variants of the taccabulin compounds in chapter 5, and attempt to develop compounds with a greater efficacy against the cancer targets screened against here.

Chapter 7. Experimental

7.1 General Considerations

Instrumentation

Proton (^1H) and carbon (^{13}C) magnetic resonance spectra were recorded using a Bruker DPX 300, a Bruker DRX 500 or a Bruker Advance 500 spectrometer using an internal deuterium lock. ^1H -NMR chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane and coupling constant (J) are quoted in Hz. ^{13}C -NMR spectra were recorded with broadband proton decoupling at 100 MHz or 125 MHz, using the same machines.

Assignments were made on the basis of chemical shift and coupling data, using ^1H - ^{13}C HMQC, DEPT, HMBC and nOe experiments where necessary. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer, with absorption reported in wavenumbers (cm^{-1}). High-resolution electrospray mass spectra (ESI-MS) were obtained on a Bruker MicroTOF-Q or Bruker MaXis Impact spectrometer in positive or negative mode. Melting points were determined using a Griffin D5 variable temperature apparatus and are uncorrected. Gas chromatograms were recorded on an Agilent machine fitted with a Capillary Column HP-5 (5% phenylmethylsiloxane) HP 19091J-413 (30 mm x 320 μm x 0.25 μm), with the following method:

- Method 1 : 1 μL injection volume, inlet temperature: 250 $^{\circ}\text{C}$, inlet pressure: 10.00 psi, temperature column: 50 $^{\circ}\text{C}$ - hold time: 1 min, from 50 $^{\circ}\text{C}$ to 325 $^{\circ}\text{C}$ with 20 $^{\circ}\text{C}/\text{min}$ ramp, 325 $^{\circ}\text{C}$ - hold time: 2 min
- Method 2: 1 μL injection volume, inlet temperature: 250 $^{\circ}\text{C}$, inlet pressure: 10.00 psi, temperature column: 50 $^{\circ}\text{C}$ - hold time: 2 min, from 50 $^{\circ}\text{C}$ to 100 $^{\circ}\text{C}$ with 15 $^{\circ}\text{C}/\text{min}$ ramp, from 100 $^{\circ}\text{C}$ to 120 $^{\circ}\text{C}$ with 5 $^{\circ}\text{C}/\text{min}$ ramp, from 120 $^{\circ}\text{C}$ to 250 $^{\circ}\text{C}$ with 15 $^{\circ}\text{C}/\text{min}$ ramp

Experimental Procedures

All reactions were carried out under an inert atmosphere of nitrogen, unless stated. Toluene, methanol, diethyl ether, acetonitrile, DCM, chloroform and THF were dried prior to use using a Pure Solv MD solvent purification system (SPS). All other solvents and reagents were obtained from commercial sources and used without purification. The molecular weight of iridium trichloride hydrate was considered on an anhydrous basis since the hydration stoichiometry was unknown and, therefore, the yields for the synthesis of the complexes starting with this reagent was underestimated. Flash column chromatography was conducted using Fischer Matrix silica gel (35-70 μm). Thin layer chromatography was conducted using pre-coated silica plates (Merck silica Kieselgel 60F₂₅₄). Spots were visualized using UV fluorescence ($\lambda_{\text{max}} = 254 \text{ nm}$) and chemical staining with potassium permanganate.

7.2 General Procedures

General procedure A: Synthesis of substrate 96

To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) or $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene was added *N*-Boc-2,2-dimethylpropanediamine (229 μl , 1.13 mmol) and benzyl alcohol (118 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and purification by flash chromatography eluting with 10% MeOH in DCM yielded **96**.

General procedure B: Synthesis of substrate 97

To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) or $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene was added *N*-Boc-2,2-dimethylpropanediamine (229 μl , 1.13 mmol) and 1-phenylethanol (136 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and purification by flash chromatography eluting with 10% MeOH in DCM yielded **97**.

General procedure C: Synthesis of substrate 98

To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) or $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene was added *N*-Boc-2,2-dimethylpropanediamine (229 μl , 1.13 mmol) and hexanol (142 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel.

Solvent was removed *in vacuo* and purification by flash chromatography eluting with 10% MeOH in DCM yielded **98**.

General procedure D: Synthesis of substrates 186, 190-200, 203-218, 223, 236, 243, 245-249 and 252-258

To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added the corresponding alcohol (1.13 mmol), the corresponding ketone (1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and purification by flash chromatography yielded **186, 190-200, 203-218, 223, 236, 243, 245-249** or **252-258**

General procedure E: Synthesis of substrates 202 and 257

To a stirred suspension of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml) was added the corresponding alcohol (1.13 mmol), the corresponding ketone (1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and purification by flash chromatography yielded **202** or **257**.

General procedure F: Synthesis of substrates 186, 210 and 217

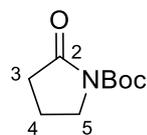
To toluene (1.0 ml) was added the corresponding alcohol (1.13 mmol), the corresponding ketone (1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and purification by flash chromatography yielded **186, 210** or **217**.

General procedure G: Synthesis of 178

To toluene (1.0 ml) was benzyl alcohol (118 μl , 1.13 mmol) and acetophenone (132 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the reaction was analysed by ^1H NMR, using mesitylene as an internal standard, to determine conversion.

6.3 Experimental Procedures

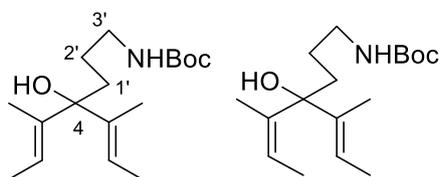
***N*-Boc-2-pyrrolidinone (164)**



To a stirred solution of 4-dimethylaminopyridine (254 mg, 2.08 mmol) in MeCN (16 ml) was added 2-pyrrolidinone (1.58 ml, 20.8 mmol) and di-*tert*-butyl carbonate (5.00 g, 22.9 mmol). The solution was left to stir for 16 h before being concentrated *in vacuo* and diluted with EtOAc (30 ml) and H₂O (30 ml). The phases were separated, and the aqueous was washed with further EtOAc (3 x 30 ml). The organic phases were combined, washed with brine (30 ml) and saturated aqueous NH₄Cl (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to yield **164** as a pale yellow oil (3.77 g, 20.4 mmol, 98%).

¹H NMR (400 MHz, CDCl₃, δ/ppm): 3.69 (2H, t, *J* = 7.2 Hz, *H*-5), 2.44 (2H, t, *J* = 8.0 Hz, *H*-3), 1.94 (2H, ap pent, *J* = 7.6 Hz, *H*-4), 1.46 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 174.4 (*C*-2), 150.3 (C(O)O), 82.7 (C(CH₃)₃), 46.5 (*C*-5), 32.9 (*C*-3), 28.0 (C(CH₃)₃), 17.3 (*C*-4); HRMS (ESI+) *m/z*: Calculated for C₉H₁₉N₂O₃ (M+NH₄⁺): 203.1390, found: 203.1387; calculated for C₉H₁₅NNaO₃ (M+Na⁺): 208.0944, found: 208.0944; calculated for C₉H₁₅KNO₃ (M+K⁺): 224.0684, found: 224.0679; calculated for C₁₈H₃₀N₂NaO₆ (2M+Na⁺): 393.1996, found: 393.2001. Spectroscopic data consistent with literature values.⁸⁰

***N*-Boc-4-(3'-aminopropyl)-3,5-dimethyl-hepta-2,5-dien-4-ol (165)**

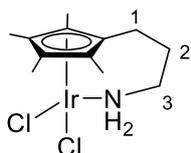


Prepared by a modified version of the reported method of Ito *et al.*⁸¹ Lithium wire (700 mg, 101 mmol) was cut into small pieces, washed with hexane and suspended in stirred Et₂O (30 ml), followed by 2-bromo-2-butene (5.2 ml, 51 mmol, mixture of *cis* and *trans* isomers) added dropwise. The reaction stirred for 2 h. *N*-Boc-2-pyrrolidinone **164** (3.13 g, 16.9 mmol) in diethyl ether (30 ml) was added dropwise and the reaction mixture was stirred for 2 h and quenched by slow addition of saturated aq. NH₄Cl solution (40 ml). The phases were separated and the aqueous phase was extracted with Et₂O (3 x 40 ml). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*.

Purification by flash chromatography eluting with 20% EtOAc in hexane yielded **165** (2.44 g, 8.23 mmol, 49%) as a 1:1 mixture of *trans-trans* and *cis-trans* isomers as a colourless oil.

$R_f = 0.46$ (hexane-EtOAc 80:20); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 5.60 (2H, q, $J = 7.0$ Hz, 2CH for *trans-trans*), 5.37 (2H, dq, $J = 1.2, 7.2$ Hz, 2CH for *cis-trans*), 4.60 (2H, br s, NH), 3.16 (4H, br s, 2H-3'), 1.79-1.77 (2H, m, 2OH), 1.75-1.60 (30H, m, 2CH₂, 8CH₃), 1.46 (18H, s, 2C(CH₃)₃); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 156.1 (C(O)), 139.5 (C_qCH₃), 139.2 (C_qCH₃) 137.8 (C_qCH₃), 122.7 (CH for *cis-trans*), 122.6 (CH for *cis-trans*) 119.1 (CH for *trans-trans*), 80.7 (C(CH₃)₃), 80.1 (C-4), 79.5 (C-4), 41.0, (C-3'), 36.8 (C-1'), 34.6 (C-1'), 28.4 (C(CH₃)), 24.4 (C-2'), 24.1 (C-2'), 23.1 (CH₃), 22.8 (CH₃), 14.8 (CH₃), 14.3 (CH₃), 13.4 (CH₃), 12.4 (CH₃); HRMS (ESI+) m/z : Calculated for C₁₇H₃₂NO₃ (M+H⁺): 298.2377, found: 298.2368; calculated for C₁₇H₃₅N₂O₃ (M+NH₄⁺): 315.2642, found: 315.2632; calculated for C₁₇H₃₁NNaO₃: 320.2196, found: 320.2197. Spectroscopic data consistent with literature values.⁵⁶

IrCl₂[η^5 : η^1 C₅(CH₃)₄(CH₂)₃NH₂](73**)**



Method 1: Prepared by the method reported by Lanaro.⁵⁶ To a stirred mixture of iridium(III) chloride hydrate (510 mg, 1.68 mmol) and NaHCO₃ (140 mg, 1.68 mmol) in MeOH (21 ml) was added ligand **165** (1.00 g, 3.36 mmol). The reaction mixture was heated in a microwave reactor for 2 h at 130 °C. The reaction mixture was cooled to RT then concentrated *in vacuo*. Purification by flash chromatography eluting with 2% MeOH in DCM afforded a yellow solid which was recrystallized from DCM-hexane (v/v = 1/3), to yield **73** (341 mg, 747 μmol , 44%) as a yellow solid.

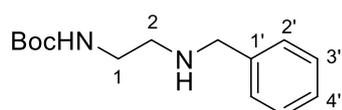
Method 2: Prepared by a modified version of the method of Ito *et al.*⁸¹ To a stirred mixture of iridium(III) chloride hydrate (69 mg, 230 μmol) and NaHCO₃ (20 mg, 230 μmol) in MeOH (1.0 ml) was added **182** (100 mg, 460 μmol). The reaction was heated to 60 °C for 5 h before being cooled to RT and concentrated *in vacuo*. Purification by flash chromatography eluting with 2% MeOH in DCM afforded a yellow solid which was recrystallised from DCM-hexane (v/v = 1/3), to yield **73** (22 mg, 51 μmol , 22%) a yellow solid.

$R_f = 0.25$ (DCM-methanol 95:5); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 3.96 (2H, br s, NH₂), 2.71-2.67 (2H, m, H-3), 2.16 (2H, t, $J = 6.5$ Hz, H-1), 1.95-1.90 (2H, m, H-2), 1.76 (6H, s, 2CH₃), 1.65 (6H, s, 2CH₃); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 90.8 (C_qIr), 88.7 (C_qIr), 41.8

(C-3), 39.7 (C-1), 19.2 (C-2), 9.3 (CH₃), 9.0 (CH₃), one carbon (C_qIr) not observed. HRMS (ESI+) *m/z*: Calculated for and C₁₂H₂₀³⁵Cl¹⁹³IrN (M-Cl⁻): 406.0900, found: 406.0892. Spectroscopic data consistent with literature values.⁵⁶

Chapter 2 Compounds

tert-Butyl [2-(benzylamino)ethyl]carbamate (**92**)

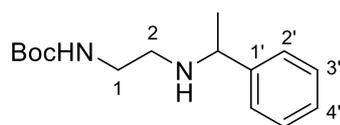


To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl, 1.13 mmol) and benzyl alcohol (118 μl, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **92** as a colourless oil (238 mg, 949 μmol, 84%).

To a stirred suspension of [Cp*IrCl₂]₂ (8.4 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl, 1.13 mmol) and benzyl alcohol (118 μl, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **92** as a colourless oil (170 mg, 678 μmol, 60%).

R_f = 0.28 (DCM-MeOH 90:10); ¹H NMR (500 MHz, CDCl₃, δ/ppm): 7.27-7.24 (4H, m, *Ar*), 7.20-7.17 (1H, m, *Ar*), 3.73 (2H, s, CH₂*Ar*), 3.17 (2H, ap q, *J* = 5.5 Hz, *H*-1), 2.69 (2H, t, *J* = 6.0 Hz, *H*-2), 1.37 (9H, s, C(CH₃)₃), 2 NH signals not observed; ¹³C NMR (125 MHz, CDCl₃, δ/ppm): 156.3 (C(O)N), 138.9 (C-1'), 128.6 (*Ar*), 128.4 (*Ar*), 127.4 (*Ar*), 79.3 (C(CH₃)₃), 53.2 (CH₂*Ar*), 48.4 (C-1), 31.6 (C-2), 28.5 (C(CH₃)₃); IR (ν_{max}, neat, cm⁻¹): 3368, 3005, 2924, 1658, 1580, 1508, 1251, 740; HRMS (ESI+) *m/z*: Calculated for C₁₄H₂₃N₂O₂ (M+H⁺): 251.1754, found: 251.1752. Spectroscopic data comparable to literature values, with some variation in splitting patterns.⁸²

***tert*-Butyl {2-[(1-phenylethyl)amino]ethyl}carbamate (**93**)**

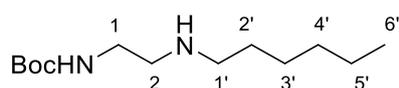


To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl , 1.13 mmol) and 1-phenylethanol (136 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **93** as a colourless oil (36 mg, 140 μmol , 12%).

To a stirred suspension of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl , 1.13 mmol) and 1-phenylethanol (136 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **93** as a colourless oil (21 mg, 190 μmol , 17%).

$R_f = 0.33$ (DCM-MeOH 90:10); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.34-7.21 (5H, m, *Ar*), 4.88 (1H, br s, NHC(O)) 3.76 (1H, q, $J = 8.0$ Hz, *CH*), 3.21-3.10 (2H, m, *H-1*), 2.63 (1H, app quint, $J = 6.5$ Hz, *H-2a*) 2.53 (1H, app. quint, 6.0 Hz, *H-2b*), 1.44 (9H, s, $(\text{C}(\text{CH}_3)_3)$), 1.35 (3H, d, $J = 8$ Hz, CH_3), 1 *NH* signal not observed; $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ/ppm): 156.1 ($\text{C}(\text{O})\text{N}$), 145.2 (*C-1'*), 138.9 (*Ar*), 128.7 (*Ar*), 127.0 (*Ar*), 79.2 ($\text{C}(\text{CH}_3)_3$), 58.0 (*CH*), 47.0 (*C-1*), 40.6 (*C-2*), 28.4 ($\text{C}(\text{CH}_3)_3$), 24.3 (CH_3); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 265.1911, found: 265.1904. Spectra consistent with literature values.⁸³

***tert*-Butyl [2-(hexylamino)ethyl]carbamate (**94**)**



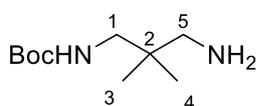
To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl , 1.13 mmol) and hexanol (142 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **94** as a colourless oil (102 mg, 418 μmol , 37%).

To a stirred suspension of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml) was added *N*-Boc-ethylenediamine (179 μl , 1.13 mmol) and hexanol (142 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. Solvent was removed *in vacuo* and the

residue purified by flash chromatography eluting with 10% MeOH in DCM to yield **94** as a colourless oil (64 mg, 260 μmol , 23%).

$R_f = 0.31$ (DCM-MeOH 90:10); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 3.29-3.21 (2H, m, $H-1$), 2.78-2.72 (2H, m, $H-2$), 2.62 (2H, t, $J = 7.0$ Hz, $H-1'$), 1.49 (2H, ap t, $J = 7.0$ Hz, $H-2'$), 1.44 (9H, s, $(\text{C}(\text{CH}_3)_3)$), 1.34-1.24 (6H, m, $H-3'$, 4', 5'), 0.87 (3H, t, $J = 7.0$ Hz, $H-6'$) $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ/ppm): 153.0 ($\text{C}(\text{O})\text{N}$), 72.3 ($\text{C}(\text{CH}_3)_3$), 49.4 ($\text{C}-1$), 49.1 ($\text{C}-1'$), 31.7 ($\text{C}-2$), 29.4 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_3$), 26.9 (CH_2), 22.6 (CH_2), 19.0 (CH_2), 14.0 ($\text{C}-6'$); HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{29}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 245.2223, found: 245.2218. Spectroscopic data consistent with literature values.⁸⁴

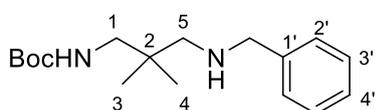
***N*-Boc-2,2-dimethylpropanediamine (95)**



Prepared by the method reported in patent EP1550657 A1, 2009⁸⁵. To a stirred solution of triethylamine (2.7 ml, 19. mmol) and 2,2-dimethylpropanediamine (2.35 g, 19.6 mmol) in DCM (100 ml) was added a solution of Boc_2O (2.25 g, 9.81 mmol) in DCM (4 ml). The reaction mixture was left to stir for 48 h at RT. H_2O (60 ml) was added and the reaction allowed to stir for 5 minutes at RT. The resulting phases were separated and the aqueous layer was extracted with DCM (3 x 60 ml). The combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to yield **95** (1.70 g, 8.41 mmol, 86%) as a white solid.

mp 77.3-78.2 $^\circ\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 5.15 (1H, br s, $\text{NHC}(\text{O})$), 3.01 (2H, d, $J = 6.5$ Hz, $H-1$), 2.50-2.43 (2H, m, $H-5$), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.38 (2H, br s, NH_2), 0.87 (6H, s, $H-3,4$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ/ppm): 156.4 ($\text{C}(\text{O})\text{N}$), 79.0 ($\text{C}(\text{CH}_3)_3$), 50.8 ($\text{C}-5$), 48.7 ($\text{C}-1$), 35.8, ($\text{C}-2$), 28.6 ($\text{C}(\text{CH}_3)_3$), 23.3 ($\text{C}-3,4$); HRMS (ESI+) m/z : Calculated for $\text{C}_{10}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 203.1754, found: 203.1748. Spectroscopic data consistent with literature values.⁸⁶

***tert*-Butyl [3-(benzylamino)-2,2-dimethylpropyl]carbamate (96)**



Following general procedure A, **96** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash

chromatography gave **96** as a colourless oil (241 mg, 825 μmol , 73%)

Following general procedure A, **96** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **96** as a colourless oil (251 mg, 856 μmol , 76%).

Following general procedure A, **96** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash chromatography gave **96** as a colourless oil (231 mg, 791 μmol , 70%).

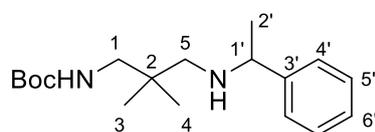
Following general procedure A, **96** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **96** as a colourless oil (264 mg, 904 μmol , 80%).

To a stirred suspension of either catalyst **73** (5.0 mg, 11.3 μmol) or $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (either 1.0 ml or 0.5 ml) was added *N*-Boc-2,2-dimethylpropanediamine (229 mg, 1.13 mmol) and benzyl alcohol (120 μl , 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel. At time intervals, a 50 μl or 25 μl sample was taken, dissolved in DCM, filtered through a silica plug and analysed by GC to determine their conversion, using method 1:

Catalyst 73				[Cp*IrCl ₂] ₂			
1 M		2 M		1 M		2 M	
Time (min)	Conversion (%)	Time (min)	Conversion (%)	Time (min)	Conversion (%)	Time (min)	Conversion (%)
1	0	1	0.33	1	0.04	1	0.33
15	0.13	15	0.75	15	0.06	15	0.72
30	0.40	30	1.16	30	0.06	90	0.43
90	1.49	60	2.43	90	0.10	120	0.68
120	2.31	90	5.63	120	0.08	240	0.84
240	4.12	120	5.46	240	0.103	300	0.82
300	6.19	229	9.97	300	0.11	360	0.98
260	7.27	289	11.53	260	0.11	420	0.98
420	8.45	349	13.68	420	0.22	1440	2.08
1440	30.27	409	14.93	1440	0.3		
		1440	30.53				

$R_f = 0.38$ (DCM-MeOH 90:10); ¹H NMR (500 MHz, CDCl₃, δ/ppm): 7.37-7.33 (4H, m, Ar), 7.29-7.26 (1H, m, Ar), 3.79 (2H, s, CH₂Ar), 3.05 (2H, d, $J = 6.0$ Hz, H-1), 2.46 (2H, s, H-5), 1.48 (9H, s, C(CH₃)₃), 0.92 (6H, s, 2CH₃), 2 NH signals not observed; ¹³C NMR (125 MHz, CDCl₃, δ/ppm): 156.5 (C(O)N), 140.5 (C-1'), 128.4 (Ar), 128.1 (Ar), 127.0 (Ar), 78.5 (C(CH₃)₃), 59.0 (C-1), 54.7 (CH₂Ar), 50.3 (C-5), 34.7 (C-2), 28.5 (C(CH₃)₃), 24.1 (CH₃); HRMS (ESI+) m/z : Calculated for C₁₇H₂₉N₂O₂(M+H⁺): 293.2224, found 293.2225; calculated for C₁₇H₂₈N₂NaO₂: 315.2043, found 315.2038.

***tert*-Butyl {3-[(1-phenylethyl)amino]-2,2-dimethylpropyl}carbamate (**97**)**



Following general procedure B, **97** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash chromatography gave **97** as a colourless oil (124 mg, 407 μmol, 36%).

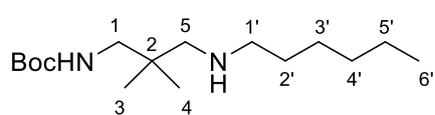
Following general procedure B, **97** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **97** as a colourless oil (197 mg, 644 μmol , 57%).

Following general procedure B, **97** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash chromatography gave **97** as a colourless oil (100 mg, 328 μmol , 29%).

Following general procedure B, **97** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **97** as a colourless oil (156 mg, 509 μmol , 45%).

$R_f = 0.40$ (DCM-MeOH 90:10); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.33-7.22 (5H, m, *Ar*), 3.65 (1H, q, $J = 6.5$, *CH*), 2.98 (2H, m, *H-1*), 2.33 (1H, d, $J = 12.0$ Hz, *H-5a*), 2.18 (1H, d, $J = 12.0$ Hz, *H-5b*), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.34 (3H, d, $J = 6.5$ Hz, CCH_3), 0.87 (3H, s, C_qCH_3), 0.83 (3H, s, C_qCH_3), 2 *NH* signals not observed; $^{13}\text{C NMR}$ (125 MHz, CDCl_3 , δ/ppm): 156.5 ($\text{C}(\text{O})\text{N}$), 145.9 (*C-1'*), 128.5 (*Ar*), 126.9 (*Ar*), 126.6 (*Ar*), 78.6 ($\text{C}(\text{CH}_3)_3$), 59.0 (*C-1*), 57.1 (*CH*), 49.9 (*C-5*), 34.7 (*C-2*), 28.5 ($\text{C}(\text{CH}_3)_3$), 24.5 (CHCH_3), 24.1 (C_qCH_3), 24.0 (C_qCH_3); HRMS (ESI+) m/z : Calculated for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 307.2380, found: 307.2386.

tert-Butyl [3-(hexylamino)-2,2-dimethylpropyl]carbamate (**98**)



Following general procedure C, **98** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash chromatography gave **98** as a colourless oil (168 mg, 588 μmol , 52%).

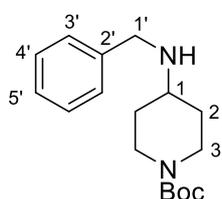
Following general procedure C, **98** was prepared using catalyst **73** (5.0 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **98** as a colourless oil (227 mg, 791 μmol , 70%).

Following general procedure C, **98** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml). Purification by flash chromatography gave **98** as a colourless oil (230 mg, 802 μmol , 71%).

Following general procedure C, **98** was prepared using [Cp*IrCl₂]₂ (8.4 mg, 11.3 μmol) in toluene (0.5 ml). Purification by flash chromatography gave **98** as a colourless oil (249 mg, 870 μmol, 77%).

R_f = 0.32 (DCM-MeOH 90:10); ¹H NMR (500 MHz, CDCl₃, δ/ppm): 2.99 (2H, d, *J* = 5.5 Hz, *H*-1), 2.54 (2H, t, *J* = 7.0 Hz, *H*-1'), 2.39 (2H, s, *H*-5), 1.48-1.41 (9H, m, *H*-9, (C(CH₃)₃), 1.33-1.23 (8H, m, *H*-2', 3', 4', 5'), 0.89-0.85 (9H, m, 2CH₃, *H*-6'), 2 NH signals not observed; ¹³C NMR (125 MHz, CDCl₃, δ/ppm): 156.8 (C(O)N), 78.6 (C(CH₃)₃), 59.8 (C-1), 50.7 (C-5), 50.5 (C-1'), 34.7 (C-2) 31.8 (CH₂), 29.9 (CH₂), 28.9 (C(CH₃)₃), 27.0 (CH₂), 24.3 (C_qCH₃), 22.9 (CH₂), 21.7 (C-6'); HRMS (ESI+) *m/z*: Calculated for C₁₆H₃₅N₂O₂ (M+H⁺): 287.2693, found 287.2695.

4-Benzylamino-piperidine-1-carboxylic acid *tert*-butyl ester (**101**)

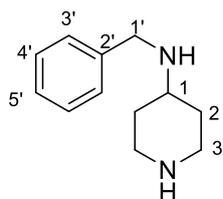


Prepared by the method reported in patent US2006/19985 A1, 2006.⁸⁷ To a stirred solution of 4-amino-*N*-Boc-piperidine (400 mg, 2.00 mmol) in MeOH (5.0 ml) was added AcOH (13 μl, 0.2 mmol), and benzaldehyde (224 μl, 2.04 mmol). The reaction was left to stir for 15 minutes before addition of NaBH₃CN (180 mg, 2.90 mmol) and a further 30 minutes stirring. The reaction mixture was diluted with H₂O (20 ml) and EtOAc (20 ml). The aqueous layer was separated and extracted with EtOAc (3 x 20 ml). The organic layers were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*.

The resulting colourless oil was purified by column chromatography eluting with 25% EtOAc in hexane to yield **101** as a colourless oil (419 mg, 1.44 mmol 44%).

R_f = 0.12 (Hex:EtOAc 75:25); ¹H NMR (400 MHz, CDCl₃, δ/ppm): 7.30 – 7.12 (5H, m, *Ar*), 3.94 (2H, br s, CH₂), 3.74 (2H, s, CH₂Ar), 2.72 (2H, ap t, *J* = 11.8 Hz, CH₂) 2.64 – 2.53 (1H, m, *H*-1), 1.78 (2H, m, CH₂), 1.38 (9H, s, C(CH₃)₃), 1.30 – 1.16 (2H, m, CH₂); ¹³C NMR (100 MHz, CDCl₃, δ/ppm) 154.8 (COOC(CH₃)₃), 140.3 (C-7), 128.5 (C-9,11), 128.1 (C-8,12), 127.0 (C-10), 79.4 (C(CH₃)₃), 54.2 (C-1), 50.8 (CH₂Ar), 42.6 (C-3), 32.4 (C-2), 28.5 (C(CH₃)₃); HRMS (ESI+) *m/z*: Calculated for C₁₇H₂₇N₂O₂ (M+H⁺): 291.2067, found: 291.2065; calculated for C₁₇H₂₆N₂NaO₂ (M+Na⁺): 313.1886, found: 313.1881. Spectroscopic data consistent with literature values.⁸⁸

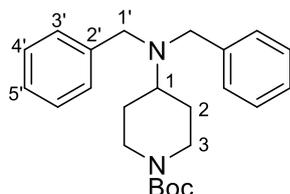
4-Benzylaminopiperidine (104)



Prepared by a modified version of the method reported in patent WO2009/37294 A1, 2009.⁸⁹ To a stirred solution of **101** (300 mg, 1.03 mmol) in DCM (2 ml) was added TFA (500 μ l, 6.53 mmol). The solution was left to stir for 3 h before an addition of further TFA (220 μ l, 2.87 mmol). After a final 3 h, the reaction mixture was concentrated *in vacuo*. Saturated aq. NaHCO₃ (4 ml) and aq. NaOH solution (2 M, 1.0 ml) were added before the solution was extracted with DCM (3 x 10 ml). The organic layers were combined and EtOAc was added (4 ml), before being washed with H₂O (10 ml) and brine (10 ml), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give **104** as a colourless oil (65 mg, 342 μ mol, 33%)

¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.41 – 7.15 (5H, m, *Ar*), 3.82 (2H, s, CH₂Ar), 3.19 – 3.04 (2H, m, CH₂), 2.67 – 2.55 (3H, m, CH₂), 1.92 (2H, m, CH₂), 1.39 – 1.21 (2H, m, CH₂); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 140.6 (C-2'), 128.5 (*Ar*), 128.1 (*Ar*), 127.0 (*Ar*), 54.5 (C-1), 50.6 (CH₂Ar), 45.3 (C-3), 34.0 (C-2); HRMS (ESI+) *m/z*: Calculated for C₁₂H₁₉N₂ (M+H⁺): 191.1543, found: 191.1540. Spectroscopic data consistent with literature values.⁹⁰

4-Dibenzylaminopiperidine-1-carboxylic acid *tert*-butyl ester (103)



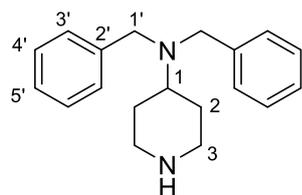
To a stirred solution of STAB (635 mg, 3.00 mmol) and 4-amino-1-Boc-piperidine (500 mg, 2.50 mmol) in DCE (5.0 ml) was added benzaldehyde (275 μ l, 2.71 mmol). The reaction mixture was left to stir for 16 h before addition of further STAB (.635 mg, 3.00 mmol) and benzaldehyde (275 μ l, 2.71 mmol). After 5 h a final addition of STAB (318 mg, 1.50 mmol) and benzaldehyde (140 μ l, 1.35 mmol) was made and the reaction mixture was left to stir for 19 h.

Saturated aq. NaHCO₃ solution (25 ml) was added to the reaction mixture, followed by H₂O (2.5 ml) and DCM (7.5 ml). The phases were separated and the aqueous extracted with DCM (3 x 20 ml). The organic layers were combined, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to yield a white solid. The solid was dried by vacuum filtration and washed with MeOH to yield **103** as a white solid (818 mg, 2.15 mmol, 86%).

¹H NMR (300 MHz, CDCl₃, δ /ppm): 7.41 – 7.38 (m, 4H, *H*-4'), 7.32 – 7.27 (m, 4H, *H*-3'), 7.25 – 7.20 (m, 2H, *H*-5'), 3.64 (s, 4H, CH₂Ar), 3.18 (2H, m, CH₂), 2.66 (1H, tt, *J*₁ = 3.6 Hz,

$J_2 = 12.0$ Hz, CH), 2.52 (2H, t, $J = 11.1$, CH_2), 1.90-1.81 (2H, m, CH_2), 1.61 (2H, qd, $J_1 = 3.9$, $J_2 = 12.3$ Hz, CH_2) 1.50 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 154.7 ($COOC(CH_3)_3$), 140.0 ($C-2'$), 129.2 ($C-4'$), 128.5 ($C-3'$), 126.5 ($C-5'$), 79.5 ($C(CH_3)_3$), 56.6 ($C-1$), 53.9 (CH_2Ar), 46.8 ($C-3$), 29.0 ($C-2$). 27.9 ($C(CH_3)$); HRMS (ESI+) m/z : Calculated for $C_{24}H_{33}N_2O_2$ ($M+H^+$): 381.2542, found: 381.2540. Spectroscopic data consistent with literature values.⁹⁰

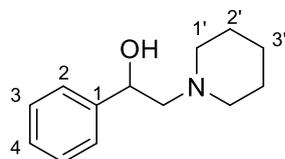
4-Dibenzylaminopiperidine (105)



Prepared by the method reported in patent WO2009/37294 A1, 2009.⁸⁹ To a stirred solution of **103** (400 mg, 1.05 mmol) in DCM (2.5 ml) was added TFA (660 μ l, 8.73 mmol). The solution was left to stir for 3 h before an addition of further TFA (0.33 μ l, 4.40 mmol). After a final 3 h, the reaction mixture was concentrated *in vacuo*. Saturated aq. $NaHCO_3$ (4.0 ml) and aq. NaOH solution (2 M, 1.0 ml) were added before the solution was extracted with DCM (3 x 10 ml). The organics were combined and EtOAc was added (4.0 ml), before being washed with H_2O (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield **105** as a colourless oil (80.0 mg, 284 μ mol, 27%).

1H NMR (300 MHz, $CDCl_3$, δ/ppm): 7.42 – 7.36 (4H, m, $H-4'$), 7.34 – 7.26 (4H, m, $H-3'$), 7.26 – 7.21 (m, 2H, $H-5'$), 3.67 (4H, s, CH_2Ar), 3.16 (2H, m, CH_2), 2.63 (1H, tt, $J_1 = 3.6$ Hz, $J_2 = 12.0$ Hz, CH), 2.52 (2H, t, $J = 11.1$, CH_2), 1.91-1.80 (2H, m, CH_2), 1.62 (2H, qd, $J_1 = 3.9$, $J_2 = 12.3$ Hz, CH_2), 1 NH signal not observed; ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 140.1 ($C-2'$), 128.5 ($C-4'$), 128.3 ($C-3'$), 126.8 ($C-5'$), 56.4 ($C-1$), 53.9 (CH_2Ar), 46.5 ($C-3$), 28.9 ($C-2$); HRMS (ESI+) m/z : Calculated for $C_{19}H_{25}N_2$ ($M+H^+$): 281.2012, found: 281.2010. Spectroscopic data consistent with literature values.⁹⁰

1-Phenyl-2-(piperidin-1-yl)ethan-1-ol (107)

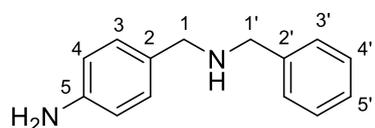


To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 1-phenyl-1,2-ethanediol (156 mg, 1.13 mmol) in PhMe (1.0 ml) was added piperidine (112 μ l, 1.13 mmol). The reaction was heated to 110 $^{\circ}C$ for 24 h, before being concentrated *in vacuo*. Purified by flash

chromatography eluting with 2-10% MeOH in DCM to yield **107** as a white solid (155 mg, 757 μmol mmol, 67%).

$R_f = 0.36$ (DCM:MeOH 95:5); ^1H NMR (500 MHz, CDCl_3 , δ/ppm): 7.59-7.33 (5H, m, *Ar*), 4.77 (1H, dd, $J_1 = 3.5$ Hz, $J_2 = 10.0$ Hz, *CH*), 2.75 (2H, ap br s, CHCH_2), 2.55-2.46 (4H, m, CH_2), 1.71-1.62 (4H, m, CH_2) 1.49 (2H, m, CH_2), *OH* not observed; ^{13}C NMR (125 MHz, CDCl_3 , δ/ppm): 142.5 (*C-1*), 128.3 (*Ar*), 127.4 (*Ar*), 125.9 (*Ar*), 68.7 (*CH*), 67.0 (CHCH_2), 54.5 (*C-1'*), 26.2 (*C-2'*), 24.3 (*C-3'*); IR (ν_{max} , neat, cm^{-1}): 3505, 3394, 3029, 2926, 2860, 1617, 1260, 1052; HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{20}\text{NO}$ ($\text{M}+\text{H}^+$): 206.1539, found: 206.1533. Spectroscopic data consistent with literature values.⁹¹

4-(Benzylaminomethyl)phenylamine (**113**)



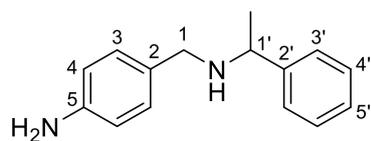
Method 1: To a stirred solution of catalyst **73** (5.0 mg, 11.3 μmol) and 4-aminobenzylamine (128 μl , 1.13 mmol) in PhMe (1.0 ml) was added benzyl alcohol (118 μl , 1.13 mmol). The

reaction was heated to 110 $^\circ\text{C}$ for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **113** as a colourless oil (151 mg, 711 μmol , 62%).

Method 2: To a stirred solution of catalyst **73** (5 mg, 11.3 μmol) and 4-aminobenzyl alcohol (139 μl , 1.13 mmol) in PhMe (1.0 ml) was added benzylamine (123 μl , 1.13 mmol). The reaction was heated to 110 $^\circ\text{C}$ for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **113** as a colourless oil (79 mg, 373 μmol , 33%).

$R_f = 0.21$ (DCM:MeOH 95:5); ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.39-7.36 (5H, m, 3',4',5'), 7.16 (2H, d, $J = 8.0$ Hz, *H-3*), 6.68 (2H, d, $J = 8.0$ Hz, *H-4*), 3.83 (2H, s, *H-1'*), 3.74 (2H, s, *H-1*), 3 *NH* signals not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 143.4 (*C-5*), 139.7 (*C-2'*) 128.3 (*C-3*) 128.1 (*C-4'*), 126.8 (*C-3'*), 125.9 (*C-2*), 125.3 (*C-5'*), 113.8 (*C-4*) 53.1 (*C-1*), 52.6 (*C-1'*); HRMS (ESI+) m/z : Calculated for $\text{C}_{14}\text{H}_{17}\text{N}_2$ ($\text{M}+\text{H}^+$): 213.1392, found: 213.1390.

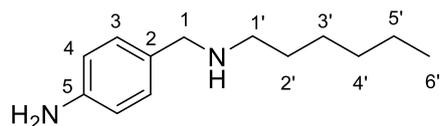
4-[(1-Phenylethylamino)methyl]aniline (**120**)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μmol) and 4-aminobenzylamine (128 μl , 1.13 mmol) in PhMe (1.0 ml) was added 1-phenylethanol (136 μl , 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **120** as a colourless oil (59 mg, 260 μmol , 23%).

R_f = 0.25 (DCM:MeOH 95:5); ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.34-7.29 (5H, m, 3', 4', 5'), 7.09 (2H, d, J = 8.4 Hz, H -3), 6.67 (2H, d, J = 8.4 Hz, H -4), 3.84 (1H, q, J = 6.8 Hz, H -1'), 3.70 (2H, s, H -1), 1.41 (3H, d, J = 6.8 Hz, CH_3), 3 NH signals not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 144.5 (C -2'), 143.4 (C -5), 128.1 (C -3), 127.9 (C -4'), 126.7 (C -5'), 125.7 (C -3'), 125.4 (C -2), 113.5 (C -4) 58.2 (C -1'), 50.2 (C -1) 20.7 (CH_3); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{19}\text{N}_2$ ($\text{M}+\text{H}^+$): 227.1548, found: 227.1551.

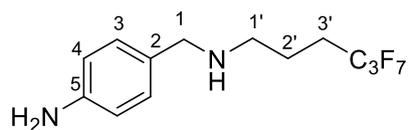
4-Amino-*N*-hexylbenzylamine (**121**)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μmol) and 4-aminobenzylamine (128 μl , 1.13 mmol) in PhMe (1.0 ml) was added *n*-hexanol (142 μl , 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **121** as a colourless oil (102 mg, 493 μmol , 44%).

R_f = 0.27 (DCM:MeOH 95:5); ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.27 (2H, d, J = 8.0 Hz, H -3), 6.67 (2H, d, J = 8.0 Hz, H -4), 3.70 (2H, s, H -1), 3.58 (2H, t, J = 8.6 Hz, H -1'), 3.54-3.49 (2H, m, CH_2), 1.51-1.47 (2H, m, CH_2), 1.32-1.25 (4H, m, 2 CH_2), 0.82 (3H, t, J = 6.8 Hz, H -6'), 3 NH signals not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 143.8 (C -5), 127.7 (C -3), 124.3 (C -2), 111.9 (C -4), 52.3 (C -1'), 49.9 (C -1), 31.6 (CH_2), 29.4 (CH_2), 26.8 (CH_2), 22.7 (CH_2), 21.1 (C -6') ; HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{23}\text{N}_2$ ($\text{M}+\text{H}^+$): 207.1861, found: 207.1860. Spectroscopic data comparable to literature values, with some variation in splitting patterns.⁹²

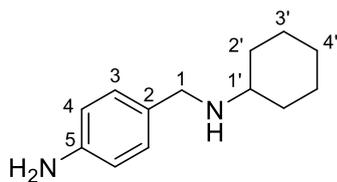
4-Amino-*N*-4,4,5,5,6,6,6-heptafluorohexylbenzylamine (**122**)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 4-aminobenzylamine (128 μ l, 1.13 mmol) in PhMe (1.0 ml) was added 4,4,5,5,6,6,6-hexafluorohexanol (185 μ l, 1.13 mmol). The reaction was heated to 110 $^{\circ}$ C for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **122** as a colourless oil (229 mg, 689 μ mol, 41%).

R_f = 0.25 (DCM:MeOH 95:5); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.00 (2H, ap t, J = 6.8 Hz, H -3), 6.55 (2H, ap dq, J_1 = 2.0 Hz, J_2 = 8.4 Hz, H -4), 3.57 (2H, s, H -1), 3.55 (2H, t, J = 6 Hz, H -1'), 2.10-1.98 (2H, m, CH_2), 1.75-1.64 (2H, m, CH_2), 3 NH signals not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 141.5 (C -5), 126.0 (C -3), 121.2 (C -2), 110.9 (C -4), 50.5, (C -1'), 30.6 (CH_2), 26.1 (CH_2), 24.1 (CH_2), 18.4 (CH_2), 15.5 (C -6'); HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{16}\text{F}_7\text{N}_2$ ($\text{M}+\text{H}^+$): 333.1202, found: 333.1203.

4-Amino-*N*-cyclohexylbenzylamine (**123**)



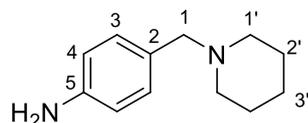
Method 1: To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 4-aminobenzylamine (128 μ l, 1.13 mmol) in PhMe (1.0 ml) was added cyclohexanol (118 μ l, 1.13 mmol). The reaction was heated to 110 $^{\circ}$ C for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography 5-10% eluting with MeOH in DCM gave **123** as yellow oil (28 mg, 136 μ mol, 12%).

Method 2: To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 4-aminobenzyl alcohol (139 μ l, 1.13 mmol) in PhMe (1.0 ml) was added cyclohexylamine (129 μ l, 1.13 mmol). The reaction was heated to 110 $^{\circ}$ C for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography 5-10% eluting with MeOH in DCM gave **123** as yellow oil (152 mg, 746 μ mol, 66%)

R_f = 0.33 (DCM:MeOH 95:5); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.13 (2H, d, J = 6.4 Hz, H -4), 6.58 (2H, d, J = 6.4 Hz, H -3), 3.61 (2H, s, H -1), 2.53-2.47 (1H, m, H -1'), 1.95-1.88 (2H, m, CH_2), 1.71-1.64 (2H, m, CH_2), 1.26-1.09 (6H, m, 3CH_2), 3 NH signals not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 144.2 (C -5), 126.1 (C -3), 125.9 (C -2), 113.6 (C -4), 57.9 (C -

1), 51.5 (C-1'), 33.2 (C-2'), 27.8 (C-4') 25.3 (C-3'); HRMS (ESI+) m/z : Calculated for $C_{13}H_{21}N_2$ (M+H⁺): 205.1705, found: 205.1708.

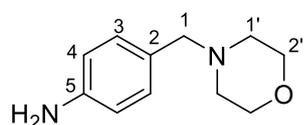
1-(4-Aminobenzyl)piperidine (125)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 4-aminobenzyl alcohol (139 μ l, 1.13 mmol) in PhMe (1.0 ml) was added piperidine (112 μ l, 1.13 mmol). The reaction was heated to 110 °C for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **125** as an off-white solid (82 mg, 429 μ mol, 38%).

R_f = 0.38 (DCM:MeOH 95:5); mp 86.5-87.8 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.03 (2H, ap p, J = 8.0 Hz, H -4), 6.53 (2H, ap p, J = 8.0 Hz, H -3), 3.34 (2H, s, H -1), 2.30-2.25 (4H, m, 2CH₂), 1.48 (4H, ap p, J = 5.6 Hz, 2CH₂), 1.33 (2H, ap q J = 5.6 Hz, CH₂), 2 NH signals not observed; ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 144.7 (C-5), 130.8 (C-3), 130.4 (C-2), 128.2 (C-4), 62.1 (C-1), 54.5 (2C-1'), 24.5 (2C-2'), 24.0 (C-3'); HRMS (ESI+) m/z : Calculated for $C_{12}H_{19}N_2$ (M+H⁺): 190.1548, found: 190.1544. Spectroscopic data consistent with literature values.⁹³

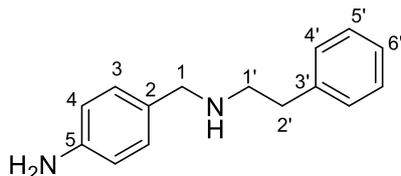
1-(4-Aminobenzyl)morpholine (126)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μ mol) and 4-aminobenzyl alcohol (139 μ l, 1.13 mmol) in PhMe (1.0 ml) was added morpholine (97 μ l, 1.13 mmol). The reaction was heated to 110 °C for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **126** as a white solid (26 mg, 136 μ mol, 12%).

R_f = 0.21 (DCM:MeOH 95:5); mp 101.2-101.9 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.05 (2H, ap dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, H -4), 6.57 (2H, ap dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, H -3), 3.68 (4H, m, 2CH₂) 3.57 (2H, s, H -1), 2.40-2.32 (4H, m, 2CH₂), 2 NH signals not observed; ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 144.5 (C-5), 131.1 (C-3), 130.7 (C-2), 128.7 (C-4), 66.9 (C-1), 62.1 (C-2'), 54.3 (C-1'); HRMS (ESI+) m/z : Calculated for $C_{11}H_{17}N_2O$ (M+H⁺): 193.1341, found: 193.1340. Spectroscopic data consistent with literature values.⁹³

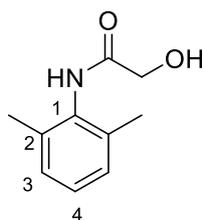
1-(4-aminobenzyl)-2-phenylethylamine (**127**)



To a stirred solution of catalyst **73** (5.0 mg, 11.3 μmol) and 4-aminobenzyl alcohol (139 μl , 1.13 mmol) in PhMe (1.0 ml) was added 2-phenylethylamine (144 μl , 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h, before being concentrated *in vacuo*. Purification by flash chromatography eluting with 5-10% MeOH in DCM gave **127** as a yellow oil (92 mg, 407 μmol , 36%).

$R_f = 0.38$ (DCM:MeOH 95:5); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 7.22-7.19 (3H, m, C_6H_5), 7.14-7.11 (2H, m, C_6H_5), 7.00 (2H, d, $J = 6.4$ Hz, $H-4$), 6.56 (2H, d, $J = 6.4$ Hz, $H-3$), 3.53 (2H, s, $H-1$), 2.82 (2H, t, $J = 5.6$ Hz, $H-1'$), 2.76 (2H, t, 5.6 Hz, $H-2'$), 3 NH signals not observed; $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 143.2 ($C-5$), 138.3 ($C-3'$), 128.7 ($C-5'$), 128.9 ($C-4'$), 128.4 ($C-3$), 126.7 ($C-2$), 126.0 ($C-6'$), 113.8 ($C-4$), 52.9 ($C-1$), 49.8 ($C-1'$), 33.8 ($C-2'$); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{19}\text{N}_2$ ($\text{M}+\text{H}^+$): 227.1548, found: 227.1546.

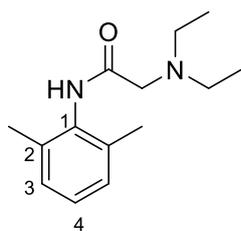
N-(2,6-Dimethylphenyl)-2-hydroxyacetamide (**151**)



Prepared partially by a modified version of the procedure used by Lin *et al.*⁹⁴ To a stirred solution mixture of 2,6-dimethylaniline (4.7 ml, 33.0 mmol) in DCM (32 ml) was added Na_2CO_3 (1.74 g, 16.5 mmol). The reaction was suspended in a bath of cold water and stirred while chloroacetyl chloride (3.2 ml, 30.0 mmol) was added slowly. After 19 h, the reaction was poured onto H_2O (35 ml), and the DCM was removed *in vacuo*, and reaction was fitted with a condenser and heated to 100 $^{\circ}\text{C}$. After 7 days the reaction was allowed to cool to RT and extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give **151** as colourless crystals (3.07 g, 17.2 mmol, 52%).

mp 90.4-91.1 $^{\circ}\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.13 (3H, m, Ar), 4.19 (2H, s, CH_2), 2.24 (6H, s, 2CH_3), 1 NH signal not observed; $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 170.1 (CO), 135.2 ($C-1$), 131.9 ($C-2$), 127.9 ($C-3$), 127.4 ($C-4$), 61.8 (CH_2), 18.7 (2CH_3); IR (ν_{max} , neat, cm^{-1}): 3360, 2940, 2931, 1632, 1576, 1467, 1076, 770, 727; HRMS (ESI+) m/z : Calculated for: $\text{C}_{10}\text{H}_{13}\text{NO}_2$ ($\text{M}+\text{H}^+$): 179.0946, found: 179.0950. Spectroscopic data consistent with literature values.⁹⁴

2-Diethylamino-*N*-(2,6-dimethylphenyl)acetamide (**146**)

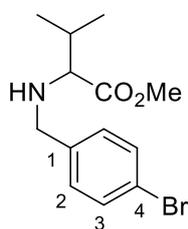


To a stirred solution of catalyst **73** (5.0 mg, 11.3 μmol) and **151** (203 μl , 1.13 mmol) in PhMe (1.0 ml) was added diethylamine (1.0 ml, 9.67 mmol). The reaction was heated to 90 $^{\circ}\text{C}$ for 24 before before being concentrated *in vacuo*. Purification by flash chromatography eluting with 30% EtOAc in hexane gave **146** as a white solid (66 mg, 283 μmol , 25%).

To a stirred solution of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) and **151** (203 μl , 1.13 mmol) in PhMe (1.0 ml) was added diethylamine (1.0 ml, 9.67 mmol). The reaction was heated to 90 $^{\circ}\text{C}$ for 24 before being concentrated *in vacuo*. Purification by flash chromatography eluting with 30% EtOAc in hexane gave **146** as a white solid (37 mg, 158 μmol , 14%).

$R_f = 0.27$ (Hex:EtOAc 70:30); mp 67.2–67.8 $^{\circ}\text{C}$; $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.12–7.06 (3H, m, *Ar*), 3.22 (2H, s, COCH_2), 2.72 (4H, q, $J = 7.0$ Hz, CH_2CH_3), 2.21 (6H, s, CHCH_3), 1.16 (6H, t, $J = 7.0$ Hz, CH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 170.1 (CO), 134.9 (C-1), 131.7 (C-2), 127.6 (C-3), 127.0 (C-4), 56.9 (COCH_2), 49.0 (CH_2CH_3), 18.3 (CHCH_3), 12.2 (CH_2CH_3); IR (ν_{max} , neat, cm^{-1}): 3256, 2968, 2800, 1737, 1663, 1492, 1423, 1292; HRMS (ESI+) m/z : Calculated for: $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$): 235.1810, found: 235.1808. Spectroscopic data consistent with literature values.⁹⁵

Methyl *N*-(4-bromobenzyl)-valinate (**158**)



To a stirred solution of catalyst **73** (5.0 mg, 1.13 μmol), triethylamine (315 μl , 2.26 mmol) and valine methyl ester hydrochloride (189 mg, 1.13 mmol) in PhMe was added 4-bromobenzyl alcohol (211 mg, 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h before being concentrated *in vacuo*. Purification by flash chromatography eluting with 30% EtOAc in hexane gave **158** as a colourless oil (44 mg, 150 μmol , 13%).

To a stirred solution of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 1.13 μmol), triethylamine (315 μl , 2.26 mmol) and valine methyl ester hydrochloride (189 mg, 1.13 mmol) in PhMe (1.0 ml) was added 4-bromobenzyl alcohol (211 mg, 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h before being concentrated *in vacuo*. Purification by flash chromatography eluting with 30% EtOAc in hexane gave **158** as a colourless oil (44 mg, 150 μmol , 13%).

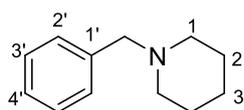
To a stirred solution of catalyst **73** (5.0 mg, 1.13 μmol), triethylamine (315 μl , 2.26 mmol) and valine methyl ester hydrochloride (189 mg, 1.13 mmol) in DMF (1.0 ml) was added 4-bromobenzyl alcohol (211 mg, 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h before being concentrated *in vacuo*. Purification by flash chromatography eluting with 30% EtOAc in hexane gave **158** as a colourless oil (20 mg, 68 μmol , 6%).

To a stirred solution of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 1.13 μmol), triethylamine (315 μl , 2.26 mmol) and valine methyl ester hydrochloride (189 mg, 1.13 mmol) in DMF was added 4-bromobenzyl alcohol (211 mg, 1.13 mmol). The reaction was heated to 110 $^{\circ}\text{C}$ for 24 h before being concentrated *in vacuo*. Purification by chromatography eluting with 30% EtOAc in hexane gave **158** as a colourless oil (37 mg, 120 μmol , 11%).

$R_f = 0.32$ (Hex:EtOAc 70:30); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.47 (2H, d, $J = 7.5$ Hz, $H-2$), 7.16 (2H, d, $J = 7.5$ Hz, $H-3$), 4.01-3.94 (2H, m, CH_2Ar), 3.75 (3H, s, OCH_3), 3.22 (1H, d, $J = 1.5$ Hz, NHCH) 1.97-1.90 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.08 (6H, d, $J = 6.5$ Hz, 2CH_3), 1 NH signal not observed; $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 173.1 (CO), 135.3 (C-1), 131.3 (C-3), 129.5 (C-2), 120.3 (C-4), 63.2 (NHCH), 51.1 (OCH_3), 28.2 (CH_2Ar), 18.7(CHCH_3), 17.2 (2CH_3) HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{19}^{79}\text{BrNO}_2$ ($\text{M}+\text{H}^+$): 300.0599, found: 300.0602. Spectroscopic data comparable to literature values, with some variation in splitting patterns.⁹⁶

Chapter 3 Compounds

Benzylpiperidine (76)



To a stirred suspension of catalyst **73** (17 mg, 39 μmol) in toluene (1.5 ml), was added benzyl alcohol (120 μl , 1.13 mmol) and piperidine (112 μl , 1.13 mmol). The reaction mixture was heated to 110 $^{\circ}\text{C}$ for 24 h before being concentrated *in vacuo* and purified by flash chromatography, eluting with 10-20% EtOAc in hexane, to obtain **76** as a colourless oil (135 mg, 768 μmol , 68%).

To a stirred suspension of either catalyst **73** or $[\text{Cp}^*\text{IrCl}_2]_2$, benzyl alcohol and piperidine in toluene, DMF or NMP. The reaction mixture was heated to 110 $^{\circ}\text{C}$ for 18 h. The reaction

mixture was diluted with DCM before 50 μ l was taken and added to 1.0 ml of DCM, filtered through a silica plug and analysed by GC to determine their conversions, using method 2:

Catalyst	Benzyl Alcohol	Piperidine	Solvent Volume (ml)	PhMe	DMF	NMP
Catalyst 73 (250 μ g, 565 nmol)	60 μ l (565 μ mol)	56 μ l (565 μ mol)	1.7	92%	38%	49%
[Cp*IrCl ₂] ₂ (450 μ g, 565 nmol)	60 μ l (565 μ mol)	56 μ l (565 μ mol)	1.7	3%	1%	2%
Catalyst 73 (500 μ g, 1.13 μ mol)	120 μ l (1.13 mmol)	112 μ l (1.13 mmol)	1.0	94%	67%	72%
[Cp*IrCl ₂] ₂ (900 μ g, 1.13 μ mol)	120 μ l (1.13 mmol)	112 μ l (1.13 mmol)	1.0	5%	2%	4%
Catalyst 73 (1.00 mg, 2.26 μ mol)	240 μ l (2.26 mmol)	224 μ l (2.26 mmol)	0.56	96%	69%	81%
[Cp*IrCl ₂] ₂ (1.80 mg, 2.26 μ mol)	240 μ l (2.26 mmol)	224 μ l (2.26 mmol)	0.56	37%	6%	3%
Catalyst 73 (25 μ g, 56.5 nmol)	60 μ l (565 μ mol)	56 μ l (565 μ mol)	1.7	1%	1%	0%
[Cp*IrCl ₂] ₂ (45 μ g, 56.5 nmol)	60 μ l (565 μ mol)	56 μ l (565 μ mol)	1.7	0%	0%	0%
Catalyst 73 (50 μ g, 113 nmol)	120 μ l (1.13 mmol)	112 μ l (1.13 mmol)	1.0	1%	2%	4%
[Cp*IrCl ₂] ₂ (90 μ g, 113 nmol)	120 μ l (1.13 mmol)	112 μ l (1.13 mmol)	1.0	0%	0%	1%
Catalyst 73 (100 μ g, 226 nmol)	240 μ l (2.26 mmol)	224 μ l (2.26 mmol)	0.56	1%	1%	1%
[Cp*IrCl ₂] ₂ (180 μ g, 302 nmol)	240 μ l (2.26 mmol)	224 μ l (2.26 mmol)	0.56	0%	0%	0%
Catalyst 73 (133 μ g, 302 nmol)	240 μ l (2.26 mmol)	224 μ l (2.26 mmol)	0.56	5%	13%	3%

[Cp*IrCl ₂] ₂ (240 μg, 451 nmol)	240 μl (2.26 mmol)	224 μl (2.26 mmol)	0.56	1%	1%	3%
Catalyst 73 (199 μg, 451 nmol)	240 μl (2.26 mmol)	224 μl (2.26 mmol)	0.56	4%	11%	25%
[Cp*IrCl ₂] ₂ (360 μg, 2.26 μmol)	240 μl (2.26 mmol)	224 μl (2.26 mmol)	0.56	1%	1%	1%
Catalyst 73 (399 μg, 905 nmol)	240 μl (2.26 mmol)	224 μl (2.26 mmol)	0.56	86%	90%	51%
[Cp*IrCl ₂] ₂ (721 μg, 905 nmol)	240 μl (2.26 mmol)	224 μl (2.26 mmol)	0.56	8%	2%	4%

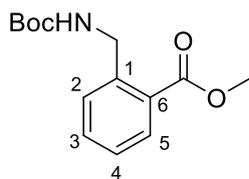
To a 7 ml screw-top vial was added either catalyst **73** or [Cp*IrCl₂]₂, 240 μl benzyl alcohol (2.26 mmol), 224 μl piperidine (2.26 mmol) either toluene, DMF or NMP (0.60 ml) and either AcOH, DIPEA, or H₂O. The reaction mixture was heated to 110 °C for 18 h. The reaction mixture was diluted with DCM before 50 μl was taken and added to 1.0 ml of DCM, filtered through a silica plug and analysed by GC:

Catalyst	Additive	PhMe	DMF	NMP
Catalyst 73 (199 μ g, 451 nmol)	393 μ l DIPEA (2.26 mmol)	3%	8%	8%
[Cp*IrCl ₂] ₂ (393 μ g, 2.26 μ mol)	393 μ l DIPEA (2.26 mmol)	1%	0%	4%
Catalyst 73 (199 μ g, 451 nmol)	13 μ l AcOH (226 μ mol)	16%	8%	34%
[Cp*IrCl ₂] ₂ (393 μ g, 2.26 μ mol)	13 μ l AcOH (226 μ mol)	2%	0%	1%
Catalyst 73 (199 μ g, 451 nmol)	4 μ l H ₂ O (226 μ mol)	1%	5%	13%
[Cp*IrCl ₂] ₂ (393 μ g, 2.26 μ mol)	4 μ l H ₂ O (226 μ mol)	1%	1%	2%

R_f: = 0.90 (Hex:EtOAc 80:20); ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.35-7.18 (5H, m, *H*-1',2',3',4'), 3.46 (2H, s, CH₂), 2.37 (4H, ap br s, *H*-1), 1.59-1.54 (4H, m, *H*-2), 1.43 (2H, ap br s, *H*-3). ¹³C NMR (125 MHz, CDCl₃, δ /ppm): 138.5 (*C*-1), 129.4 (*Ar*), 128.2 (*Ar*), 127.0 (*Ar*), 64.0 (CH₂), 54.6 (*C*-1'), 26.0 (*C*-2'), 24.5 (*C*-3'). HRMS (ESI+) *m/z*: Calculated for C₁₂H₁₈N (M+H⁺): 176.1434, found: 176.1468. Spectroscopic data consistent with literature values.⁹⁷

Chapter 4 Compounds

N-Boc-Methyl-2-(aminomethyl)benzoate (171)

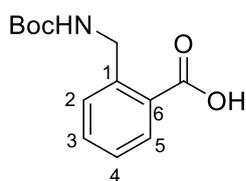


To a stirred solution of methyl-2-(aminomethyl)benzoate hydrochloride (500 mg, 2.48 mmol) in THF (10 ml) was added di-*tert*-butyl carbonate (0.63 ml, 2.74 mmol) and triethylamine (0.70 ml, 5.02 mmol). The mixture was left to stir for 17.5 h, after which saturated aq. NH₄Cl (10 ml) was added. The phases were separated and the aqueous was extracted with DCM (20 ml x 3). The organic layers were combined, concentrated under vacuum and diluted in hexane to precipitate triethylamine hydrochloride. The solution was dried over anhydrous Na₂SO₄,

filtered and concentrated under vacuum to obtain **171** (651 mg, 2.46 mmol, 99%) as a colourless oil.

^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.88 (1H, ap d, $J = 7.7$ Hz, $H-4$), 7.47 – 7.35 (2H, m, $H-2.5$), 7.28 – 7.22 (1H, m, $H-4$), 4.43 (2H, d, $J = 6.5$ Hz, CH_2), 3.82 (3H, s, CH_3), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 167.7 (COOMe), 155.8 ($\text{COC}(\text{CH}_3)$), 146.74 ($\text{C}-1$), 140.9 ($\text{C}-3$), 132.8 ($\text{C}-2$), 130.9 ($\text{C}-5$), 128.7 ($\text{C}-6$), 127.4 ($\text{C}-4$), 85.1 ($\text{C}(\text{CH}_3)$) 52.1 ($\text{C}-8$), 43.7 (CH_2), 28.4 ($\text{C}(\text{CH}_3)$); HRMS (ESI+) m/z : calculated for $\text{C}_{14}\text{H}_{20}\text{NO}_4$ ($\text{M}+\text{H}^+$): 266.1392, found: 266.1381.

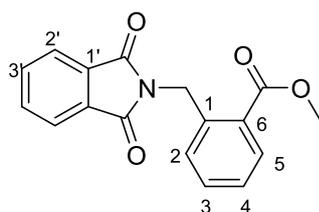
***N*-Boc-2-(aminomethyl)benzoic acid (178)**



To a stirred solution of **171** (500 mg, 1.89 mmol) in THF (9.2 ml) and H_2O (9.2 ml) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (160 mg, 3.80 mmol). The mixture was left to stir for 21.5 h before being diluted with HCl (1 M, 30 ml) and EtOAc (30 ml). The phases were separated and the aqueous extracted with further EtOAc (3 x 30 ml). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under vacuum to obtain **178** (362 mg, 1.44 mmol, 76%) as a white solid.

mp = 135.0-135.7 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 8.17 (1H, d, $J = 7.5$ Hz, $H-5$), 7.48 (1H, ap t, $J = 7.2$ Hz, $H-3$), 7.37 (2H, m, $H-2, 4$), 4.58 (2H, d, $J = 6.7$ Hz, CH_2), 1.47 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 169.8 (COOH), 158.5 (NHCO), 141.7 ($\text{C}-1$), 132.5 ($\text{C}-3$), 132.4 ($\text{C}-2$), 132.2 ($\text{C}-5$), 128.5 ($\text{C}-6$), 128.0 ($\text{C}-4$), 81.1 (CCH_3), 45.7 (CH_2), 28.6 (CCH_3); HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{17}\text{NNaO}_4$ ($\text{M}+\text{Na}^+$): 274.1050, found: 270.1049, calculated for $\text{C}_{13}\text{H}_{16}\text{NNa}_2\text{O}_4$ ($\text{M}+2\text{Na}^+-\text{H}$): 296.0869, found: 296.0867.

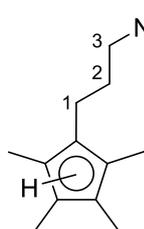
2-(2-Methoxycarbonylbenzyl)phthalimide (180)



To a stirred solution of potassium phthalimide (970 mg, 5.24 mmol) in DMF (10 ml) was added methyl-2-(bromomethyl)-benzoate (1.00 g, 4.37 mmol). After 2 h, solvent was removed under vacuum and diluted with H_2O (30 ml). The product was extracted with CHCl_3 (30 ml x3), and the organics combined, dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to yield obtain **180** (797 mg, 2.70 mmol, 86%) as a white solid.

mp = 121.7 °C; ¹H NMR (400 MHz, CDCl₃, δ/ppm): 8.00 (1 H, ap dd, *J* = 7.8, 1.0 Hz, *H*-5), 7.90 (2H, ap dd, *J*₁ = 5.5 Hz, *J*₂ = 3.0 Hz, *H*-2'), 7.76 (2H, dd, *J* = 5.4, 3.1 Hz, *H*-3'), 7.44 (1H, ap td, *J*₁ = 7.7, *J*₂ = 1.2 Hz, *H*-3), 7.33 (1H, ap t, *J* = 7.6 Hz, *H*-4), 7.20 (1 H, d, *J* = 7.8 Hz, *H*-2), 5.37 (2H, s, CH₂), 3.99 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 168.3 (COOMe), 167.7 (2CON), 137.7 (*C*-1), 134.4 (*C*-3), 134.2 (*C*-3'), 134.1 (*C*-1'), 132.6 (*C*-2), 131.1 (*C*-6), 129.2 (*C*-5), 127.4 (*C*-4), 123.6 (*C*-2'), 52.4 (CH₃), 39.9 (CH₂); HRMS (ESI+) *m/z*: Calculated for C₁₇H₁₃NNaO₄ (M+Na⁺): 318.0737, found: 318.0733, calculated for C₃₄H₂₆N₂NaO₈ (2M+Na⁺): 613.1518, found: 613.1566.

3-(Tetramethylcyclopentadienyl)propan-1-ammonium chloride (**182**)

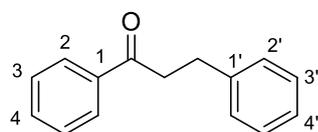


Prepared by a modified version of the method reported by Ito *et al.*⁸¹ To a stirred solution of **165** (500 mg, 1.68 mmol) in MeOH (2 ml) was added HCl (2 M in ether, 1.3 ml) and the reaction was left to stir at RT. After 20 h, the reaction was concentrated *in vacuo*. The residue was washed with Et₂O to yield **182** (217 mg, 1.00 mmol 60%) as a white solid. Analysed as an unresolved mixture of isomers.

¹H NMR (400 MHz, CDCl₃, δ/ppm): 8.08 (3H, br s, NH₃), 2.75-2.64 (2H, m, *H*-3), 2.49-2.25 (2H, m, CH₂), 1.96-1.70 (2H, m, CH₂), 1.81 (6H, s, CH₃), 1.75 (6H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 139.8 (C_qCH₃), 139.6 (C_qCH₃), 138.8 (C_qCH₃), 136.6 (C_qCH₃), 136.2 (C_qCH₃), 135.9 (C_qCH₃), 134.6 (C_qCH₃), 133.9 (C_qCH₃), 133.0 (C_qCH₃), 58.5 (*C*-3), 58.1 (*C*-3), 55.3 (CH), 51.6 (CH), 49.2 (CH), 40.4 (*C*-1'), 40.4 (*C*-1'), 40.3 (CH₂), 40.3 (CH₂), 25.8 (CH₂), 24.9 (CH₂), 24.7 (CH₂), 23.5 (CH₂), 23.0 (CH₂), 14.3 (CH₃), 12.1 (CH₃), 11.7 (CH₃), 11.5 (CH₃), 11.2 (CH₃), 11.0 (CH₃); HRMS (ESI+) *m/z*: Calculated for C₁₄H₂₆N (M+H⁺): 208.2060, found: 208.2057. Spectroscopic data consistent with literature values⁵⁶

Chapter 5 Compounds

1,3-Diphenylpropan-1-one (**186**)



Following general procedure D, **186** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **186** as a white solid (234 mg, 1.11 mmol, 98%).

To a stirred suspension of catalyst **73** in toluene (1.0 ml) was added benzyl alcohol (118 μ l, 1.13 mmol) and acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 6 h in a sealed vessel. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **186** as a white solid (181 mg, 859 μ mol, 76%).

Following general procedure F, **186** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **186** as a white solid (107 mg, 509 μ mol, 45%).

To a stirred suspension of benzyl alcohol (118 μ l, 1.13 mmol) in toluene (1.0 ml) was added acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 6 h in a sealed vessel. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **186** as a white solid (45 mg, 215 μ mol, 19%).

Following general procedure G, **186** was prepared using catalyst **73** (5.0 mg, 11.3 μ mol). Analysis by ^1H NMR determined a conversion greater than 98%.

Following general procedure G, **186** was prepared using catalyst **73** (2.5 mg, 5.65 μ mol). Analysis by ^1H NMR determined a conversion greater than 98%.

Following general procedure G, **186** was prepared using catalyst **73** (500 μ g, 1.13 μ mol). Analysis by ^1H NMR determined a conversion greater than 98%.

Following general procedure G, **186** was prepared using catalyst **73** (250 μ g, 565 nmol). Analysis by ^1H NMR determined a conversion of 89%.

Following general procedure G, **186** was prepared using catalyst **73** (50 μg , 113 nmol). Analysis by ^1H NMR determined a conversion of 49%.

Following general procedure G, **186** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol). Analysis by ^1H NMR determined a conversion greater than 98%.

Following general procedure G, **186** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (4.2 mg, 5.65 μmol). Analysis by ^1H NMR determined a conversion greater than 98%.

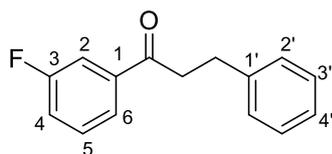
Following general procedure G, **186** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (840 μg , 1.13 μmol). Analysis by ^1H NMR determined a conversion of 61%.

Following general procedure G, **186** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (420 μg , 565 nmol). Analysis by ^1H NMR determined a conversion of 36%.

Following general procedure G, **186** was prepared using $[\text{Cp}^*\text{IrCl}_2]_2$ (84 μg , 113 nmol). Analysis by ^1H NMR determined a conversion of 29%.

$R_f = 0.94$ (Hex:EtOAc 90:10); mp 71.2-72.0 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.94 (2H, d, $J = 8.6$ Hz, $H-2$), 7.53 (1H, t, $J = 7.6$ Hz, $H-4$), 7.42 (2H, ap t, $J = 7.8$ Hz, $H-3$), 7.30-7.17 (5H, m, $H-2'$, $3'$, $4'$), 3.28 (2H, t, $J = 7.5$ Hz, $H-\text{COCH}_2$), 3.06 (2H, t, $J = 7.5$ Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 199.2 (CO), 138.0 (C-1), 137.8 (C-1'), 129.2 (C-3), 128.7 (C-4), 128.6 (C-2), 128.4 (C-3'), 128.2 (C-2'), 127.1 (C-4'), 40.6 (COCH₂), 30.3 (CH₂Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{15}\text{O}$ ($\text{M}+\text{H}^+$): 211.1117, found: 211.1112; calculated for $\text{C}_{15}\text{H}_{14}\text{NaO}$ ($\text{M}+\text{Na}^+$): 233.0937, found: 233.0931. Spectra consistent with literature values.⁹⁸

1-(3-Fluorophenyl)-3-phenyl-1-propanone (**190**)

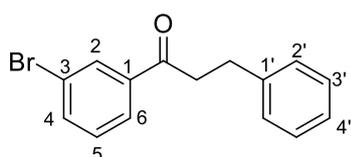


Following general procedure D, **190** was prepared from benzyl alcohol (118 μl , 1.13 mmol) and 3'-fluoroacetophenone (139 μl , 1.13 mmol). Purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **190** as a white solid (162 mg, 712 μmol , 63%).

$R_f = 0.92$ (Hex:EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.78 (1H, d, $J = 7.6$ Hz, $H-2$), 7.69 (1H, ap dt, $J_1 = 2.0$, $J_2 = 10.0$ Hz, $H-6$), 7.48 (1H, ap q, $J = 8.0$ Hz, $H-5$), 7.36 (2H, ap t, $J = 7.2$ Hz, $H-3'$), 7.32-7.25 (4H, m, $H-4$, $2'$, $4'$), 3.33 (2H, ap t, $J = 7.6$ Hz, $H-\text{COCH}_2$),

3.12 (2H, t, $J = 7.6$ Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 197.0 (CO), 163.4 (C-3), 141.2 (C-1'), 139.3 (C-1), 130.1 (C-5), 128.6 (C-2'), 128.3 (C-3'), 126.2 (C-4'), 124.0 (C-6), 119.8 (C-4), 114.0 (C-2), 40.5 (COCH_2), 30.2 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{14}\text{FO}$ ($\text{M}+\text{H}^+$): 229.1029. found: 229.1027. Spectroscopic data consistent with literature values.⁹⁹

1-(3-Bromophenyl)-3-phenyl-1-propanone (191)

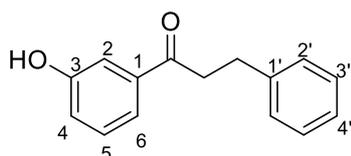


Following general procedure D, **191** was prepared from benzyl alcohol (118 μl , 1.13 mmol) and 3'-bromoacetophenone (149 μl , 1.13 mmol). Purification by flash chromatography eluting with 0-20% EtOAc in hexane gave **191** as an off-white solid (211 mg,

735 μmol , 65%).

$R_f = 0.87$ (Hex:EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.98 (1H, ap t, $J = 1.6$ Hz, $H-6$), 7.77 (1H, ap dq, $J_1 = 0.8$ Hz, $J_2 = 7.6$, $H-5$), 7.57 (1H, ap q, $J = 8.0$ Hz, $H-4$), 7.26-7.18 (3H, m, $H-4$, 3'), 7.17-7.10 (3H, m, $H-2'$, 4'), 3.18 (2H, t, $J = 7.2$ Hz, $H-\text{COCH}_2$), 2.97 (2H, t, $J = 7.2$ Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 197.2 (CO), 141.0 (C-1'), 138.2 (C-1), 134.9 (C-3) 130.7 (C-5), 131.0 (C-2'), 128.7 (C-3'), 127.9 (C-4'), 125.5 (C-6), 125.2 (C-4), 123.9 (C-2), 40.3 (COCH_2), 29.8 (CH_2Ar); IR (ν_{max} , neat, cm^{-1}): 3020, 2915, 2870, 1692, 1561, 1194, 1015, 746; HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{14}^{79}\text{BrO}$ ($\text{M}+\text{H}^+$): 289.0228. found: 289.0223. Spectroscopic data consistent with literature values.¹⁰⁰

1-(3-Hydroxyphenyl)-3-phenyl-1-propanone (192)



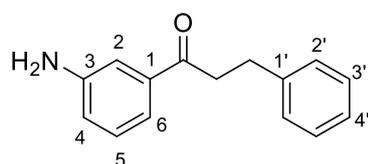
Following general procedure D, **192** was prepared from benzyl alcohol (118 μl , 1.13 mmol) and 3'-hydroxyacetophenone (154 mg, 1.13 mmol). Purification by flash chromatography eluting 0-20% EtOAc in hexane gave **192** as an off-white solid (20 mg, 90

μmol , 8%).

$R_f = 0.81$ (Hex:EtOAc 90:10); mp 106.2-107.4 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.67-7.22 (9H, m, Ar), 3.51 (2H, t, $J = 7.6$ Hz, $H-\text{COCH}_2$), 3.20 (2H, t, $J = 7.6$ Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 199.5 (CO), 155.8 (C-3), 141.9 (C-1'), 138.8 (C-1), 131.5

(C-5), 129.2 (C-3'), 128.7 (C-2'), 127.2 (C-4'), 122.3 (C-4), 121.9 (C-6), 115.7 (C-2), 40.8 (COCH₂), 30.9 (CH₂Ar); IR (ν_{\max} , neat, cm⁻¹): 3454, 2931, 1767, 1690, 1591, 1497, 1441, 1362; HRMS (ESI+) m/z : Calculated for C₁₅H₁₅O₂ (M+H⁺): 227.1072. found: 227.1066.

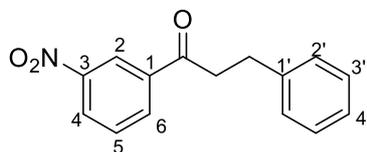
1-(3-Aminophenyl)-3-phenyl-1-propanone (**193**)



Following general procedure D, **193** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 3'-aminoacetophenone (153 mg, 1.13 mmol). Purification by flash chromatography eluting with eluting 0-40% EtOAc in hexane gave **193** as white solid (239 mg, 1.06 mmol, 94%).

R_f = 0.16 (Hex:EtOAc 90:10); mp 79.1-80.6 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.36-7.21 (8H, m, Ar), 6.91-6.87 (1H, m, Ar), 3.83 (2H, br s, NH₂), 3.28 (2H, t, J = 7.6 Hz, H-COCH₂), 3.08 (2H, t, J = 7.6 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 199.3 (CO), 146.1 (C-3), 141.2 (C-1'), 137.8 (C-1), 130.2 (C-5), 128.1 (C-3'), 127.8 (C-2'), 126.5 (C-4'), 119.3 (C-4), 118.0 (C-6), 113.5 (C-2), 40.2 (COCH₂), 30.3 (CH₂Ar); IR (ν_{\max} , neat, cm⁻¹): 3462, 3368, 3029, 2925, 1671, 1631, 1601, 1455, 1178; HRMS (ESI+) m/z : Calculated for C₁₅H₁₅NONa (M+Na⁺): 248.1051. found: 248.1047. Spectroscopic data consistent with literature values.¹⁰⁰

1-(3-Nitrophenyl)-3-phenyl-1-propanone (**194**)

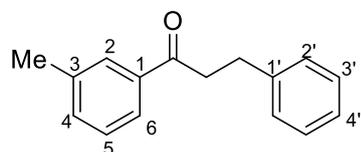


Following general procedure D, **194** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 3'-nitroacetophenone (187 mg, 1.13 mmol). Purification by flash chromatography 0-10% EtOAc in hexane gave **194** as a yellow solid (20 mg, 79 μ mol, 7%).

R_f = 0.62 (Hex:EtOAc 90:10); mp 79.1-80.6 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 8.68 (1H, ap t, J = 8.0 Hz, H-2), 8.35-8.32 (1H, m, H-6), 8.20 (1H, ap d, J = 8.0 Hz, H-4), 7.59 (1H, t, J = 8.0 Hz, H-5), 7.26-7.13 (5H, m, Ar), 3.29 (2H, t, J = 8.0 Hz, H-COCH₂), 3.03 (2H, t, J = 7.6 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 196.9 (CO), 147.9 (C-3), 140.5 (C-1'), 138.1 (C-1), 134.1 (C-5), 130.9 (C-3'), 128.1 (C-4), 127.9 (C-2'), 127.6 (C-4'), 126.8 (C-6), 123.4 (C-2), 41.1 (COCH₂), 30.5 (CH₂Ar); IR (ν_{\max} , neat, cm⁻¹): 3462, 3368, 3029, 2925,

1671, 1631, 1601, 1455, 1178; HRMS (ESI+) m/z : Calculated for $C_{15}H_{14}NO_3$ ($M+H^+$): 256.0974. found: 256.0974. Spectroscopic data consistent with literature values.¹⁰¹

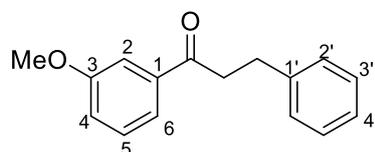
1-(3-Methylphenyl)-3-phenyl-1-propanone (**195**)



Following general procedure D, **195** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 3'-methylacetophenone (154 μ l, 1.13 mmol). Purification by flash chromatography 0-20% EtOAc in hexane gave **195** as a colourless oil (185 mg, 825 μ mol, 73%).

R_f = 0.73 (Hex:EtOAc 90:10); 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.86-7.79 (2H, m, *Ar*), 7.41-7.23 (7H, m, *Ar*), 3.33 (2H, t, J = 8.0 Hz, *H-COCH*₂), 3.11 (2H, t, J = 8.0 Hz, *CH*₂*Ar*), 2.44 (3H, s, *CH*₃); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 198.2 (*CO*), 140.7 (*C-1'*), 139.1 (*C-3*), 137.0 (*C-1*), 133.8 (*C-4*), 128.8 (*C-3*), 128.7 (*C-2'*), 128.7 (*C-2*), 128.5 (*C-5*), 126.0 (*C-6*), 125.1 (*C-4'*), 40.9 (*COCH*₂), 30.1 (*CH*₂*Ar*), 21.1 (*CH*₃); IR (ν_{max} , neat, cm^{-1}): 3023, 2918, 1679, 1598, 1496, 1365, 1291, 1157; HRMS (ESI+) m/z : Calculated for $C_{16}H_{17}O$ ($M+H^+$): 225.1279, found: 225.1283. Spectroscopic data consistent with literature values.¹⁰²

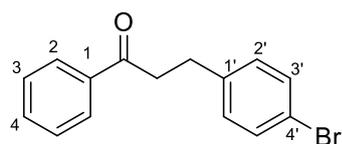
1-(3-Methoxyphenyl)-3-phenyl-1-propanone (**196**)



Following general procedure D, **196** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 3'-methoxyacetophenone (153 μ l, 1.13 mmol). Purification by flash chromatography 0-20% EtOAc in hexane gave **196** as a colourless oil (212 mg, 881 μ mol, 78%).

R_f = 0.68 (Hex:EtOAc 90:10); 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.57 (1H, d, J = 8.0 Hz, *H-6*), 7.53 (1H, br s, *H-2*), 7.42-7.23 (6H, m, *Ar*), 7.15-7.13 (1H, m, *Ar*) 3.88 (3H, s *OCH*₃), 3.33 (2H, t, J = 7.2 Hz, *COCH*₃), 3.11 (2H, t, J = 7.2 Hz, *CH*₂*Ar*); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 199.4 (*CO*), 141.4 (*C-3*), 138.4 (*C-1'*), 137.0 (*C-1*), 133.9 (*C-5*), 128.6 (*Ar*), 128.6 (*Ar*), 128.5 (*Ar*), 128.5 (*Ar*), 126.2 (*C-4*), 125.3 (*C-2*), 40.6 (*OCH*₃), 30.2 (*COCH*₂), 21.4 (*CH*₂*Ar*); IR (ν_{max} , neat, cm^{-1}): 3018, 2941, 1681, 1595, 1291, 1190, 1045, 997; HRMS (ESI+) m/z : Calculated for $C_{16}H_{17}O_2$ ($M+H^+$): 241.1229, found: 241.1226. Spectroscopic data consistent with literature values.¹⁰³

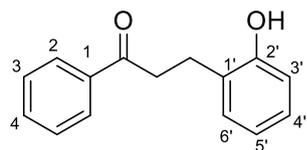
1-Phenyl-3-(4-bromophenyl)-1-propanone (**197**)



Following general procedure D, **197** was prepared from 4-bromobenzyl alcohol (211 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **197** as a white solid (153 mg, 531 μ mol, 47%).

R_f = 0.87 (Hex:EtOAc 90:10); mp 70.8-71.9 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.97 (2H, d, J = 7.2 Hz, H -2), 7.59 (1H, t, J = 7.6 Hz, H -4), 7.48 (2H, ap t, J = 7.6 Hz, H -3), 7.43 (2H, d, J = 7.6 Hz, H -3'), 7.16 (2H, d, J = 8.0 Hz, H -2'), 3.31 (2H, t, J = 8.0 Hz, COCH_2), 3.06 (2H, t, J = 8.0 Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 198.8 (CO), 140.3 (C-1'), 136.8 (C-1), 133.2 (C-4), 131.6 (C-3), 130.3 (C-2), 128.7 (C-3'), 128.0 (C-2'), 119.2 (C-4'), 40.1 (COCH_2), 29.5 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{13}^{79}\text{BrONa}$ ($\text{M}+\text{Na}^+$): 311.0048, found: 311.0042. Spectroscopic data consistent with literature values.¹⁰⁰

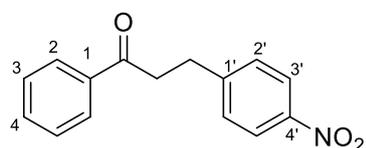
1-Phenyl-3-(2-hydroxyphenyl)-1-propanone (**198**)



Following general procedure D, **198** was prepared from 2-hydroxybenzyl alcohol (140 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **198** as a yellow oil (18 mg, 79 μ mol, 7%).

R_f = 0.54 (Hex:EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.96 (2H, d, J = 7.6 Hz, H -2), 7.57 (2H, ap t, J = 7.6 Hz, H -4), 7.51 (2H, ap t, J = 7.6 Hz, H -3), 7.16-7.08 (2H, m, H -4', 6'), 6.91-6.85 (2H, m, H -3', 5'), 3.40 (2H, t, J = 6.4 Hz, COCH_2) 3.01 (2H, t, J = 6.4 Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 201.3 (CO), 152.4 (C-2'), 135.9 (C-1), 133.4 (C-4), 131.0 (C-6') 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 127.7 (Ar), 120.1 (C-5'), 117.6 (C-3'), 40.2 (COCH_2), 26.3 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}^+$): 227.1072, found: 227.1073. Spectroscopic data consistent with literature values.¹⁰⁴

1-Phenyl-3-(4-nitrophenyl)-1-propanone (**199**)

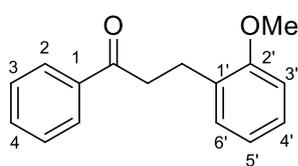


Following general procedure D, **199** was prepared from 4-nitrobenzyl alcohol (173 mg, 1.13 mmol) and acetophenone

(132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **199** as a yellow solid (29 mg, 113 μ mol, 10%).

R_f = 0.48; mp 106.5-107.3 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 8.10 (2H, d, J = 8.8 Hz, H -3'), 7.95-7.83 (2H, m, H -2), 7.55 (1H, t, J = 7.2 Hz, H -4) 7.45-7.39 (4H, m, H -3,2'), 3.33 (2H, t, J = 7.6 Hz, COCH_2), 3.14 (2H, t, J = 7.6 Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 199.1 (CO), 148.9 (C-1'), 146.1 (C-4'), 135.7 (C-1), 132.8 (C-4), 130.1 (C-2'), 128.6 (Ar), 128.1 (Ar), 123.5 (C-3'), 40.1 (COCH_2), 30.2 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{14}\text{NO}_3$ ($\text{M}+\text{H}^+$): 256.0978, found: 256.0974. Spectroscopic data consistent with literature values.¹⁰¹

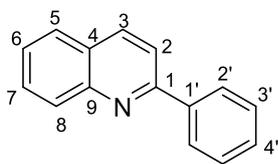
1-Phenyl-3-(2-methoxyphenyl)-1-propanone (200)



Following general procedure D, **200** was prepared from 2-methoxybenzyl alcohol (118 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **200** as a colourless oil (206 mg, 859 μ mol, 76%).

R_f = 0.91 (Hex;EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 8.01 (2H, d, J = 7.2 Hz, H -2), 7.68 (1H, t, J = 7.6 Hz, H -4), 7.48 (2H, ap t, J = 7.2 Hz, H -3), 7.27-7.21 (2H, m, H -4', 6'), 6.96-6.86 (2H, m, H -3', 5'), 3.87 (3H, s, OCH_3), 3.31 (2H, t, J = 8.4 Hz, COCH_2), 3.09 (2H, t, J = 8.4 Hz, CH_2Ar); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 200.0 (CO), 157.6 (C-2'), 137.0 (C-1), 133.0 (C-4), 130.2 (C-1'), 129.6 (C-6'), 128.6 (Ar), 128.2 (Ar), 127.6 (C-4), 120.6 (C-5'), 110.3 (C-3'), 55.2 (OCH_3), 39.0 (COCH_2), 25.8 (CH_2Ar); IR (ν_{max} , neat, cm^{-1}): 3060, 2941, 1698, 1592, 1259, 1039, 731; HRMS (ESI+) m/z : Calculated for $\text{C}_{16}\text{H}_{16}\text{O}_2\text{Na}$: 263.1048, found: 263.1045. Spectroscopic data consistent with literature values.¹⁰⁰

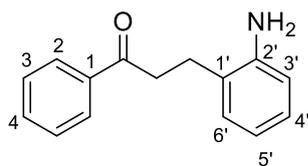
2-Phenylquinoline (202)



Following general procedure E, **202** was prepared from 2-aminobenzyl alcohol (139 mg, 1.13 mmol) and acetophenone (132 mg, 1.13 mmol). Purification by flash chromatography eluting 0-20% EtOAc in hexane gave **202** as a white solid (114 mg, 554 μ mol, 49%).

$R_f = 0.32$ (90:10 Hex:EtOAc); mp 84.7-85.6 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 8.27-8.20 (4H, m, Ar), 7.87 (1H, d, $J = 8.4$ Hz, Ar), 7.83 (1H, d, $J = 8.0$ Hz, Ar), 7.78 (1H, t, $J = 7.2$ Hz, Ar), 7.58-7.49 (4H, m, Ar); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 157.3 (C-1), 148.7 (C-9), 139.1 (Ar), 136.5 (Ar), 129.6 (Ar), 129.5 (Ar), 129.1 (Ar), 128.7 (Ar), 127.3 (Ar), 127.2 (Ar), 127.0 (Ar), 126.1 (Ar), 118.8 C-2); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{12}\text{N}$ ($\text{M}+\text{H}^+$): 206.0970, found: 206.0967. Spectroscopic data consistent with literature values.¹⁰⁵

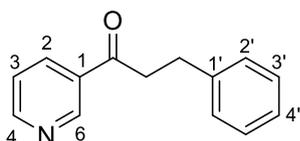
1-Phenyl-3-(2-aminophenyl)-1-propanone (203)



Following general procedure D, **203** was prepared from 2-aminobenzyl alcohol (139 mg, 1.13 mmol) and acetophenone (132 mg, 1.13 mmol). Purification by flash chromatography eluting with 0-40% EtOAc in hexane gave **203** as colourless oil (237 mg, 1.06 mmol, 93%).

$R_f = 0.18$ (90:10 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 8.10 (2H, d, $J = 7.2$ Hz, H-2), 7.60 (1H, ap t, $J = 7.2$ Hz, H-3), 7.37 (2H, ap t, $J = 7.2$ Hz, H-3) 7.37-7.30 (4H, m, Ar), 3.35 (2H, t, $J = 8.0$ Hz, COCH_2), 3.12 (2H, t, $J = 8.0$ Hz, CH_2Ar); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 199.7 (CO), 153.1 (C-2'), 136.7 (C-1), 133.5 (C-4), 132.1 (C-6'), 129.4 (C-4'), 128.3 (Ar), 128.0 (Ar), 127.0 (C-1'), 123.9 (C-5'), 123.1 (C-3), 39.9 (COCH_2), 24.1 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{15}\text{H}_{15}\text{N}$ ($\text{M}+\text{H}^+$): 248.1051, found: 248.1047.

3-Phenyl-1-(3-pyridinyl)-1-propanone (204)

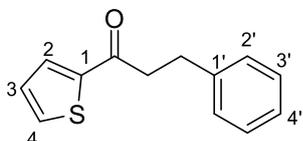


Following general procedure D, **204** was prepared from benzyl alcohol (118 μl , 1.13 mmol) and 3-acetylpyridine (124 μl , 1.13 mmol). Purification by flash chromatography eluting with 0-30% EtOAc in hexane gave **204** as a colourless oil (112 mg, 531 μmol , 47%).

$R_f = 0.23$ (Hex:EtOAc 90:10); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 9.10 (1H, br s, H-6), 8.71 (1H, br s, 1H, H-4), 8.17 (1H, d, $J = 7.6$ Hz, H-2), 7.38-7.35 (1H, m, H-3), 7.26-7.13 (5H, m, Ar), 3.26 (2H, t, $J = 8.0$ Hz, COCH_2), 3.02 (2H, t, $J = 8.0$ Hz, CH_2Ar); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 196.9 (CO), 152.8 (C-4), 149.2 (C-6), 140.2 (C-1'), 134.8 (C-2), 131.7 (C-1), 128.6 (Ar), 128.2 (Ar), 126.7 (C-4'), 123.1 (C-3), 40.1 (COCH_2), 29.2 (CH_2Ar); HRMS (ESI+)

m/z : Calculated for $C_{14}H_{14}NO$ ($M+H^+$): 212.1075, found: 212.1069. Spectroscopic data consistent with literature values.¹⁰⁶

3-Phenyl-1-(2-thienyl)propan-1-one (205)

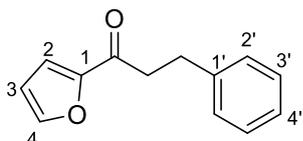


Following general procedure D, **205** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 2-acetylthiophene (122 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-30%

EtOAc in hexane gave **205** as a colourless oil (129 mg, 599 μ mol, 53%).

R_f = 0.28 (Hex:EtOAc 90:10); 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.80 (1H, d, J = 3.6 Hz, $H-2$), 7.68 (1H, d, J = 3.6 Hz, $H-4$), 7.34-7.18 (6H, m, Ar), 3.02 (2H, t, J = 7.6 Hz, $COCH_3$), 2.92 (2H, t, J = 7.6 Hz, CH_2Ar); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 191.8 (CO), 144.5 (C-1), 141.3 (C-1'), 133.2 (C-2), 131.5 (C-4), 128.6 (C-2'), 128.4 (C-3'), 127.9 (C-3), 126.0 (C-4'), 40.9 ($COCH_2$), 30.1 (CH_2CO); HRMS (ESI+) m/z : Calculated for $C_{13}H_{13}OS$ ($M+H^+$): 217.0687, found: 217.0690. Spectroscopic data consistent with literature values.¹⁰⁷

1-(Furan-2-yl)-3-phenylpropan-1-one (206)

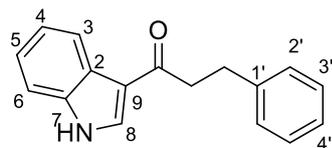


Following general procedure D, **206** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 2-acetylfuran (63 μ l, 1.13 mmol).

Purification by flash chromatography eluting with 0-30% EtOAc in hexane gave **206** as a colourless oil (154 mg, 768 μ mol, 68%).

R_f = 0.32 (Hex:EtOAc 90:10); 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.59 (1H, d, J = 8.0 Hz, $H-4$), 7.31 (2H, ap t, J = 8.0 Hz, Ar), 7.27-7.10 (4H, m, Ar), 6.55 (1H, dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, Ar), 3.19 (2H, t, J = 7.2 Hz, $COCH_2$), 2.98 (2H, t, J = 7.2 Hz, CH_2Ar); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 187.1 (CO), 151.8 (C-1), 146.1 (C-4), 141.7 (C-1'), 128.6 (Ar), 128.3 (Ar), 126.1 (C-4'), 116.3 (C-2), 111.9 (C-3), 40.9 ($COCH_2$), 30.1 (CH_2CO); HRMS (ESI+) m/z : Calculated for $C_{13}H_{13}O$ ($M+H^+$): 201.0916, found: 201.0911. Spectroscopic data consistent with literature values.¹⁰⁸

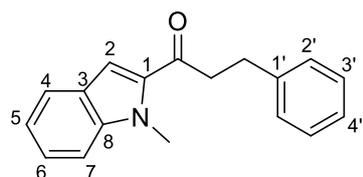
1-(1*H*-Indol-3-yl)-3-phenylpropan-1-one (**207**)



Following general procedure D, **207** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and 3-acetylindole (180 mg, 1.13 mmol). Purification by flash chromatography eluting 0-40% EtOAc in hexane gave **207** as a yellow solid (25 mg, 102 μ mol, 9%).

R_f = 0.19 (Hex:EtOAc 90:10); mp 160.8.1-161.5 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 8.43 (1H, ap d, J = 3.2 Hz, H -5), 8.20-8.16 (1H, m, H -6), 7.44-7.40 (1H, m, Ar), 7.31-7.20 (4H, m, Ar), 7.20-7.10 (3H, m, Ar), 3.18 (2H, t, J = 7.6 Hz, COCH_2), 3.03 (2H, t, J = 7.6 Hz, CH_2Ar), 1 NH signal not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 193.1 (CO), 141.5 (C -7), 136.2 (C -1'), 133.5 (C -3'), 128.4 (Ar), 128.2 (Ar), 125.6 (Ar), 125.3 (Ar), 122.5 (Ar), 121.6 (Ar), 121.2 (Ar), 116.1 (C -3), 112.1 (C -6), 40.4 (COCH_2), 30.6 (CH_2CO); HRMS (ESI+) m/z : Calculated for $\text{C}_{17}\text{H}_{16}\text{NO}$ ($M+H^+$): 250.1232, found: 250.1236. Spectroscopic data consistent with literature values.¹⁰⁹

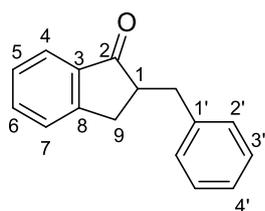
1-(1-Methyl-1*H*-indol-3-yl)-3-phenylpropan-1-one (**208**)



Following general procedure D, **208** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and *N*-methyl-3-acetylindole (196 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-20 EtOAc in hexane gave **208** as an off-white solid (285 mg, 1.08 mmol, 96%).

R_f = 0.32 (90:10 Hex:EtOAc); mp 58.1-58.6 $^{\circ}$ C; ^1H NMR (500 MHz, CDCl_3 , δ /ppm): 8.39 (1H, m, Ar), 7.28-7.13 (9H, m, Ar), 3.83 (3H, s, NCH_3), 3.23-3.08 (4H, m, 2CH_2); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 195.2 (CO), 140.9 (C -1'), 136.8 (C -8), 134.1 (C -1), 128.5 (Ar), 128.4 (Ar), 126.1 (Ar), 126.0 (Ar), 123.1 (C -4), 122.7 (Ar), 122.5 (Ar), 116.3 (C -7), 108.9 (C -2), 41.8 (COCH_2), 33.5 (CH_3), 30.7 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{18}\text{H}_{17}\text{NNaO}$ ($M+\text{Na}^+$): 286.1208, found: 286.1205. Spectroscopic data consistent with literature values.¹¹⁰

2-Benzyl-1-indanone (209)

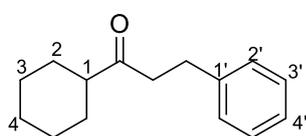


Following general procedure D, **209** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and indanone (149 mg, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **209** as a colourless oil (198 mg, 893 μ mol, 79%).

Following general procedure E, **209** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and indanone (149 mg, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **209** as a colourless oil (136 mg, 610 μ mol, 54%).

R_f = 0.18 (Hex:EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.71 (1H, d, J = 7.6 Hz, H -4), 7.50 (1H, ap td, J_1 = 1.2 Hz, J_2 = 7.6 Hz, H -6), 7.34-7.13 (7H, m, Ar), 3.33 (1H, dd, J_1 = 4.0 Hz, J_2 = 13.6, CH), 3.10 (1H, ap dd, J_1 = 7.6 Hz, 16.8 Hz, H -9), 2.96-2.90 (1H, m, H -9), 2.79 (1H, dd, J_1 = 4.0 Hz, J_2 = 16.8 Hz, $CH_2\text{Ph}$), 2.60 (1H, dd, J_1 = 10.4 Hz, J_2 = 14.0 Hz, $CH_2\text{Ph}$); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 207.4 (CO), 153.4 (C -8), 139.2 (C -1'), 136.7 (C -3), 135.0 (C -6), 128.9 (Ar), 128.5 (Ar), 127.5 (C -5), 126.2 (C -4'), 126.1 (C -7), 124.0 (C -4), 48.8 (CH), 36.9 ($CH_2\text{Ph}$), 32.7 (C -9); IR (ν_{max} , neat, cm^{-1}): 3062, 3027, 1708, 1609, 1496, 1328, 1290, 1181; HRMS (ESI+) m/z : Calculated for $\text{C}_{16}\text{H}_{15}\text{O}$ ($\text{M}+\text{H}^+$): 223.1123, found: 223.1119. Spectroscopic data consistent with literature values.¹¹¹

1-(Cyclohexyl)-3-phenyl-1-propanone (210)



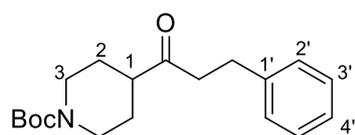
Following general procedure D, **210** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and cyclohexyl methyl ketone (156 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **210** as a yellow oil (137 mg, 633 μ mol, 56%).

Following general procedure F, **210** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and cyclohexyl methyl ketone (156 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **210** as a yellow oil (37 mg, 170 μ mol, 15%).

R_f = 0.82 (Hex:EtOAc 90:10); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.33-7.28 (3H, m Ar), 7.24-7.20 (2H, m, Ar), 2.92 (2H, t, J = 7.6 Hz, COCH_2), 2.79 (2H, t, J = 7.6 Hz, CH_2Ar), 2.48 (1H, tt, J_1 = 3.2 Hz, J_2 = 10.8 Hz, H -4), 1.86-1.76 (5H, m, Cy), 1.40-1.20 (5H, m, Cy); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 213.2 (CO), 141.4 (C -1'), 128.5 (C -3'), 128.3 (C -2'), 126.0

(C-4'), 51.0 (C-1), 42.3 (COCH₂), 29.6 (CH₂Ar), 28.4 (C-2), 25.9 (C-4), 25.7 (C-3); HRMS (ESI+) *m/z*: Calculated for C₁₅H₂₁O (M+H⁺): 217.1592, found: 217.1548. Spectroscopic data consistent with literature values.¹¹²

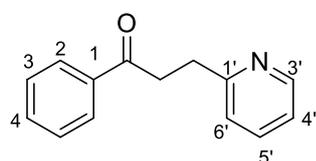
***tert*-Butyl 4-(3-phenylpropanoyl)piperidine-1-carboxylate (211)**



Following general procedure D, **211** was prepared from benzyl alcohol (118 μ l, 1.13 mmol) and *N*-Boc-4-acetylpiperidine (257 mg, 1.13 mmol). Purification by flash chromatography eluting with 0-30% EtOAc in hexane gave **211** as a white solid (186 mg, 588 μ mol, 52%).

R_f = 0.65 (90:10 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7-19.7.11 (2H, m, *H*-2), 7.09-7.04 (3H, m, *Ar*), 4.02-3.96 (2H, m, CH₂), 2.93-2.85 (2H, m, CH₂), 2.80-2.73 (4H, m, CH₂), 2.42-2.35 (1H, m, CH₂), 1.78-1.75 (2H, m, CH₂), 1.59-1.48 (2H, m, CH₂) 1.43 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 205.3 (CO), 153.9 (NCOO), 140.8 (C-1'), 128.5 (*Ar*), 128.2 (*Ar*), 125.9 (C-4'), 80.4 (C(CH₃)₃), 49.5 (C-1), 43.1 (CH₂), 42.0 (CH₂), 30.0 (CH₂), 28.3 (CH₂), 26.2 (C(CH₃)₃); IR (ν_{\max} , neat, cm⁻¹): 1696, 1441, 1408, 1352, 1214, 1146, 1172, 704; HRMS (ESI+) *m/z*: Calculated for C₁₉H₂₈NO₃ (M+H⁺): 318.2069, found: 318.2063. Spectroscopic data consistent with literature values.¹¹³

1-Phenyl-3-(pyridyl)-1-propanone (212)

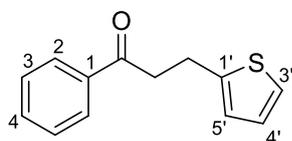


Following general procedure D, **212** was prepared from 2-pyridinemethanol (109 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **212** as a yellow oil (24 mg, 114 μ mol, 10%).

R_f = 0.36 (90:10 Hex:EtOAc); ¹H NMR 400 MHz, CDCl₃, δ /ppm): 8.49 (2H, d, *J* = 4.4 Hz, *H*-2), 8.03 (2H, d, *J* = 7.2 Hz, *H*-3), 7.54-7.40 (3H, m, *Ar*), 7.28 (1H, d, *J* = 8.0 Hz, *H*-6'), 7.10 (1H, ap t, *J* = 6.4 Hz, *H*-4'), 3.49 (2H, t, *J* = 7.2 Hz, COCH₂), 3.27 (2H, t, *J* = 8.0 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 199.4 (CO), 160.2 (C-1'), 148.9 (C-3'), 136.8 (*Ar*), 136.5 (*Ar*), 133.5 (C-4), 128.1 (*Ar*), 127.8 (*Ar*), 123.1 (C-6'), 20.9 (C-4'), 37.6 (COCH₃), 31.0 (CH₂Ar); IR (ν_{\max} , neat, cm⁻¹): 3020, 2939, 2861, 1670, 1602, 1502, 1423, 1032; HRMS (ESI+)

m/z : Calculated for $C_{14}H_{14}NO$ ($M+H^+$): 212.1075, found: 212.1067. Spectroscopic data consistent with literature values.¹¹²

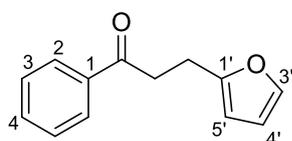
1-Phenyl-3-(thiophen-2-yl)propan-1-one (213)



Following general procedure D, **213** was prepared from 2-thiophenemethanol (129 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **213** as a white solid (173 mg, 802 μ mol, 71%).

R_f = 0.54 (90:10 Hex:EtOAc); mp 45.4-46.0 °C; 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.82 (2H, d, J = 7.6 Hz, H -2), 7.41 (1H, t, J = 7.6 Hz, H -4), 7.30 (2H, ap t, J = 7.6 Hz, H -3), 6.98 (1H, d, J = 5.2 Hz, H -3'), 6.78 (1H, ap t, J = 4.8 Hz, H -4'), 6.72 (1H, ap br s, H -5') 3.22-3.13 (4H, m, $2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 197.9 (CO), 143.7 (C -1'), 136.4 (C -1), 133.0 (C -4), 128.6 (Ar), 127.1 (Ar), 126.3 (C -4'), 124.4 (C -3'), 123.1 (C -5'), 40.2 (COCH₂), 24.1 (CH_2Ar); IR (ν_{max} , neat, cm^{-1}): 3111, 2923, 1972, 1685, 1591, 1442, 1361, 1207; HRMS (ESI+) m/z : Calculated for $C_{13}H_{13}OS$ ($M+H^+$): 217.0687, found: 217.0689. Spectroscopic data consistent with literature values.¹¹⁴

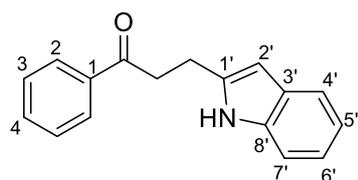
1-Phenyl-3-(furan-2-yl)propan-1-one (214)



Following general procedure D, **214** was prepared from 2-furfuryl alcohol (98 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **214** as a white solid (138 mg, 689 μ mol, 61%).

R_f = 0.43 (90:10 Hex:EtOAc); mp 38.6-39.7 °C; 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 8.01 (2H, d, J = 7.6 Hz, H -2), 7.60 (1H, t, J = 6.0 Hz, H -4), 7.50 (2H, ap t, J = 7.6 Hz, H -3), 7.35 (1H, ap br s, H -3'), 6.32 (1H, ap br s, H -4'), 6.09 (1H, ap br s, H -5'), 3.37 (2H, t, J = 7.6 Hz, COCH₂), 3.13 (2H, d, J = 7.6 Hz, CH_2Ar); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 198.8 (CO), 154.6 (C -1'), 141.1 (C -3'), 136.8 (C -1), 133.1 (C -4), 128.4 (Ar), 128.3 (Ar), 110.1 (C -4'), 104.9 (C -5'), 36.5 (COCH₃), 22.3 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $C_{13}H_{13}O_2$ ($M+H^+$): 201.0916, found: 201.0911. Spectroscopic data consistent with literature values.¹¹⁵

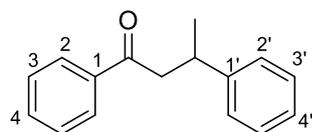
3-(1*H*-Indol-2-yl)-1-phenylpropan-1-one (**215**)



Following general procedure D, **215** was prepared from 1*H*-indole-2-methanol (166 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-40% EtOAc in hexane gave **215** as a white solid (26 mg, 106 μ mol, 12%).

R_f = 0.31 (80:20 Hex:EtOAc); mp 128.9-130.0 °C; ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.98 (2H, d, J = 7.6 Hz, H -2), 7.83 (1H, br s, NH), 7.55 (1H, t, J = 6.4 Hz, H -4), 7.51-7.46 (3H, m, Ar), 7.30 (1H, d, J = 7.6 Hz, H -4'), 7.14-7.02 (2H, m, Ar), 6.31-6.23 (1H, m, Ar), 3.42 (2H, t, J = 7.6 Hz, COCH_2), 3.21 (2H, t, J = 7.6 Hz, CH_2Ar), 1 NH signal not observed; ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 198.0 (CO), 137.2 (C-1), 136.4 (C-8), 132.8 (C-4), 128.6 (Ar), 128.5 (Ar), 127.6 (Ar), 127.1 (Ar), 121.4 (Ar), 121.25 (Ar), 121.22 (Ar), 112.7 (C-7), 103.9 (C-2) 38.4 (COCH_3), 30.4 (CH_2Ar); IR (ν_{max} , neat, cm^{-1}): 3310, 2918, 1669, 1572, 1456, 1271, 1195, 1085; HRMS (ESI+) m/z : Calculated for $\text{C}_{17}\text{H}_{15}\text{NNaO}$ ($\text{M}+\text{Na}^+$): 272.1051, found 272.1049.

1,3-Diphenylbutane-1-one (**216**)



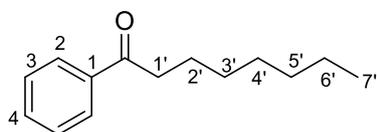
Following general procedure D, **216** was prepared from 1-phenylethanol (136 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **216** as a colourless oil (172 mg, 768 μ mol, 68%).

Following general procedure F, **216** was prepared from 1-phenylethanol (136 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting 0-10% EtOAc in hexane gave **216** as a colourless oil (43 mg, 192 μ mol, 17%).

R_f = 0.91 (90:10 Hex:EtOAc); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.90 (2H, d, J = 7.6 Hz, H -2), 7.49 (1H, t, J = 7.2 Hz, H -4), 7.41 (2H, t, J = 7.6 Hz, Ar), 7.31-7.20 (5H, m, Ar), 3.56-3.48 (1H, m, CH_3CH), 3.37-3.19 (2H, m, COCH_2), 1.37 (3H, d, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 198.9 (CO), 145.9 (C-1'), 138.1 (C-1), 133.0 (C-4), 128.7 (Ar), 128.6 (Ar), 127.9 (Ar), 126.5 (Ar), 126.1 (Ar), 46.9 (CH_2), 33.1 (CH), 20.9 (CH_3); IR (ν_{max} , neat, cm^{-1}): 3021, 2970, 2913, 1690, 1605, 1449, 1270, 1172; HRMS (ESI+) m/z : Calculated

for $C_{16}H_{17}O$ ($M+H^+$): 225.1279, found: 225.1274. Spectroscopic data consistent with literature values.¹¹⁶

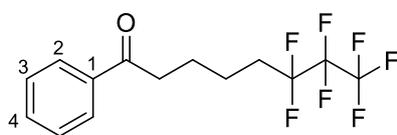
1-Phenyl-1-octanone (**217**)



Following general procedure D, **217** was prepared from 1-hexanol (142 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0–10% EtOAc in hexane gave **217** as a colourless oil (178 mg, 870 μ mol, 77%).

R_f = 0.86; 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.90 (2H, d, J = 7.2 Hz, $H-2$), 7.51 (1H, t, J = 7.2 Hz, $H-4$), 7.42 (2H, ap t, J = 7.2 Hz, $H-3$) 3.01 (2H, t, J = 7.6 Hz, $H-1'$), 1.78–1.71 (2H, m, CH_2), 1.40–1.25 (8H, m, $4CH_2$), 0.86 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 200.1 (CO), 136.1 (C-1), 133.0 (C-4), 128.6 (Ar), 128.1 (Ar), 39.0 (C-1'), 32.3 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS (ESI+) m/z : Calculated for $C_{14}H_{22}O$ ($M+H^+$): 205.1592, found: 205.1589. Spectroscopic data consistent with literature values.¹¹⁷

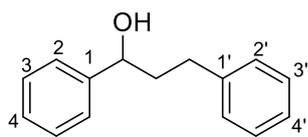
1-Phenyl-6,6,7,7,8,8,8-heptafluorooctan-1-one (**218**)



Following general procedure D, **218** was prepared from 4,4,5,5,6,6,6-heptafluorohexan-1-ol (258 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0–10% EtOAc in hexane gave **218** as a colourless oil (164 mg, 497 μ mol, 44%).

R_f = 0.85; 1H NMR (400 MHz, $CDCl_3$, δ /ppm): 7.92 (2H, d, J = 7.2 Hz, $H-2$), 7.48 (1H, t, J = 7.2 Hz, $H-4$), 7.40 (2H, ap t, J = 7.2 Hz, $H-3$) 3.01 (2H, t, J = 7.6 Hz, CO CH_2), 1.78–1.71 (2H, m, CH_2), 1.60–1.41 (4H, m, $2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 199.7 (CO), 135.7 (C-1), 133.4 (C-4), 128.5 (Ar), 128.4 (Ar), 39.2 (CO CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 23.8 (CF_2), 21.7 (CF_2), 11.9 (CF_3); HRMS (ESI+) m/z : Calculated for $C_{14}H_{14}F_7O$ ($M+H^+$): 331.0933, found: 331.0938.

1,3-Diphenylpropan-1-ol (**219**)



To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added benzyl alcohol (118 μl , 1.13 mmol) and acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel, before addition of IPA (1.0 ml) and heating at 80 $^{\circ}\text{C}$ for a further 24 h. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **219** as a colourless oil (132 mg, 622 μmol , 55%).

To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added benzyl alcohol (118 μl , 1.13 mmol) and acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel, before addition of IPA (1.0 ml) and heating at reflux for a further 24 h. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **219** as a colourless oil (213 mg, 1.01 mmol, 89%).

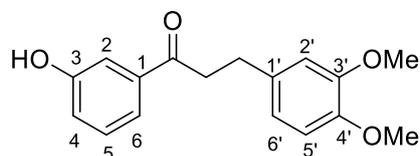
To a stirred suspension of $[\text{Cp}^*\text{IrCl}_2]_2$ (8.4 mg, 11.3 μmol) in toluene (1.0 ml) was added benzyl alcohol (118 μl , 1.13 mmol) and acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel, before addition of IPA (1.0 ml) and heating at reflux for a further 24 h. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **219** as a colourless oil (221 mg, 1.04 mmol, 92%).

To a stirred suspension of benzyl alcohol (118 μl , 1.13 mmol) in toluene (1.0 ml) was added acetophenone (132 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel, before addition of IPA (1.0 ml) and heating at reflux for a further 24 h. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **219** as a colourless oil (96 mg, 452 μmol , 40%).

$R_f = 0.68$ (90:10 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 7.27-7.24 (4H, m, *Ar*), 7.21-7.17 (3H, m, *Ar*), 7.11-7.08 (3H, m, *Ar*), 4.59 (1H, dd, $J_1 = 5.6$ Hz, $J_2 = 8.0$ Hz, *CHOH*), 2.70 (2H, m, *CHOHCH}_2*), 2.09-1.89 (2H, m, *CH}_2\text{Ar}*); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 144.2 (*C-1*), 141.3 (*C-1'*), 128.3 (*Ar*), 128.2 (*Ar*), 128.2 (*Ar*), 127.6 (*Ar*), 126.8 (*Ar*), 126.0 (*Ar*), 73.2 (*CHOH*), 40.4 (*CHOHCH}_2*), 32.4 (*CH}_2\text{Ar}*); HRMS (ESI+) m/z : Calculated for

C₁₅H₁₆NaO (M+Na⁺): 235.1099, found: 235.1095. Spectroscopic data consistent with literature values.¹¹⁸

1-(3-Hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-1-propanone (223)

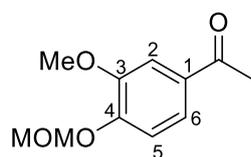


Following general procedure D, **223** was prepared from 3,4-dimethoxybenzyl alcohol (164 μ l, 1.13 mmol) and 3'-hydroxyacetophenone (154 mg, 1.13 mmol). Purification by flash chromatography eluting 0-20% EtOAc in hexane gave

223 as a white solid (220 mg, 768 μ mol, 68%).

R_f = 0.57 (90:10 Hex:EtOAc); mp 120.3-121.0 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.58 (1H, s, *H*-2), 7.54 (1H, s, *H*-2'), 7.46 (1H, d, *J* = 7.6 Hz, *H*-6), 7.27 (1H, ap t, *J* = 7.6 Hz, *H*-5), 7.05 (1H, d, *J* = 8.4 Hz, *H*-4), 6.80 (2H, ap br s, *H*-5', 6'), 3.80 (6H, s, 2CH₃), 3.26 (2H, t, *J* = 7.2 Hz, COCH₂), 2.99 (2H, t, *J* = 7.2 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 199.8 (CO), 155.4 (*C*-3), 147.3 (*C*-4'), 146.5 (*C*-3'), 137.2 (*C*-1), 133.2 (*C*-1'), 129.5 (*C*-5), 122.3 (*C*-4), 120.1 (*C*-6'), 114.2 (*C*-6), 113.4 (*C*-2), 111.8 (*C*-2'), 111.0 (*C*-5), 55.8 (OCH₃), 55.6 (OCH₃), 40.7 (COCH₃), 29.1 (CH₂Ar); IR (ν_{\max} , neat, cm⁻¹): 3420, 2953, 1671, 1590, 1441, 1350, 1230, 1153; HRMS (ESI+) *m/z*: Calculated for C₁₇H₁₈O₄ (M+H⁺): 286.1205, found: 286.1201. Spectroscopic data consistent with literature values.¹¹⁹

1-[3-Methoxy-4-(methoxymethoxy)phenyl]-ethanone (235)



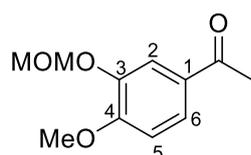
Prepared via the method reported in patent WO2018/11376 A1, 2018¹²⁰.

To a stirred mixture of 3'-methoxy-4'-hydroxyacetophenone (1.00 g, 6.02 mmol) and K₂CO₃ (2.50 g, 18.1 mmol) in MeCN (1.2 ml) was added chloromethyl methyl ether (0.9 ml, 12 mmol). The reaction was stirred at RT for 16 h and solvent was removed *in vacuo*. The residue was diluted with H₂O (20 ml) and EtOAc (20 ml), and the phases were separated. The aqueous was washed with further EtOAc (3 x 20 ml), the organics were combined and dried over anhydrous MgSO₄, filtered and concentrated under vacuum to give **235** as a white solid (999 mg, 4.76 mmol, 79%).

mp 51.8-52.7 °C; ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.73 (1H, ap d, *J* = 2.4 Hz, *H*-2), 7.63 (1H, ap dd, *J*₁ = 2.0 Hz, *J*₂ = 8.4 Hz, *H*-6) 6.90 (1H, ap d, *J* = 8.4 Hz, *H*-5), 5.24 (2H, s, OCH₂O),

3.91 (3H, s, ArOCH₃), 3.49 (3H, s, OCOCH₃), 2.52 (3H, s, COCH₃); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 196.6 (CO), 154.0 (C-3), 146.2 (C-4), 130.5 (C-1), 124.3 (C-6), 115.8 (C-5), 110.7 (C-2), 95.5 (CH₂), 56.4 (OCH₃), 56.1 (OCH₃), 26.3 (COCH₃); IR (ν_{max}, neat, cm⁻¹): 2959, 1667, 1585, 1503, 1471, 1274, 1127, 811; HRMS (ESI+) *m/z*: Calculated for C₁₁H₁₄NaO (M+Na⁺): 233.0790, found: 233.0793. Spectroscopic data consistent with literature values.¹²¹

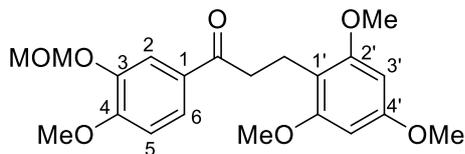
1-[3-(Methoxymethoxy)-4-methoxyphenyl]-ethanone (**261**)



Prepared via a modified version of the method reported in patent WO2018/11376 A1, 2018.¹²⁰ To a stirred mixture of 3'-hydroxy-4'-methoxyacetophenone (1.00 g, 6.02 mmol) and K₂CO₃ (2.50 g, 18.06 mmol) in MeCN (1.2 ml) was added chloromethyl methyl ether (0.9 ml, 12.04 mmol). The reaction was stirred at RT for 16 h and solvent was removed *in vacuo*. The residue was diluted with H₂O (20 ml) and EtOAc (20 ml), and the phases were separated. The aqueous was washed with further EtOAc (3 x 20 ml), the organics were combined and dried over anhydrous MgSO₄, filtered and concentrated under vacuum to give **261** as a white solid (936 mg, 445 μmol, 74%).

mp 44.1-44.7 °C; ¹H NMR (400 MHz, CDCl₃, δ/ppm): 7.53 (1H, s, *H*-2), 7.52-7.50 (1H, m, *H*-6) 7.16 (1H, d, *J* = 8.4 Hz, *H*-5), 5.29 (2H, s, OCH₂O), 3.93 (3H, s, ArOCH₃), 3.50 (3H, s, OCOCH₃), 2.56 (3H, s, COCH₃); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 196.7 (CO), 154.8 (C-4), 149.6 (C-3), 131.6 (C-1), 123.0 (C-6), 114.4 (C-5), 110.6 (C-2), 95.0 (CH₂), 56.5 (OCH₃), 56.1 (OCH₃), 26.4 (COCH₃); IR (ν_{max}, neat, cm⁻¹): 2962, 1672, 1581, 1501, 1468, 1270, 1125, 809; HRMS (ESI+) *m/z*: Calculated for C₁₁H₁₄NaO (M+Na⁺): 233.0790, found: 233.0786. Spectroscopic data consistent with literature values.¹²¹

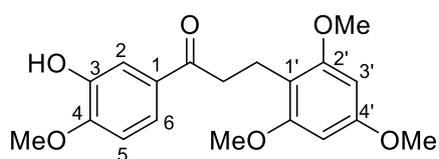
1-[3-(Methoxymethoxy)-4-methoxyphenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-one (**247**)



Following general procedure D, **247** was prepared from 2,4,6-trimethoxybenzyl alcohol (224 mg, 1.13 mmol) and **261** (238 mg, 1.13 mmol). Purification by flash chromatography eluting 10-40% EtOAc in hexane gave **247** as a white solid (331 mg, 848 μmol, 75%).

$R_f = 0.38$ (Hex:EtOAc 60:40); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 7.70 (1H, ap d, $J = 2.0$ Hz, $H-2$), 7.62 (1H, ap dd, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, $H-6$), 6.83 (1H, d, $J = 8.4$ Hz, $H-5$), 6.06 (2H, s, $H-3'$), 5.18 (2H, s, OCH_2O), 3.86 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.70 (6H, s, $\text{C}-2'\text{OCH}_3$), 3.44 (3H, s, OCOCH_3), 2.98-2.87 (4H, m, 2CH_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 199.3 (CO), 159.6 ($\text{C}-4'$), 158.4 ($\text{C}-2'$), 153.7 ($\text{C}-4$), 146.1 ($\text{C}-3$), 130.5 ($\text{C}-1$), 124.0 ($\text{C}-6$), 116.0 ($\text{C}-1'$), 110.6 (Ar), 110.0 (Ar), 95.5 (OCH_2O), 90.5 ($\text{C}-3'$), 56.4 (OCH_3), 56.1 (OCH_3), 55.6 (OCH_3), 55.4 (OCH_3), 38.4 (COCH_2), 18.5 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{21}\text{H}_{27}\text{O}_7$ ($\text{M}+\text{H}^+$): 391.1757, found: 391.1754.

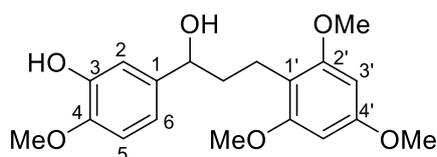
1-[3-Hydroxy-4-methoxyphenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-one (236)



Following the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **247** (69 mg, 177 μmol) in MeOH (5.0 ml) was added HCl (3 M, 1.0 ml).⁷⁶ The solution was heated to 65 $^\circ\text{C}$ for 3 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc (30 ml) and H_2O (30 ml), and the phases separated. The organic was washed with further H_2O (30 ml), brine (2 x 20 ml), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **236** as a white solid (58 mg, 161 μmol , 91%).

$R_f = 0.32$ (Hex:EtOAc 60:40); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 7.55 (1H, ap d, $J = 2.0$ Hz, $H-2$), 7.51 (1H, ap dd, $J_1 = 2.0$ Hz, $J_2 = 8.5$ Hz, $H-6$), 6.80 (1H, d, $J = 8.5$ Hz, $H-5$), 6.06 (2H, s, $H-3'$), 3.88 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.72 (6H, s, 2OCH_3), 2.96-2.93 (2H, m, COCH_2), 2.91-2.87 (2H, m, CH_2Ar) 1 OH signal not observed; $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 199.6 (CO), 159.6 ($\text{C}-4'$), 158.8 ($\text{C}-2'$), 150.3 ($\text{C}-4$), 145.3 ($\text{C}-3$), 130.9 ($\text{C}-1$), 121.6 ($\text{C}-6$), 114.6 ($\text{C}-5$), 110.0 (Ar), 109.8 (Ar), 90.5 ($\text{C}-3'$), 56.0 (OCH_3), 55.6 (OCH_3), 55.4 (OCH_3), 38.6 (COCH_2), 18.6 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{19}\text{H}_{22}\text{NaO}_6$ ($\text{M}+\text{Na}^+$): 369.1314, found: 369.1311.

1-[3-Hydroxy-4-methoxyphenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-ol (**241**)

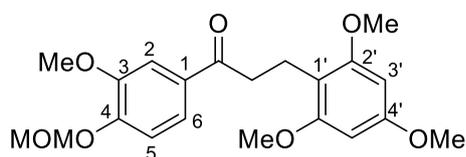


Following a modified version of the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **226** (29 mg, 81 μ mol) in MeOH (5.0 ml) at 0 °C was added NaBH₄ (29 mg, 767 mmol).⁷⁶ The reaction was left to stir for 1 h, before being

allowed to warm to RT and left to stir for a further 15 h. The reaction mixture was concentrated *in vacuo* and diluted with CHCl₃ (30 ml) and H₂O (30 ml). The phases were separated and the aqueous was extracted with further CHCl₃ (3 x 30 ml). The organic layers were combined and washed with further H₂O (2 x 50 ml) and brine (2 x 50 ml), before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **241** as a white solid (18 mg, 51 μ mol, 63%).

R_f = 0.22 (Hex:EtOAc 60:40); ¹H NMR (500 MHz, CDCl₃, δ /ppm): 6.89 (1H, s, *H*-2), 6.76 (1H, d, *J* = 8.0 Hz, *H*-6), 6.72 (1H, d, *J* = 8.0 Hz, *H*-5), 6.08 (2H, s, *H*-3'), 4.34 (1H, dd, *J*₁ = 4.0 Hz, *J*₂ = 9.0 Hz, *CHOH*), 3.79 (3H, s, OCH₃), 3.74 (9H, s, 3OCH₃), 2.66 (2H, t, *J* = 6.5 Hz, COCH₂), 1.83-1.78 (2H, m, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 159.4 (*C*-4'), 158.8 (*C*-2'), 145.6 (*Ar*), 145.4 (*Ar*), 138.2 (*C*-1), 117.4 (*C*-6), 112.4 (*C*-5), 110.4 (*Ar*), 110.0 (*Ar*), 90.7 (*C*-3'), 72.7 (*CHOH*), 56.0 (OCH₃), 55.8 (OCH₃), 55.4 (OCH₃), 38.5 (*CHOHCH*2), 18.7 (CH₂Ar); HRMS (ESI+) *m/z*: Calculated for C₁₉H₂₄NaO₆ (M+Na⁺): 371.1471, found: 371.1468.

1-[3-Methoxy-4-(methoxymethoxy)phenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-one (**236**)



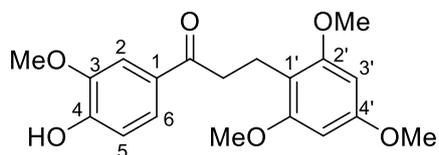
Following general procedure D, **236** was prepared from 2,4,6-trimethoxybenzyl alcohol (224 mg, 1.13 mmol) and **231** (238 mg, 1.13 mmol). Purification by flash

chromatography eluting with 20-40% EtOAc in hexane gave **236** as a white solid (344 mg, 882 μ mol, 78%).

R_f = 0.36 (Hex:EtOAc 60:40); ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.54-7.53 (1H, m, *H*-2), 7.50 (1H, ap br s, *H*-6), 7.08 (1H, d, *J* = 11.6 Hz, *H*-5), 6.06 (2H, s, (*H*-3')), 5.22 (2H, s, OCH₂O), 3.86 (3H, s, OCH₃), 3.73 (3H, s, OCH₃), 3.70 (6H, s, *C*-2'OCH₃), 3.44 (3H, s, OCOCH₃), 3.00-2.87 (4H, m, 2CH₂); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 199.1 (CO), 156.2 (*C*-4'), 155.8 (*C*-

2'), 153.1 (C-3), 145.7 (C-4), 129.8 (C-1), 124.5 (C-6), 115.6 (C-1'), 110.1 (Ar), 109.8 (Ar), 95.5 (OCH₂O), 90.8 (C-3'), 56.1 (OCH₃), 56.0 (OCH₃), 55.5 (OCH₃), 55.4 (OCH₃), 38.1 (COCH₂), 18.5 (CH₂Ar); HRMS (ESI⁺) *m/z*: Calculated for C₂₁H₂₇O₇ (M+H⁺): 391.1757, found: 391.1752.

1-[3-Methoxy-4-hydroxyphenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-one (229)

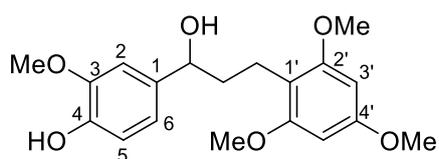


Following the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **236** (69 mg, 177 μmol) in MeOH (5.0 ml) was added HCl (3 M, 1.0 ml).⁷⁶ The solution was heated to 65 °C for 3 h before being concentrated *in vacuo*. The

residue was dissolved in EtOAc (30 ml) and H₂O (30 ml), and the phases separated. The organic was washed with further H₂O (30 ml), brine (2 x 20 ml), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **229** as an off-white solid (47 mg, 135 μmol, 76%).

R_f = 0.29 (Hex:EtOAc 60:40); ¹H NMR (500 MHz, CDCl₃, δ/ppm): 7.52 (1H, ap dd, *J*₁ = 2.0 Hz, *J*₂ = 8.5 Hz *H*-2), 7.48 (1H, d, *J* = 2.0 Hz, *H*-6), 6.85 (1H, d, *J* = 8.5 Hz, *H*-5), 6.07 (2H, s, *H*-3'), 3.87 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 3.71 (6H, s, 2OCH₃), 2.98-2.88 (4H, m, 2CH₂), 1 OH signal not observed; ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 198.4 (CO), 158.6 (C-4'), 157.8 (C-2'), 149.0 (C-4), 145.4 (C-3), 129.1 (C-1), 122.6 (C-6), 112.7 (C-5), 109.0 (Ar), 108.9 (Ar), 89.5 (C-3'), 55.0 (OCH₃), 54.6 (OCH₃), 54.3 (OCH₃), 37.1 (COCH₂), 17.6 (CH₂Ar); HRMS (ESI⁺) *m/z*: Calculated for C₁₉H₂₂NaO₆ (M+Na⁺): 369.1314, found: 369.1315. Spectroscopic data consistent with literature values.⁷⁶

1-[3-Methoxy-4-hydroxyphenyl]-3-(2,4,6-trimethoxyphenyl)-propan-1-ol (242)



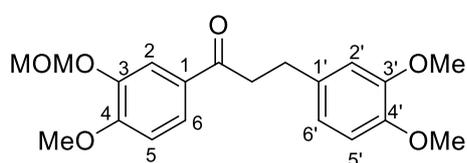
Following a modified version of the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **229** (23 mg, 63 μmol) in MeOH (5.0 ml) at 0 °C was added NaBH₄ (29 mg, 767 mmol).⁷⁶ The reaction was left to stir for 1 h, before being

allowed to warm to RT and left to stir for a further 15 h. The reaction mixture was concentrated *in vacuo* and diluted with CHCl₃ (30 ml) and H₂O (30 ml). The phases were separated and the aqueous was extracted with further CHCl₃ (3 x 30 ml). The organic layers

were combined and washed with further H₂O (2 x 50 ml) and brine (2 x 50 ml), before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **242** as a white solid (18 mg, 51 μmol, 83%).

R_f = 0.24 (Hex:EtOAc 60:40); ¹H NMR (500 MHz, CDCl₃, δ/ppm): 6.85 (1H, s, *H*-2), 6.73 (1H, d, *J* = 8.0 Hz, *H*-6), 6.69 (1H, d, *J* = 8.0 Hz, *H*-5), 6.07 (2H, s, *H*-3'), 4.34 (1H, dd, *J*₁ = 4.0 Hz, *J*₂ = 9.0 Hz, *CHOH*), 3.78 (3H, s, *OCH*₃), 3.76 (9H, s, 3*OCH*₃), 2.62 (2H, t, *J* = 6.5 Hz, *COCH*₂), 1.81-1.74 (2H, m, *CH*₂*Ar*); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 159.6 (*C*-4'), 158.5 (*C*-2'), 145.4 (*Ar*), 145.3 (*Ar*), 137.9 (*C*-1), 117.2 (*C*-6), 112.3 (*C*-5), 110.3 (*Ar*), 109.8 (*Ar*), 90.9 (*C*-3'), 72.6 (*CHOH*), 55.9 (*OCH*₃), 55.8 (*OCH*₃), 55.6 (*OCH*₃), 38.2 (*CHOHCH*₂), 19.0 (*CH*₂*Ar*); HRMS (ESI⁺) *m/z*: Calculated for C₁₉H₂₄NaO₆ (M+Na⁺): 371.1471, found: 371.1475.

1-[3-(methoxymethoxy)-4-methoxyphenyl]-3-(3,4-dimethoxyphenyl)-propan-1-one (**249**)

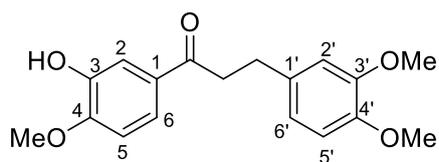


Following general procedure D, **249** was prepared from 3',4'-dimethoxybenzyl alcohol (204 mg, 1.13 mmol) and **261** (238 mg, 1.13 mmol). Purification by flash chromatography eluting with 20-50% EtOAc in hexane

gave **249** as a white solid (338 mg, 938 μmol, 83%).

R_f = 0.40 (Hex:EtOAc 60:40); ¹H NMR (400 MHz, CDCl₃, δ/ppm): 7.69 (1H, *J* = 4.8 Hz, *H*-2), 7.58 (1H, ap dd, *J*₁ = 4.8 Hz, *J*₂ = 10.8 Hz, *H*-6), 6.85 (1H, d, *J* = 11.6 Hz, *H*-5), 6.74-6.70 (3H, m, *Ar*), 5.19 (2H, s, *OCH*₂*O*), 3.87 (3H, s, *OCH*₃), 3.80 (3H, s, *OCH*₃), 3.79 (3H, s, *OCH*₃), 3.45 (3H, s, *OCH*₃), 3.15 (2H, t, *J* = 12.8 Hz, *COCH*₂), 2.92 (2H, t, *J* = 12.8 Hz, *CH*₂*Ar*); ¹³C NMR (100 MHz, CDCl₃, δ/ppm): 200.4 (*CO*), 153.4 (*C*-4), 152.9 (*Ar-OCH*₃), 152.7 (*Ar-OCH*₃), 146.0 (*C*-3), 135.1 (*C*-1'), 130.4 (*C*-1), 123.5 (*C*-6), 120.5 (*C*-6'), 115.9 (*C*-2'), 113.8 (*Ar*), 113.4 (*Ar*), 110.2 (*C*-5), 90.1 (*OCH*₂*O*), 56.8 (*OCH*₃), 56.6 (*OCH*₃), 56.3 (*OCH*₃), 56.2 (*OCH*₃), 38.4 (*COCH*₂), 18.8 (*CH*₂*Ar*); HRMS (ESI⁺) *m/z*: Calculated for C₂₀H₂₅O₆ (M+H⁺): 361.1651, found: 361.1648.

1-[3-Hydroxy-4-methoxyphenyl]-3-(3,4-dimethoxyphenyl)-propan-1-one (246)

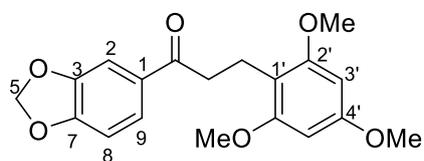


Following the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **249** (69 mg, 218 μ mol) in MeOH (5.0 ml) was added HCl (3 M, 1.0 ml).⁷⁶ The solution was heated to 65 $^{\circ}$ C for 3 h before being concentrated *in vacuo*. The residue

was dissolved in EtOAc (30 ml) and H₂O (30 ml), and the phases separated. The organic was washed with further H₂O (30 ml), brine (2 x 20 ml), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **246** as a white solid (59 mg, 188 μ mol, 86%).

R_f = 0.31 (Hex:EtOAc 60:40); ¹H NMR (500 MHz, CDCl₃, δ /ppm): 7.47 (1H, br s, *H*-2), 7.46-7.45 (1H, m, *H*-6), 6.80 (1H, d, *J* = 9.0 Hz, *H*-5), 6.72-6.69 (3H, m, *Ar*), 3.87 (3H, s, OCH₃), 3.79 (3H, s, OCH₃) 3.78 (3H, s, OCH₃), 3.14 (2H, t, *J* = 8.0 Hz, COCH₂), 2.92 (2H, t, *J* = 8.0 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 198.0 (CO), 150.6 (C-4), 148.9 (C-4'), 147.3 (C-3'), 145.5 (C-3), 134.1 (C-1'), 130.7 (C-1), 121.5 (C-6'), 120.1 (C-6), 114.2 (C-1'), 111.8 (*Ar*), 111.4 (*Ar*), 109.9 (*Ar*), 56.1 (OCH₃), 56.0 (OCH₃), 55.9 (OCH₃), 40.4 (COCH₂), 30.9 (CH₂Ar); HRMS (ESI+) *m/z*: Calculated for C₁₈H₁₉NaO₅ (M+Na⁺): 338.1130, found: 338.1134.

1-(Benzo[d][1,3]dioxol-5-yl)-3-(2,4,6-trimethoxyphenyl)-1-propanone (243)

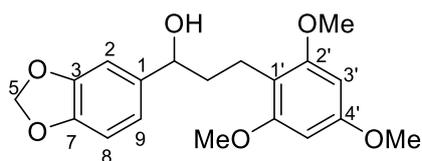


Following general procedure D, **243** was prepared from 2,4,6-trimethoxybenzyl alcohol (224 mg, 1.13 mmol) and 3',4'-(methylenedioxy)acetophenone. Purification by flash chromatography eluting 10-40% EtOAc in hexane gave **243**

as an off-white solid (311 mg, 904 μ mol, 80%).

R_f = 0.31 (80:20 Hex:EtOAc); ¹H NMR (500 MHz, CDCl₃, δ /ppm): 7.53 (1H, d, *J* = 10.8 Hz, *H*-9), 7.43 (1H, s, *H*-2), 6.75 (1H, d, *J* = 10.8 Hz, *H*-8), 6.06 (2H, s, *H*-5), 5.96 (2H, s, OCH₂O), 3.74 (3H, s, C-4'OCH₃), 3.71 (6H, s, C-2'OCH₃), 2.94-2.88 (4H, m, 2CH₂); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 198.9 (CO), 159.7 (C-4'), 158.8 (C-2'), 151.4 (C-1), 132.0 (C-3'), 129.8 (*Ar*), 129.4 (*Ar*), 109.9 (*Ar*), 108.6 (*Ar*), 107.8 (*Ar*), 103.7 (C-8), 90.5 (OCH₂O), 55.6 (C-4'OCH₃), 55.4 (C-2'OCH₃), 38.6 (COCH₂), 18.6 (CH₂Ar); HRMS (ESI+) *m/z*: Calculated for C₁₉H₂₁O₆ (M+H⁺): 345.1338, found: 345.1340.

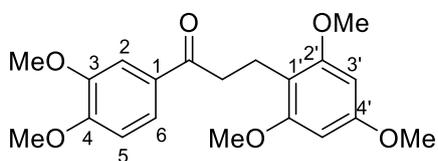
1-(Benzo[d][1,3]dioxol-5-yl)-3-(2,4,6-trimethoxyphenyl)-1-propanol (**230**)



To a stirred suspension of catalyst **73** (5.0 mg, 11.3 μmol) in toluene (1.0 ml) was added 2,4,6-trimethoxybenzyl alcohol (224 mg, 1.13 mmol) and 3',4'-(methylenedioxy)acetophenone (186 mg, 1.13 mmol) and NaOH (45 mg, 1.13 mmol). The reaction mixture was heated at reflux for 24 h in a sealed vessel, before addition of IPA (1.0 ml) and heating at reflux for a further 24 h. The reaction mixture was concentrated *in vacuo*, and purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **240** as a white solid (289 mg, 836 μmol , 74%).

$R_f = 0.30$ (80:20 Hex:EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 6.77 (1H, s, *H*-2), 6.68 (2H, d, $J = 8.0$ Hz, *H*-9), 6.63 (2H, ap d, $J = 8.0$ Hz, *H*-3'), 5.81 (2H, s, OCH_2O), 4.32 (1H, dd, $J_1 = 5.5$ Hz, $J_2 = 8.5$ Hz, *CHOH*), 3.71 (9H, s, OCH_3), 3.00 (1H, br s, *OH*), 2.67-2.61 (2H, m, CHOHCH_2), 1.80-1.75 (2H, m, CH_2Ar); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 159.5 (*C*-4'), 158.7 (*C*-2'), 147.5 (*C*-7), 146.4 (*C*-3), 138.9 (*C*-1), 119.4 (*C*-9), 10.9 (*Ar*), 108.1 (*Ar*), 106.6 (*C*-2), 100.9 (OCH_2O), 90.7 (*C*-3'), 72.8 (*CHOH*), 55.8 (OCH_3), 55.4 (OCH_3), 38.7 (CHOHCH_2), 18.6 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{19}\text{H}_{23}\text{O}_6$ ($\text{M}+\text{H}^+$): 347.1495, found: 347.1491. Spectroscopic data consistent with literature values.⁷⁶

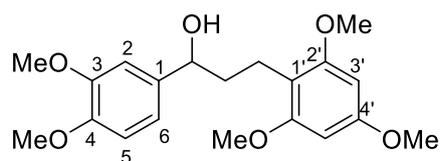
1-(3,4-Dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)-1-propanone (**245**)



Following general procedure D, **245** was prepared from 2,4,6-trimethoxybenzyl alcohol (224 mg, 1.13 mmol) and 3,4-dimethoxyacetophenone (204 mg, 1.13 mmol). Purification by flash chromatography eluting 10-40% EtOAc in hexane gave **245** as an off-white solid (301 mg, 836 μmol , 74%).

$R_f = 0.34$ (80:20 Hex:EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ/ppm): 6.91 (1H, s, *H*-2), 6.82-6.78 (2H, m, *H*-5, 6), 6.15 (2H, s, *H*-3'), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.77 (9H, s, OCH_3), 3.40 (2H, t, $J = 7.5$ Hz, COCH_2), 3.16 (2H, t, $J = 7.5$ Hz, CH_2Ar); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 198.1 (*CO*), 158.1 (*Ar*), 157.6 (*Ar*), 147.2 (*Ar*), 138.4 (*Ar*), 137.8 (*Ar*), 119.2 (*C*-6), 109.7 (*Ar*), 109.5 (*Ar*), 109.2 (*Ar*), 89.1 (*C*-3'), 56.1 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 55.7 (OCH_3), 40.1 (COCH_2), 23.2 (CH_2Ar); HRMS (ESI+) m/z : Calculated for $\text{C}_{20}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}^+$): 361.1651, found: 361.1648.

1-(3,4-Dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)-1-propanol (**244**)

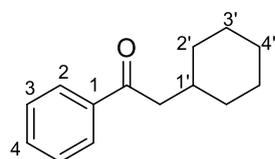


Following a modified version of the procedure used by Spring *et al.*⁷⁶, to a stirred solution of **244** (69 mg, 190 μmol) in MeOH (5.0 ml) at 0 °C was added NaBH₄ (29 mg, 767 mmol).⁷⁶ The reaction was left to stir for 1 h,

before being allowed to warm to RT and left to stir for a further 15 h. The reaction mixture was concentrated *in vacuo* and diluted with CHCl₃ (30 ml) and H₂O (30 ml). The phases were separated and the aqueous was extracted with further CHCl₃ (3 x 30 ml). The organic layers were combined and washed with further H₂O (2 x 50 ml) and brine (2 x 50 ml), before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 40-60% EtOAc in hexane gave **244** as a white solid (59 mg, 165 μmol , 86%).

R_f = 0.36 (50:50 Hex:EtOAc); ¹H NMR (500 MHz, CDCl₃, δ /ppm): 6.86 (1H, s, *H*-2), 6.77-6.72 (2H, m, *H*-5, 6), 6.09 (2H, s, *H*-3'), 4.37 (1H, dd, *J*₁ = 6.0 Hz, *J*₂ = 7.5 Hz, CHOH), 3.81 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.75 (9H, s, OCH₃), 2.70-2.67 (2H, m, CHOHCH₂), 1.82 (2H, q, *J* = 6.5 Hz, CH₂Ar); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 159.5 (*Ar*), 158.5 (*Ar*), 148.8 (*Ar*), 138.0 (*Ar*), 137.4 (*Ar*), 118.1 (*C*-6), 110.1 (*Ar*), 109.9 (*Ar*), 109.1 (*Ar*), 90.7 (*C*-3'), 72.6 (CHOH), 55.97 (OCH₃), 55.93 (OCH₃), 55.86 (OCH₃), 55.83 (OCH₃), 38.6 (CHOHCH₂), 18.8 (CH₂Ar); HRMS (ESI+) *m/z*: Calculated for C₂₀H₂₇O₆ (M+H⁺): 363.1808, found: 363.1804.

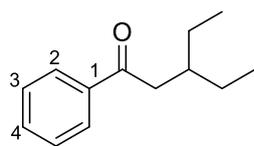
2-Cyclohexyl-1-phenylethan-1-one (**254**)



Following general procedure D, **254** was prepared from cyclohexanol (119 μl , 1.13 mmol) and acetophenone (132 μl , 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **254** as a colourless oil (91 mg, 452 μmol , 40%).

R_f = 0.89 (90:10 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃, δ /ppm): 7.84 (2H, d, *J* = 7.6 Hz, *H*-2), 7.46 (1H, t, *J* = 7.6 Hz, *H*-4), 7.37 (2H, ap t, *J* = 7.2 Hz, *H*-3), 2.80 (2H, d, *J* = 7.2 Hz, COCH₂), 1.90-1.82 (1H, m, CH), 1.70-1.52 (5H, m, Cy), 1.15-0.95 (5H, m, Cy); ¹³C NMR (100 MHz, CDCl₃, δ /ppm): 200.1 (CO), 136.9 (*C*-1), 132.6 (*C*-4), 128.5 (*Ar*), 128.3 (*Ar*), 45.1 (COCH₂), 33.1 (CH), 32.6 (Cy), 25.4 (Cy), 25.1 (Cy); IR (ν_{max} , neat, cm⁻¹): 3044, 2981, 2847, 1680, 1445, 1259, 1032, 884; HRMS (ESI+) *m/z*: Calculated for C₁₄H₁₉O (M+H⁺): 203.1436, found: 203.1431. Spectroscopic data consistent with literature values.¹²²

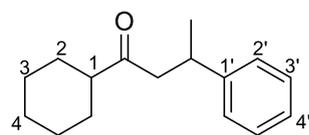
3-Ethyl-1-phenylpentan-1-one (255)



Following general procedure D, **255** was prepared from 3-pentanol (122 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **255** as a colourless oil (15 mg, 79 μ mol, 7%).

R_f = 0.93 (90:10 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 7.86-7.80 (2H, m, $H-2$), 7.51 (1H, t, $J = 7.2$ Hz, $H-4$), 7.34 (2H, ap t, $J = 7.6$ Hz, $H-3$), 2.85 (2H, d, $J = 7.2$ Hz, COCH_2), 1.97-1.95 (1H, m, CH), 1.48-1.39 (4H, m, CH_2CH_3), 0.96 (6H, t, $J = 7.2$ Hz, CH_2CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 199.8 (CO), 137.5 (C-1), 132.7 (C-4), 128.1 (Ar), 127.5 (Ar), 41.1 (COCH_2), 36.8 (CH), 24.2 (CH_2CH_3), 10.9 (CH_3); IR (ν_{max} , neat, cm^{-1}): 2954, 2928, 2880, 1691, 1453, 1283, 1191, 657; HRMS (ESI+) m/z : Calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ ($\text{M}+\text{H}^+$): 191.1436, found: 191.1440. Spectroscopic data consistent with literature values.¹²³

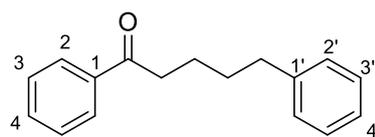
1-Cyclohexyl-3-phenylbutanone (256)



Following general procedure D, **256** was prepared from 1-phenylethanol (136 μ l, 1.13 mmol) and cyclohexyl methyl ketone (156 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **256** as a colourless oil (44 mg, 192 μ mol, 17%).

R_f = 0.87 (90:10 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ/ppm): 7.30-7.21 (2H, m, $H-2'$), 7.18-7.08 (3H, m, Ar), 3.42-3.31 (1H, m, CH), 2.83-2.61 (2H, m, COCH_2), 2.25-2.19 (1H, m, $H-1$) 1.87-1.62 (5H, m, Cy), 1.29-1.07 (7H, m, Cy, CH_3), 0.89-0.80 (1H, m, Cy); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , δ/ppm): 206.4 (CO), 146.9 (C-1'), 128.4 (C-4'), 126.2 (Ar), 125.7 (Ar), 50.4 (C-1), 47.6 (COCH_2), 33.9 (CH), 29.1 (Cy), 28.7 (Cy), 24.5 (Cy), 20.6 (CH_3); IR (ν_{max} , neat, cm^{-1}): 3023, 2910, 1726, 1617, 1483, 1375, 1141, 767; HRMS (ESI+) m/z : Calculated for $\text{C}_{16}\text{H}_{22}\text{NaO}$ ($\text{M}+\text{Na}^+$): 253.1563, found: 253.1558. Spectroscopic data consistent with literature values.¹²⁴

1,5-Diphenyl-1-pentanone (**257**)



Following general procedure D, **257** was prepared from 3-phenyl-1-propanol (154 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **257** as a yellow solid (239 mg, 1.01 mmol, 89%).

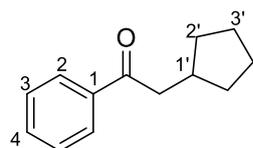
Following general procedure D, **257** was prepared from 3-phenyl-1-propen-1-ol (152 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash eluting with 0-10% EtOAc in hexane gave **257** as a yellow solid (97 mg, 407 μ mol, 36%).

Following general procedure E, **257** was prepared from 3-phenyl-1-propanol (154 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **257** as a yellow solid (180 mg, 757 μ mol, 67%).

Following general procedure E, **257** was prepared from 3-phenyl-1-propen-1-ol (152 mg, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **257** as a yellow solid (94 mg, 396 μ mol, 35%).

R_f = 0.87 (90:10 Hex:EtOAc); mp 46.1-46.7 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 7.91-7.86 (2H, m, *Ar*), 7.49-7.11 (8H, m, *Ar*), 3.10-3.02 (2H, m, COCH_2), 2.68-2.61 (2H, m, CH_2Ar), 1.83-1.65 (4H, m, 2CH_2); ^{13}C NMR (100 MHz, CDCl_3 , δ /ppm): 200.5 (CO), 141.9 ($\text{C-1}'$), 135.9 (C-1), 132.6 (C-4), 128.6 (*Ar*), 128.57 (*Ar*), 128.54 (*Ar*), 128.1 (*Ar*), 124.3 ($\text{C-4}'$), 39.2 (COCH_2), 35.6 (CH_2Ar), 30.8 (CH_2), 25.1 (CH_2); HRMS (ESI+) m/z : Calculated for $\text{C}_{17}\text{H}_{19}\text{O}$ ($\text{M}+\text{H}^+$): 239.1436, found: 239.1437. Spectroscopic data consistent with literature values.¹²⁵

2-Cyclopentyl-1-phenylethan-1-one (**258**)



Following general procedure D, **258** was prepared from cyclopentanol (103 μ l, 1.13 mmol) and acetophenone (132 μ l, 1.13 mmol). Purification by flash chromatography eluting with 0-10% EtOAc in hexane gave **258** as a yellow oil (15 mg, 79 μ mol, 7%).

R_f = 0.93 (90:10 Hex:EtOAc); ^1H NMR (400 MHz, CDCl_3 , δ /ppm): 8.04-7.96 (2H, m, *H-2*), 7.56-7.41 (3H, m, *Ar*), 2.95 (2H, d, J = 7.2 Hz, COCH_2), 2.41-2.28 (1H, m, *CH*), 2.01-1.85 (2H, m, *CyPent*), 1.76-1.50 (4H, m, *CyPent*), 1.28-1.05 (2H, m, *CyPent*); ^{13}C NMR (100 MHz,

CDCl₃, δ/ppm): 198.6 (CO), 137.9 (C-1), 133.1 (C-4), 128.5 (Ar), 128.4 (Ar), 45.1 (COCH₂), 36.7 (C-1'), 31.5 (C-2'), 24.7 (C-3'); HRMS (ESI+) *m/z*: Calculated for C₁₃H₁₇O (M+H⁺): 189.1279, found: 189.1276. Spectroscopic data consistent with literature values.¹²³

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